Understanding the behavioural and neurological response to word reading training paired with anodal tDCS in participants with Central Alexia

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Declaration of authorship

‘I, Sheila Kerry 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

Acknowledgments

I would like to thank all the participants and carers who gave their time to support this research. This work would not be possible without them, and I am truly grateful for all their efforts.

There are three main people that I need to thank, and without whom, I would be in an awful lot of trouble.

Firstly, I would like to thank Jenny Crinion for her support not only throughout this PhD but also during my MSc year. I still don't think I have managed the art of structuring my work, but without you, it would be a real mess!

Secondly, I would like to thank Zoe Woodhead. You have been a fountain of knowledge though all of my MEG related trials and tribulations. You have been a quiet source of invaluable support and guidance throughout the last four years and I cannot thank you enough.

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Lastly, but importantly, thanks to all of my friends and family who have been a source of invaluable support and understanding over the past four years.

Abstract

Central alexia (CA) is an acquired reading disorder co-occurring with a generalised language deficit (aphasia). In my thesis, through a series of three experiments, I aim to explore the reading network of 23 patients with CA and how it responds to a training application (app) called iReadMore. It is hoped that improving our understanding of the mechanisms of neural plasticity following therapy for post-stroke CA will lead to the development of more effectively targeted therapies.

The introduction outlines models of reading and our current understanding of neuroplasticity in post-stroke aphasia. Of particular importance is the view of aphasia as a network disorder. Accordingly, this thesis investigates the effective connectivity observed when reading, rather than activation within individual regions.

In the first results chapter, I compare the reading networks of CA and control participants using dynamic causal modelling (DCM) for magnetoencephalography (MEG) data. This analysis aims to identify potentially damaged and adapted connections within the reading network of CA participants.

I then report the results of a clinical trial investigating the effects of iReadMore training, paired with anodal transcranial Direct Current Stimulation (A-tDCS). This chapter aims to identify if iReadMore training improves single word reading aloud, and if A-tDCS provides an additive effect on training.

In the final results chapter, I use DCM for MEG to explore training induced changes in the reading network of CA patients. This chapter aims to identify the neural mechanisms by which iReadMore training is effective.

In chapter six, I take each of the results chapters in turn and discuss the main findings, limitations and potential future research directions. I also discuss reading therapy for CA and the clinical use of DCM as two broader topics touched upon by this thesis.

Significance Statement

The data in my thesis presents four world firsts:

1. A network level analysis of neuroplasticity within CA patients during reading. A bilateral reading network was employed by patients with CA prior to iReadMore training, which included stronger feed-forward connections between the right occipital (OCC) to right ventral occipitotemporal (vOT) and Inferior Frontal regions (IFG) when reading Words compared to False Fonts. Additionally, there was an increased sensitivity within the right IFG for viewing words. This adds to the literature on the role of the left and right hemispheres in post-stroke language reorganisations.
2. I tested a novel computerised reading therapy, iReadMore, for CA patients in a randomised control trial. When patients trained with iReadMore, reading accuracy improved by an average 8.4% on trained items. Now that iReadMore has been proven to be useful in the lab it is being developed as an app for use by the general public (target release date August 2018). This means the iReadMore therapy will hopefully benefit many more English reading patients with CA (irrespective of their global location). Scientifically, data collected from patients using the app will enable the predictions and hypotheses generated by my work to be tested in a larger population of patients. Ultimately, it is hoped this will lead towards better patient stratification and the ability to identify which patients the therapy is most effective for.
3. This was the first study to reveal a positive effect of A-tDCS when paired with a word reading re-training task in a group of CA patients. Greater word reading accuracy immediately after training was observed when participants received A-tDCS with iReadMore training compared to S-tDCS. The additive effect of A-tDCS equated to an increased in word reading accuracy of 2.6%. Participants in this study attended the lab to receive stimulation. I do not believe this is a viable option when considering the use of A-tDCS as a therapy adjunct for the wider population. Investigation into the use of A-tDCS outside of the lab are underway (Charvet et al., 2015). Now that an additive effect of A-tDCS has been

observed within the lab, it can be investigated for use at home, which may provide more ecologically valid results for clinical use.

4. I observed that iReadMore training increased the strength of connections between the left OCC to left IFG and vOT. It is suggested that iReadMore encourages increased use of visual sensory information in processing word reading. This is the first study to identify training induced modulation of the reading network in CA patients. These bottom-up effects add to the literature on the lateralisation of reading in post-stroke aphasia. They also suggest that iReadMore therapy encourages increased use of perilesional tissue in reading.

Statement of publications

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

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

1) The data presented in chapter four have been published in Brain.

Randomized trial of iReadMore word reading training and brain stimulation in central alexia. 2018. Woodhead, Z.*, Kerry, S.*, Aguilar, O., Ong, YH., Hogan, J., Pappa, K., Leff, AP. & Crinion *Brain*

**Joint first author*

2) The data presented in chapter five have been submitted to Journal of Neuroscience:

How does iReadMore therapy change the reading network of patients with central alexia? Sheila J Kerry*, Zoe V J Woodhead*, Oscar M Aguilar, William Penny, Gareth Barnes, Jennifer T Crinion and Alex P Leff. Journal of Neuroscience

**Joint first author*

Other publications from the iReadMore trial:

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. *Cortex,* under review

Lesion site dependent treatment responses after stroke. 2018. Aguilar, O., Kerry, S., Ong, YH, Callaghan, M., Crinion, J., Woodhead, Z., Price CJ, Leff, AP & Hope, T. *Journal of Neurology, Neurosurgery and Psychiatry,* doi: 10.1136/jnnp-2017-317446.

Abbreviations

AG	Angular gyrus
AIC	Akaike information criterion
ALI	Automatic Lesion Identification toolbox
ALM	Automatic linear modelling
A-tDCS	Anodal stimulation
ATL	Anterior Temporal Lobes
C-SART	Children's Sustained Attention to Response Task
CA	Central alexia
CAT	Comprehensive Aphasia Test
CDP	Communication Disability Profile
CSF	Cerebrospinal fluid
dIFG	dorsal Inferior Frontal Gyrus
fMRI	Functional MRI
GPC	Grapheme to phoneme conversion
IA	Interactive Account
IFG	Inferior frontal gyrus
ILF	Inferior longitudinal fasciculus
LTP	Long-term potentiation
MCA	Middle cerebral artery
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MT	Magnetization transfer

MTG	Middle temporal gyrus
Neale	Neale Analysis of Reading Ability test
NMDA	N-methyl-aspartate receptors
O-P	Orthography-to-phonology
O-S-P	Orthography via semantics to phonology
PCG	posterior Central Gyrus
PET	Positron emission tomography
PPT	Pyramids and palm trees test
qMRI	Quantitative MRI imaging
RT	Reaction time
SLT	Speech and language therapy
SMG	Supramarginal gyrus
SPM	Statistical Parametrical Mapping
S-tDCS	Sham stimulation
STG	Superior temporal gyrus
tDCS	Transcranial direct current stimulation
vOT	Ventral occipital-temporal cortex
vIFG	ventral Inferior Frontal Gyrus
VWFA	Visual word form area

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Outline of thesis

Chapter 1 (Introduction) focuses on two key concepts. Firstly, the history of key models of reading are explored. These are used later in my thesis to interpret the observed results. This context also provides a foundation to understand the current thinking behind models of reading, and proposals for how a damaged reading system should be targeted with therapy. The second concept is rehabilitation and neuroplasticity in post-stroke aphasia. Neuroplasticity refers to the ability of the brain to form or reorganise synaptic connections, especially in response to damage or through learning. This is explored at a number of levels. Aphasia is increasingly viewed as a network disorder. Therefore, I am interested in neuroplasticity at systems neuroscience level; in other words, the changes in connectivity between different regions involved in reading. This will be explored a) as a result of stroke damage, and b) in response to iReadMore therapy. Neuroplasticity can also be observed at the behavioural level (i.e. improved word reading accuracy and reaction time in response to training). It is hypothesised that neuroplasticity can be enhanced by the addition of anodal transcranial current stimulation (A-tDCS). I also explore this as an adjunct to enhancing behavioural induced neuroplasticity in the course of my thesis.

In Chapter 2 (methods) I describe the tools used to assess these main concepts. In order to investigate rehabilitation of reading and the additive effect of A-tDCS, I describe the study design and behavioural tests conducted in the iReadMore trial. To explore neuroplasticity at the systems level, I used dynamic causal modelling (DCM) analysis of evoked potentials within magnetoencephalography data. This involved the identification of key brain regions involved in reading, and assessing the strength of the connections between them. I describe the parameters used within DCM to assess these main questions.

Chapter 3 is concerned with how the reading network of CA participants is different to that of healthy controls. This analysis aims to identify potentially damaged and adapted connections within the reading network of CA participants. Connectivity strengths between the right and left occipital (OCC), ventral occipitotemporal (vOT) and inferior frontal regions (IFG) were compared when participants saw Words and visual stimuli matched in complexity (meaningless symbol strings; False Fonts). This type of analysis has never previously been

performed with CA participants. These findings are explored using existing neurophysiologically informed models of reading.

In Chapter 4, I report the results of a clinical trial investigating the effects of iReadMore training, paired with A-tDCS. A sufficient aphasia therapy dose is required to induce neuroplasticity (Bhogal, Teasell, & Speechley, 2003). Providing patients with this level of therapy within the NHS is challenging (Code & Petheram, 2011). There is no agreed treatment for CA. One method of retraining is mass practice of reading at the lexical level, in which patients receive sizable exposure to training stimuli in written and spoken forms and an associated picture. Clinically tested electronic training programs may provide a viable low cost option to allow patients mass practice on therapy items, without the need for the presence of a speech and language therapist. This chapter aims to identify if a reading retraining app, iReadMore, improves single word reading aloud accuracy and speed in patients with CA. This was the first study to show that iReadMore was suitable for patients with CA, and significantly improved word reading accuracy and speed.

It has been suggested that reducing the resting membrane potentials of cells active in completing a task via anodal transcranial current stimulation (A-tDCS) may enhance neuroplasticity. It is hypothesised that when A-tDCS is paired with a training task, additional gains (i.e. in the form of increased accuracy) on the task may be achieved. This is of particular interest within aphasia therapy research, as it may lead to increased therapy effects. I tested the effectiveness of A-tDCS to the left IFG delivered with iReadMore therapy.

I am interested in understanding the possible mechanisms for neuroplasticity caused by iReadMore training. Retraining animals to perform tasks impaired by a lesion triggered synaptic remapping that does not occur without training (Kleim, 2011; Kleim et al., 2002; Kleim, Pipitone, Czerlanis, & Greenough, 1998; Nudo, 2013). In chapter five, I explored the modulation of functional connectivity between the left and right IFGs, vOTs and OCCs as a result of iReadMore training. I observed that iReadMore training increased the strength of connections between the left OCC to left IFG and vOT. It is suggested that iReadMore encourages increased use of visual sensory information in processing word reading. This is the first study with CA patients to identify training modulation of

the reading network.

Finally, in Chapter 6 I outline the scientific and clinical implications of the data from this thesis. Clinically, the positive results of the iReadMore trial provide an evidence base for the release of iReadMore training app for public use. Scientifically, the results in this thesis further our understanding of the potential mechanisms of neuroplasticity within the reading network of CA patients following stroke damage and how iReadMore training modulates this.

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 Introduction

Aphasia, a generalised acquired language disorder, is the second most common major impairment after stroke. According to the Stroke Association there are 1.2 million stroke survivors in the UK (Stroke Association, 2017). In a study of over 66,000 residents of hospital-based long-term care facilities, aphasia had the strongest negative relationship that with quality of life measures compared to 60 diseases (including cancer and Alzheimer's disease; Lam & Wodchis, 2010).

Central alexia (CA) describes an acquired reading disorder that occurs within aphasia. While it can vary in its severity from patient to patient, even in its milder forms it can have a negative impact on the quality of life of those affected. There is no agreed treatment for CA, although it is suggested that a large therapy dose will be required to induce neuroplasticity (Bhogal et al., 2003). Here, I test the use of iReadMore as a way of providing CA participants with mass exposure to training. There is continued debate regarding the role of the left and right hemisphere in language reorganisation after stroke and in response to therapy (Crinion & Leff, 2015; Crosson et al., 2007; Hartwigsen & Saur, 2017; Turkeltaub, Messing, Norise, & Hamilton, 2011). It is hoped that a greater understanding of the language reorganisation post-stroke will lead to the development of better therapies.

In this thesis I aim to investigate the following research questions:

1. How does the reading network of participants with CA differ from that of healthy readers?
2. Does iReadMore improve word reading in patients with CA and does A-tDCS targeted at the left IFG enhance therapy effects?
3. How does iReadMore reading training affect the reading network of CA participants?

These questions are interesting to me both for their potential clinical implications and to further our understanding of the reading network in the lesioned brain and post-stroke neuroplasticity.

It is hoped that by ascertaining if iReadMore is clinically effective, it can be released on the Internet. This has the potential impact to improve the reading skill of people with CA globally.

Reading is a seemingly automatic process for many skilled readers (Leff & Starrfelt, 2013); however, how this process is represented in the brain is still highly debated (Carreiras, Armstrong, Perea, & Frost, 2014; Dehaene & Cohen, 2011; Dehaene, Cohen, Sigman, & Vinckier, 2005; Price & Devlin, 2003, 2011). As this is the first network level analysis of CA patients, it is hoped that it will raise potential future study questions and promote the use of network level analysis in neuroimaging studies of aphasia. While I do not expect this research alone to lead to the development of a novel form of training, I hope it will add to a body of literature on post-stroke aphasia neuroplasticity, which will lead to future developments in post stroke reading therapies. As language functions rely on a number of interconnecting regions, exploring aphasia at the network level is the next step to understanding the disorder and how better to treat it. This may also help to inform patients as to why certain aspects of reading are difficult. Over the course of my PhD, I have learnt that providing patients with a better understanding of their disorder can be helpful in itself.

The literature on reading and the brain is vast, and I cannot explore it all in this thesis. In this introduction I will introduce two key concepts necessary for understanding my research motivations and questions: (i) models of reading and (ii) post-stroke reading rehabilitation and the associated neuroplasticity that underlies it.

A brief history of the development of cognitive and neuropsychological models of reading is provided. Different models are more applicable to interpreting the various results reported in the chapters of this thesis. It is also important to understand why and how our currently thinking of the cognitive process of reading and reading therapy has developed. I will also describe CA and its subtypes in the context of these models.

Neuroplasticity refers to how the brain reorganises or forms new synapses in response to injury, experience or learning. After stroke damage, neuroplasticity is a key mechanism for recovery (Kleim & Jones, 2008; Rossini, Calautti, Pauri, & Baron, 2003). This can occur to some degree without intervention, but may be

enhanced by training. If we are to better treat CA, understanding how neuroplasticity occurs may be very important. Neuroplasticity can be investigated at many levels (e.g. cellular, systems). In the course of this thesis, I will explore neuroplasticity at the systems neuroscience level. Studies in animals and humans have demonstrated post-stroke neuroplasticity (K. Cornelissen et al., 2003; Rossini et al., 2003). Reading is a complex skill involving the use of interconnected parts of the brain (Hoffman, Lambon Ralph, & Woollams, 2015; Perrone-Bertolotti, Kauffmann, Pichat, Vidal, & Baciu, 2017; Price, 2012; Woodhead et al., 2014). It is hypothesised that neuroplasticity in post-stroke aphasia may be effective through the recruitment of alternative regions to complete a task or as a result of a change in reliance on regions already existing within the network (Crinion & Leff, 2015; Crosson et al., 2007; Hartwigsen & Saur, 2017; Turkeltaub et al., 2011). This would require a re-mapping of the network. Thus, it is important to study neuroplasticity at the systems level. The effects of neuroplasticity can be observed in changes at the behavioural level. This is important, as it is ultimately how CA patients experience the disorder (i.e. in changes to their reading accuracy post therapy).

In this introduction I will explore i) previous reading therapies for CA, ii) the potential mechanisms and use of A-tDCS for enhancing neuroplasticity in aphasia therapy, and iii) previous research into neural reorganisation in CA after stroke and how this changes in response to therapy, and iv) the theoretical background to studying neuroplasticity at the systems level using dynamic causal modelling (DCM).

1.1 A history of cognitive models of reading

This section aims to outline a brief history of models of language. It starts by detailing the work of 19th century psychologists, who first became interested in the relationship between language disorders and the brain. I then describe the development of box-and-arrow diagrams of language that explained variations in the reading patterns observed in healthy and impaired adult readers. Next, I explore how the advent of advanced computing power led connectionist psychologists to develop box-and-arrow diagrams of reading into testable computational models of reading. I then pause to describe CA, and its subtypes, within the context of these models. Finally, I describe neurophysiologically

informed models of reading that were proposed after the explosion of neuroimaging research.

I believe understanding the context in which models of reading were established is important to understanding why different models of reading were developed and why some have apparently overlapping features. With regards to this thesis, box-and-arrow and connectionist models of reading have provided the majority of the vocabulary and thinking behind the behavioural profiling of reading patterns in CA and in the developments of CA treatments, thus, these models are used to interpret the results of Chapter 4. However, neurophysiologically informed models may be better equipped for discussions regarding language networks in post-stroke CA and thus DCM models are used to interpret the findings of Chapter 3.

1.1.1 The early days

In the early part of 19th century Gall proposed that a structure-function relationship between regions of the brain and each stage of language processing could be established (Forster & Chambers, 1973). Gall assumed that functions contained within the brain would occur in pairs, organised symmetrically across the hemispheres, known as Bichat's law of symmetry. In the later part of the 19th century the work of Broca and Dax would centre articulated speech to the left hemisphere. From 1800, Marc Dax collected statistics on over 40 cases of hemiplegia, documenting the co-occurrence with speech loss (Levelt, 2013). This data was intended for presentation in 1836, prior to Broca's seminal paper presenting two cases of speechless patients with left hemisphere lesions. Dax noted that hemiplegia and speech loss only co-occurred in cases of right hemiplegia, not left. This data collection was continued by his son, Gustave Dax, but was not published until 1865. The final paper reported 87 patients with right hemiplegia and speech loss and 53 patients with left hemiplegia without speech loss. Broca's 1861 work included two detailed autopsy reports of patients with speech articulation problems, but apparent preservation in other mental capacities and language. In both cases, left frontal lesions were reported, however, the precise overlap in lesion location in these patients was attributed to coincidence (Levelt, 2013). It was not until 1865, when six more cases were added to his analysis, that he located speech loss to the third convolution of the

left frontal gyrus. Therefore, both Dax and Broca had an influential role in locating the organ of spoken language to the left frontal regions. Broca went to great lengths to point out that his localisation was not of general language, but of speech production. Wernicke would later be influential in breaking down language into its component parts and organising them in diagrammatic form as well as identifying parts of the brain important for speech processing. Later, Lissauer (1890) and Dejerine (1892) added aspects of visual processing specifically related to reading and writing to these models. Word reading disorders were classified into those with agraphia (a writing disorder), e.g. CA; and without agraphia, e.g. pure alexia or hemiaonpic alexia (R. E. Graves, 1997). *Figure 1* details how reading and writing could be added to the Wernike-Lichtheim model of language. According to this model, damage to the left angular gyrus would result in alexia with agraphia.

However, structure-function relationships between behaviour and brain were difficult to ascertain. It is now known that lesions to the left angular gyrus can result in alexia with agraphia in some patients, but not others (Price, 2018). This may be due to pre-morbid individual differences in language network organisation, or a result of different neuroplasticity following stroke damage. Additionally, obtaining accurate representations of lesion locations was challenging before the advent of MRI (Price, 2018). This meant many structure-function relationships proposed in the 19th Century became discredited (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001). As such, psychologists suggested that neuroanatomy provided little additional information regarding language processing, over the study of behaviour alone (Brain, 1964). Instead, they sought to describe in detail the different computational processes and representations required for reading with the use of box-and-arrow diagrams.

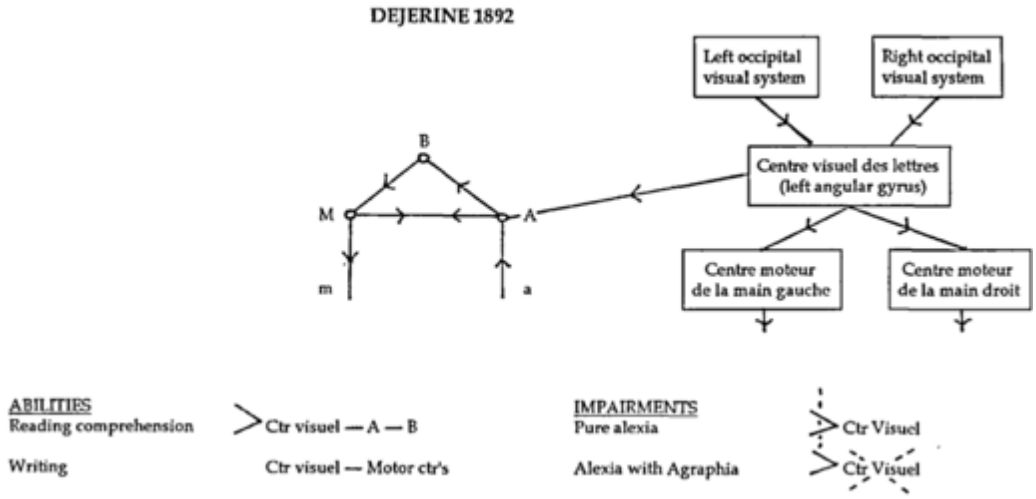


Figure 1 The Wernike-Lichtheim model with Dejerine's 1892 model taken from (R. E. Graves, 1997) with permission. It depicts a model for aphasia where; a=the auditory input, A=the auditory representation centre, B=concepts, M=motor word-representation centre, m=the resulting motor output i.e., converts M into speech output. On the right is Dejerine's models of reading and writing. This describes the left and right occipital regions feeding into a visual centre for letters. This is then fed into the point A on the Wernike-Lichtheim model or to the motor region of the left or right hand. Pure alexia results from damage to connections to the visual centre for letters, while central alexia would result from damage within the centre for visual processing. From "The legacy of the Wernicke-Lichtheim model." by R. Graves, 1997, Journal of the history of the neurosciences, 6, p. 3-20. Copyright 1997 by Taylor & Francis Group. Reprinted with permission.

1.1.2 Box-and-arrow diagrams of reading and central alexia

1.1.2.1 Dual Route Model of reading

In 1973, two key papers described a two-route system to word reading. Both detailed a route to reading that involves the application of grapheme to phoneme conversion (GPC) rules and a separate route, which draws upon a long-term memory store of how to pronounce familiar words. One paper researched word reading in healthy readers (Forster & Chambers, 1973) and the other was interested in explaining the patterns of reading observed in patients with CA (Marshall & Newcombe, 1973). Marshall and Newcombe (1973) noted that patients with CA rarely exhibited no response to written stimuli. The ability to read certain categories of written stimuli was preserved, and patients presented with

error patterns that could be used to classify patients into different CA subtypes. I will describe the cases of CA subtypes later in this chapter.

According to the dual route model of reading the direct conversion of to phonemes is useful for reading non-words or novel words, but over reliance this route would result in regularisation errors, whereby irregular words (e.g. PINT) would be read with the application of regular spelling-sound correspondences (e.g. PINT as in MINT). The lexical route copes well with irregular words. It looks up orthographic representations within the orthographic lexicon and matches it to a phonological lexicon, before the phonemes required for speech production are arranged (Coltheart et al., 2001). However, this route is unable to read novel or non-words, for which there are no long-term lexical stores (See

Figure 3).

1.1.3 Computational models of reading

Box-and-arrow diagrams of reading models were useful for describing the process of reading, but did not provide testable models. A computational model is a mathematical model, whereby different components of the reading network can be estimated. An advantage of a computational modelling is that it provides a testable model of reading. The model can also be broken to test hypotheses of damage location in CA subtypes. These proved highly influential in the 20th century and provide much of the current vocabulary used to describe the reading processes today. Additionally, these models also influenced treatments, which aimed to target damaged parts of the model, or strengthen preserved parts of the model.

1.1.3.1 Interactive Activation Model (IAM)

Connectionist models can be designed so that activation spreads through the model in a way that simulates activation patterns in the brain. According to the Interactive Activation Model (IAM) of reading (*Figure 2*) proposed by McClelland and Rumelhart (McClelland & Rumelhart, 1981) activation for feature identification nodes (e.g. the vertical line in ‘E’) is cascaded through the model to all letters nodes that contain this feature (e.g. ‘E’ and ‘H’) and words that contain these letters, while inhibiting those that do not. A crucial feature of the

model is that multiple letters can be identified in parallel, with visual processing occurring simultaneously at multiple levels of the system. This model excels at explaining the visual processing of words, but neglects the semantics and phonology of words, which are crucial for the use of words in communication.

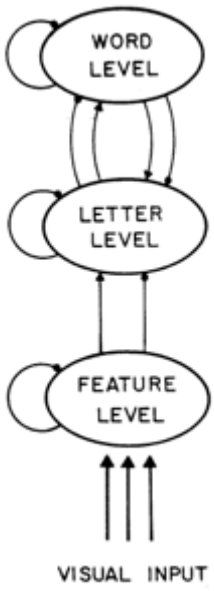


Figure 2 Interactive Activation Model of Reading (McClelland & Rumelhart, 1981). Arrows represent excitatory connections whereas dot-ended connections represent inhibitory connections. From "An interactive activation model of context effects in letter perception: I. An account of basic findings" by J. L. McClelland, & D. E. Rumelhart, 1981, Psychological Review, 88, p. 375-407. Copyright [1981] by American Psychological Association. Reprinted with permission.

1.1.3.2 Dual Route Cascade Model of reading

The Dual Route Cascade (DRC) model allowed for the testing of the dual route model of reading proposed in the 1970s.

Computational modelling requires specificity in order to generate equations for the modelling. The main difference between the dual route model of reading and the DRC is that activation is allowed to flow between levels of the model providing both excitatory and inhibitory effects within the lexical reading route (Coltheart et al., 2001). By allowing activity to flow though both streams of the DRC, the model was able to explain how, when primed with the written word "sofa", subjects pronounced the word "louch" as in "couch"; but when primed with the written word "feel", pronounced "louch" as in "touch". Activation of the orthographic lexicon fed

down the system and generated partial activation of both the routes of the model. As “touch” had been primed by “feel” there was partial activation in the lexical route. However, there was also partial activation within the non-lexical route. Both influence the output in the phoneme system.

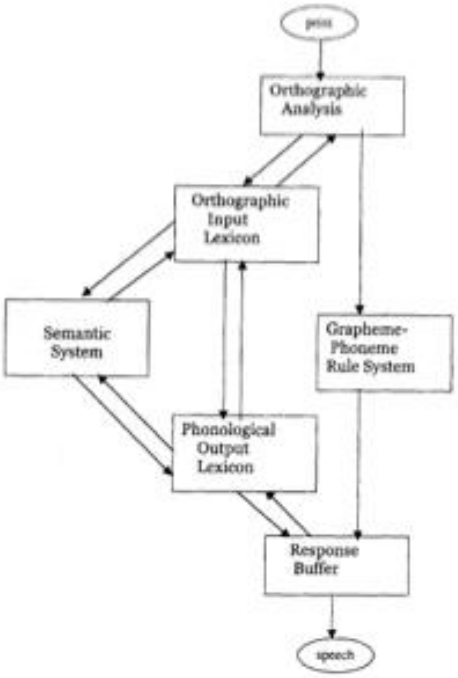


Figure 3 The basic architecture of the Dual Route Cascade model. The model outlines one feed-forward model along which grapheme to phoneme rules are applied. The lexical route (displayed on the left of the diagram) is used for whole word retrieval and contains both forwards and backwards connections. From “DRC: A dual route cascaded model of visual word recognition and reading aloud.” by M. Coltheart, K. Rastle, C. Perry, R. Langdon and J. Ziegler, 2001, Psychological review, 108, p. 204-56. Copyright [2001] by American Psychological Association. Reprinted with permission.

The DRC used the visual word recognition features outlined in the IAM to explain how letters and words are processed visually. These features served as the input to the DRC model. In Colheart et al (2001), several phenomena of reading are modelled by the DRC, such as faster reading for high frequency and high regularity words than low frequency and low regularity words. A key criticism of the DRC is that the model is pre-specified, that is, it does not “learn to read” and build up a model with exposure to written stimuli.

1.1.3.3 Triangle model of reading

The ability to read has only been widespread among the population in the last few hundred years (Gross, 2010). Therefore, in evolutionary terms, it is unlikely that a region specific for this function would have developed. Instead, the model of reading proposes that reading depends on primary systems that are already existent in the brain (Patterson & Lambon Ralph, 1999). These include regions important for visual processing (as orthographic stimuli are a specific of visual stimuli), sound representations (to pair what a word looks like to how it should be said) and semantic representations (to interpret the meaning of the word and to aid in pairing orthography with phonology; Woollams, 2013). The Triangle model is a connectionist computational model of reading, comprising of three interconnected domains; orthographic (O), phonological (P) and semantic (S) representations (See *Figure 4*).

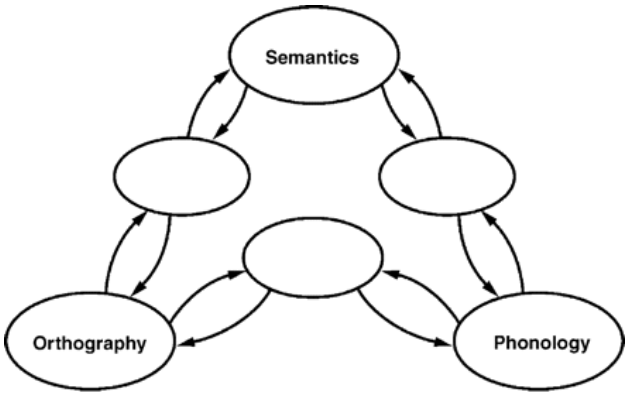


Figure 4 The Triangle Model of Reading taken from (Seidenberg, 2005). The empty circles represent hidden units where weightings between the connections occur. From "Connectionist Models of Word Reading" by M. S. Seidenberg, 2005, Current Directions in Psychological Science, 14, p. 238-242. Copyright [2005] by SAGE Publications. Reprinted with permission.

When one learns to read, a relationship is developed between novel symbols and existing speech sounds (Harm & Seidenberg, 2004) and the semantic meaning of a word, which is developed through a collection of crossmodal feature correlations across modalities (Rogers et al., 2004). The model does not specify any word stores, rather, weightings between the nodes are learnt through exposure (Seidenberg, 2005). Like the dual route model, word recognition can be

achieved through a direct O-P route or an indirect O-S-P route. However, the triangle model does not divide reading into two exclusive streams but rather specifies a weighting on the 'division of labour' (Plaut, McClelland, Seidenberg, & Patterson, 1996). All three domains are activated during word reading, but to a greater or lesser extent depending on the type of word: reading pseudowords or function words relies more on the O-P pathway, whereas the O-S-P pathway has more influence for irregular words.

1.2 Central alexia

Connectionist models have been key to developing the vocabulary around CA subtypes and mechanisms for intervention. I will pause here, to explore the subtypes of CA.

It is rare that a patient with CA with be completely unable to read. More likely is that reading will be achieved but with difficulties specific to certain word types or a common pattern of errors (Marshall & Newcombe, 1973). CA has been categorised into three subtypes, namely surface dyslexia (SD), phonological dyslexia (PD) and deep dyslexia (DD), based on the type of words affected by the deficit and the errors the patients make in reading aloud. See Figure 5 for explanations of these reading disorders in the context of cognitive models of reading.

1.2.1 Surface dyslexia

In their seminal description of surface alexia, Marshall and Newcomb (1973) documented the reading performance of participants J.C. and S.T. They found more errors for nouns compared to adjectives and verbs. Where noun errors occurred, the target word was often a substituted for a more frequent word. Visual errors (e.g. SPY>shy) were also observed. Words most vulnerable to this type of error were those that contained letters that are changed with graphemic context (e.g. s, f, c). Example of errors include INSECT>insist, INCENSE>increase. The hallmark symptoms of surface dyslexia are visual errors, regularisation of irregular words (e.g. PINT is read to rhyme with MINT), especially those with lower frequency, while non-word reading and regular word reading remains largely intact.

In line with the triangle model of reading, surface dyslexia often co-occurs with a parallel disruption to spelling which takes a similar form (Graham, Patterson, & Hodges, 2000). Surface dyslexia has largely been reported in cases of semantic dementia (gradual degradation of the anterior temporal poles, which is usually to a greater degree on the left than the right; Adlam et al., 2006; Mion et al., 2010). It has been demonstrated that the degree of general semantic impairment correlated with the impairment in reading low frequency exception words (Woollams, Ralph, Plaut, & Patterson, 2007). This effect was simulated by damaging the quality and clarity (i.e. increasing the noise) of semantic activity in the triangle model, and reflected the patient data well, accounting for 93% of the variance.

In contrast, the DRC model of reading accounts for the error profiles observed in surface alexia through damage to the orthographic input lexicon. This is demonstrated by cases where the patient can still perform lexical decision and identify the meaning of the word when spoken. The problem is that they no longer recognise the written word as familiar, as they would have done pre-stroke. Instead these patients are forced to rely on GPC rules, in the indirect pathway, which fail for exception words (Coltheart, 2006b).

1.2.2 Phonological dyslexia

The characteristic feature of phonological dyslexia is a deficit in reading non-words, while word reading is preserved (Beauvois & Derouseneá, 1979). This stems from a deficit in the translation of print to sound (Coltheart, 1996). Errors in non-word reading lead to lexicalisation of the non-word (e.g., SOOF>soot) (Whitworth, Webster, & Howard, 2005). Within word reading, an imageability effect (high>low) and an advantage in reading content words (e.g., nouns and verbs) over function words can be observed in some cases (Glosser & Friedman, 1990).

According to the triangle model of reading, phonological dyslexia stems from damage to the direct O-P pathway or phonological representations. Accordingly, phonological dyslexia should arise in the in the context of phonological impairments in non-reading tasks (Farah, 1996). A correlation between the degree of impairment on phonological tasks and non-word reading accuracy has been observed (Crisp & Lambon Ralph, 2006; Patterson & Marcel, 1977).

According to the DRC model, phonological dyslexia is borne from damage to the non-lexical reading pathway and they argue that phonological dyslexia does not always occur within the context of a generalised phonological impairment (Coltheart, 1996). Further, simulations for the DRC that reduce the rate at which the non-lexical route operates are able to simulate an advantage for pseudohomophomes over nonpseudohomophomes as observed in some cases of phonological dyslexia (Coltheart, 2006a).

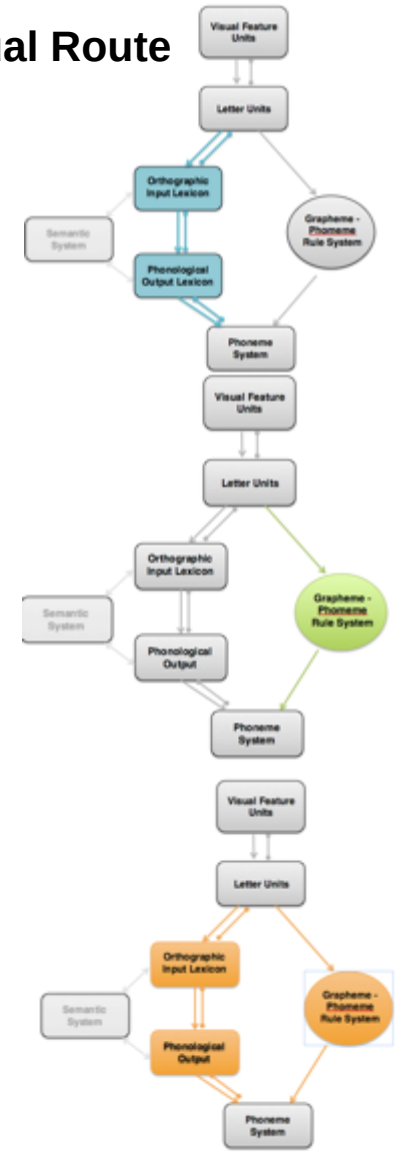
1.2.3 Deep dyslexia

Some view deep dyslexia as a form of severe phonological dyslexia, and argue that the two disorders are actually on a continuum (Crisp, Howard, & Lambon Ralph, 2011; Crisp & Lambon Ralph, 2006). Patients with deep dyslexia display the characteristics of phonological dyslexia with the addition of semantic errors. This results in the replacement of the target word with a visually different but semantically similar word (e.g. COLD>ice; Marshall & Newcombe, 1973). Patients also display visual and phonological errors, and show a deficit in reading function words.

The triangle model of reading argues deep dyslexia results from a severe deficit in the phonological representations. Support for this account comes from the recovery profiles of deep dyslexia patients that cease to make semantic errors but continue to demonstrate symptoms of phonological dyslexia (Friedman, 1996).

Within the DRC model, deep dyslexia could represent damage to both pathways, given the breadth of the word forms and errors affected. Poor non-word reading indicates damage to the non-lexical reading pathway, while semantic errors indicate a semantic processing deficit in the lexical pathway (Morton, 1980).

Dual Route



Surface dyslexia is characterised by regularisation errors for low frequency words (e.g 'PINT' as in 'MINT').

Location of damage:

DRC: Damage to direct pathway resulting in the use of indirect pathway, which fails for irregular words

Triangle model: Damage to the O-S pathway or weak semantic representations (Patterson & Lambon Ralph, 1999)**. This pathway is needed for irregular words, as the O-P pathway alone will cause regulation.**

Phonological dyslexia classically displays preserved word reading but impaired non-word reading and lexicalisation of non-words.

DRC: Damage to indirect pathway, leading to over use of direct pathway

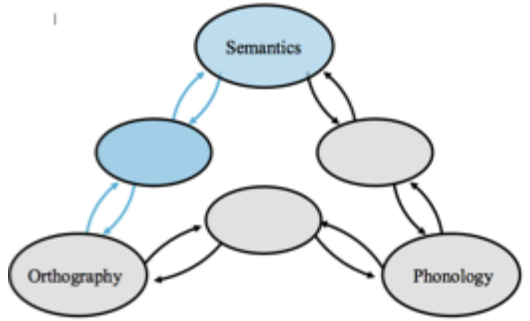
Triangle model: Under activation of phonological representations or damage to the O-P pathway. This may causes over activation of the O-S-P pathway.

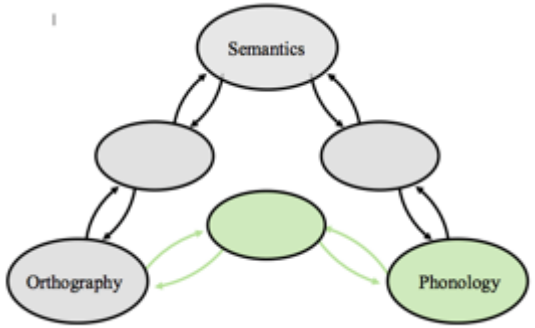
In deep dyslexia patients make semantic, morphological and visual errors. It can affect both words and non-words.

DRC: Damage to both pathways.

Triangle model: It is viewed as a more severe form of phonological dyslexia- patient can understand the meaning of the word. This indicates O and S representation are intact. Damage occurs between S-P and O-P mappings and in phonological representations

Triangle model





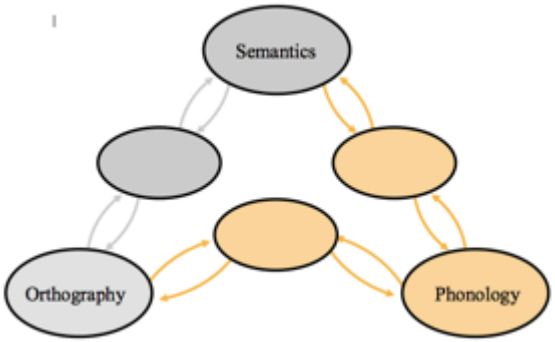


Figure 5 An outline of the three subtypes of central alexia and how the damage relates to the Dual Route Cascade (DRC) model (left) and triangle model (right). Shaded areas in the diagrams indicate the locus of damage.

1.2.4 Mixed Central Alexia

There has been an ongoing debate as to which model of reading best accounts for the deficits in the subtypes of CA (Coltheart, 2007; Woollams et al., 2007). One potential cause of the difficulty in decisively fitting the model to the patient population is that clinical cases of CA do not always fit neatly into these categorisations of CA. The PLORAS database (Predicting Language Outcome and Recovery After Stroke; Price, Seghier, & Leff, 2010; Seghier et al., 2016) contains 432 English-speaking stroke patients recruited from the community. Analysis of 64 cases of chronic CA from the PLORAS database, found 78% presented with a mixed case of CA that could not be categorised as semantic, phonological or deep dyslexia (Leff & Starrfelt, 2013). Therefore, it is ideal to design a type of reading therapy that is able to help all subtypes of CA. iReadMore is designed to be potentially useful in all CA subtypes. identifying for which subtypes CA is most applicable was not the focus of this research project. This research aimed to identify if iReadMore was able to improve word reading accuracy in patients with CA. No stratification or inclusion criteria were included regarding subtypes, and as such, this study is not adequately powered to identify the effects of iReadMore for each CA subtype. It is hoped that once iReadMore is released on the Internet, this analysis can take place with the larger data set collected from online use.

1.3 Models of reading and neuroimaging

1.3.1 Connectionist models and neuroimaging

We will now return to discussing models of reading. Cognitive neuropsychological models of reading (e.g., the DRC and triangle models) have been informed by the behavioural patterns of both brain damaged and healthy readers. These are useful as they give us a vocabulary with which to discuss key elements required for reading and propose different mechanisms by which reading is achieved. However, they are not straightforward to map onto neuroimaging studies. This is largely because, as described earlier, their aim was to describe and test the

computational processes of reading, rather than relate reading models to neuroanotomy. However, with the advent of neuroimaging, particularly functional magnetic resonance imaging (fMRI), psychologists became increasingly interested in the additional information that could be garnered by studying the brain. Unlike previous attempts to uncover the neural processes of reading in the 19th century, restricted largely to lesion studies, scientists could now study reading in the brain in vivo in healthy and impaired participants using neuroimaging methods.

Some success has been achieved in relating connectionist models to fMRI evidence (Taylor, Rastle, & Davis, 2013). The neural location of the two pathways described in the DRC have been suggested to reflect the dorsal and ventral streams of word processing (Jobard, Crivello, & Tzourio-Mazoyer, 2003). Perrone-Bertolotti et al. (2017) hypothesised a phonological task manipulation that required GPC rules would be conducted in the dorsal stream, whereas whole word lexical access with semantic manipulation would be processed along the ventral stream. In their fMRI study of healthy reading, the modulation of effective connectivity between regions of interest (vOT, dorsal Inferior Frontal Gyrus [dIFG], ventral Inferior Frontal Gyrus [vIFG], and Superior Temporal Gyrus [STG]) was compared between the two tasks. Only the connection from vOT to vIFG was significantly differently modulated for the semantic condition. While this provides some evidence in support of their hypothesis, it highlights that the functional neuroanatomy of the two routes to reading in the DRC model are not easy to distinguish with neuroimaging in healthy controls.

As the two DRC routes to reading may follow the dorsal and ventral streams of processing, it could be predicted that phonological dyslexia patients will exhibit damage along the dorsal stream whereas surface dyslexia patients will exhibit damage along the ventral route. Indeed, voxel lesion symptom mapping has shown that participants with surface dyslexia show lesions along the ventral route (left posterior middle and inferior temporal gyrus, insula, middle occipital gyrus), whereas lesions in phonological dyslexia were identified predominately in the dorsal route including the left IFG, insula and Rolandic operculum (Ripamonti et al., 2014). However, both CT and MRI data was used to identify lesion locations in this study, and CT scans may lack specificity concerning precise lesion boundaries.

Attempts to map the triangle model anatomically have also had some success. FMRI data of healthy readers as they read regular and exception words showed activation in the anterior temporal lobes (a region associated with semantic processing) significantly positively correlated with semantic reliance, whereas a negative correlation was observed between semantic reliance and activation within the postcentral gyrus (PCG). A bidirectional DCM model of the left hemisphere, involving the vOT, PCG and anterior temporal lobes (ATL) for irregular and regular word reading, identified a stronger connection from vOT to PCG when reading regular words compared to baseline, whereas this connection was not significantly modulated for irregular words. The connection from vOT to ALT and from ALT to PCG was stronger compared to baseline for both regular and irregular words. This suggests that irregular words are not processed via the O-P pathway, rather via the O-S-P pathway (Hoffman et al., 2015).

One study investigated the lesion location of surface alexia caused by stroke. Voxel based lesion symptom mapping found a positive correlation between the degree of damage to the posterior left middle temporal gyrus and regularisation errors on a word reading test. The locus of this damage is different to the bilateral anterior temporal pole damage predominately observed in semantic dementia patients who demonstrate more of a generalised semantic deficit. The authors argued that damage connecting S>P representations is responsible for the reading errors observed in surface alexia caused by stroke, and the posterior left middle temporal gyrus may be an intermediary between these representations. These finding do not contradict the triangle model of reading, but demonstrate the challenges in mapping it to the brain (Binder et al., 2016).

In a recent analysis, 43 post-stroke participants completed an MRI scan and a battery of linguistic and cognitive tests (Woollams, Halai, & Lambon Ralph, 2018). The study aimed to validate the primary systems account of reading (the basis for the triangle model of reading). A principle component analysis of the behavioural battery identified three factors that explained the variance in the data. The tests in these factors were characterised as tapping into i) phonological, ii) semantic and iii) cognitive abilities. Voxel-Based Correlation Methodology (Tyler, Marslen-Wilson, & Stamatakis, 2005) was used to associate the integrity of brain tissue with the three factors identified in the PCA and performance on various aspects of the word and non-word reading tasks. Concrete and abstract word

reading was associated with inferior frontal and temporal regions, the MTG and the fusiform and the white matter integrity of the ILF and uncinate. Concrete word reading involved the ventral pathway and the inferior and anterior aspects of the dorsal pathway, whereas abstract word reading was also associated with the superior and posterior aspects of the dorsal pathway.

Interestingly, these regions overlapped with the areas associated with the semantic and phonological maps from the PCA. This indicates that word reading uses both semantic and phonological components of reading, supporting the triangle model of reading. These areas of the dorsal pathway have been associated with lesion locations in patients with phonological alexia (Ripamonti et al., 2014). Non-word reading was associated with the integrity of the following regions; the MFG, IFG, inferior pre-central gyrus, and insular and opercular cortices as well as the white matter in the arcuate fasciculus. Although there was a large degree of overlap in the areas associated with the phonological factor from the PCA analysis and those associated with non-word reading, this did not include part of the non-word reading map in the superior frontal region. Instead, the authors note that this cluster can be explained by fluency. This data suggests that phonological dyslexia (poorer non-word reading than word reading) is associated with damage to the dorsal pathway and may include the frontal regions (MFG, IFG), parietal and central opercular cortex, where as deep dyslexia (non-word and function word reading deficit with semantic errors) may be associated with damage to both the ventral and the entire dorsal pathway (i.e. those associated with abstract word reading). It is unfortunate that the battery of tests did not include a reading test which manipulated the regularity of the words, as participants with surface alexia predominately make regularisation errors. The results of this test would have been interesting to associate with the integrity of voxels identified by the semantic component of the PCA.

Aguilar and colleagues reported 23 participants with post-stroke central alexia (the same participant group as described in this thesis) who completed a battery of reading tests and an MRI scan (Aguilar, Kerry, Crinion, et al., 2018). A PCA analysis of the reading tests identified 2 factors which characterised the variance in the data: reading aloud and reading for meaning. The reading aloud component correlated with the integrity of a cluster in the left SMG and overlapped with the posterior portion of the regions associated with the

phonological component identified in Woollams et al., 2018. The reading for meaning component was associated with the integrity of two grey matter clusters: one in the posterior left MTG and inferior temporal gyrus, and the second in the ventrolateral anterior temporal pole. Two white matter clusters were associated with reading for meaning; one from left occipital cortex to left medial temporal cortex and other included the white matter underlying the anterior portions of the anterior parahippocampal and fusiform gyri. These two grey matter peaks are included in the regions associated with the semantic component in the analysis by Woollams and colleagues. Woollams' study had a larger sample size (n=43 vs n=23) and recruited patients with chronic aphasia rather than a diagnosis of CA, which might explain the larger regions associated with voxel integrity for each of the components of the PCA and reading tests. It should also be noted that the analysis by Aguilar et al (2018) was biased towards the left parietal and temporal regions (as damage to the left inferior frontal gyrus was an exclusion criteria), which may explain some of the disparity between the Woollams et al., 2018 findings, such as the lack of association between word reading tests and left frontal regions.

1.3.2 Neurophysiologically informed models of reading

As demonstrated in **Error! Reference source not found.**, the various nodes described in the DRC and triangle models of reading are represented by distributed activation patterns across a number of regions during fMRI tasks. Rather than approaching reading from the behavioural viewpoint, some models of reading have been informed by the structure of the brain observed within human and non-human primates.

Neurophysiologically informed models can be more applicable to explaining neuroimaging data. They are often not mutually exclusive of the connectionist models proposed above, but provide a different viewpoint from which to interpret the results of neuroimaging studies.

The two prominent models that I will discuss here relate are the Local Combination Detector (LCD) model and the Interactive Account of reading.

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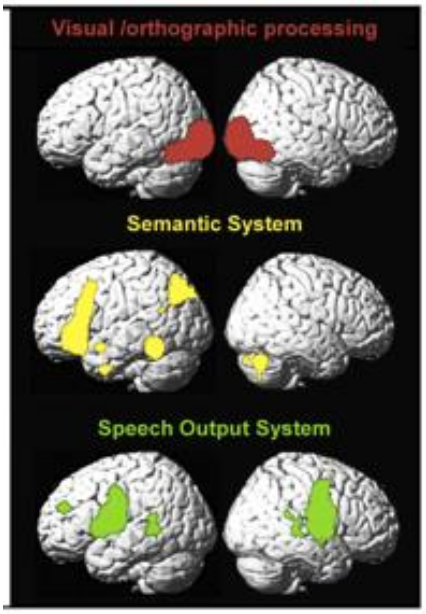

Figure 6 Brain activations for reading words aloud > rest/fixation. Segregated by speech output (green), semantic system (red) and visual/orthographic processing taken from (Price, 2018). From "The evolution of cognitive models: From neuropsychology to neuroimaging and back" by Price, 2018, Cortex, p. 1-13. Copyright [2018] by Elsevier. Reprinted with permission.

1.3.2.1 Local Combination Detector Model

The LCD model is inspired by the direct neuronal recordings of the visual system in non-human primates and neurophysiological models of invariant object recognition. According to this model, neurons become progressively more tuned to larger fragments of the word as their location moves up the ventral pathway (see Figure 7). This may start with the tuning of neurons to orientated bars in V1 and culminate in the selective tuning of familiar letter combinations, such as bigrams and quadrigrams in left vOT (Dehaene & Cohen, 2011; Dehaene et al., 2005; Glezer, Jiang, & Riesenhuber, 2009).

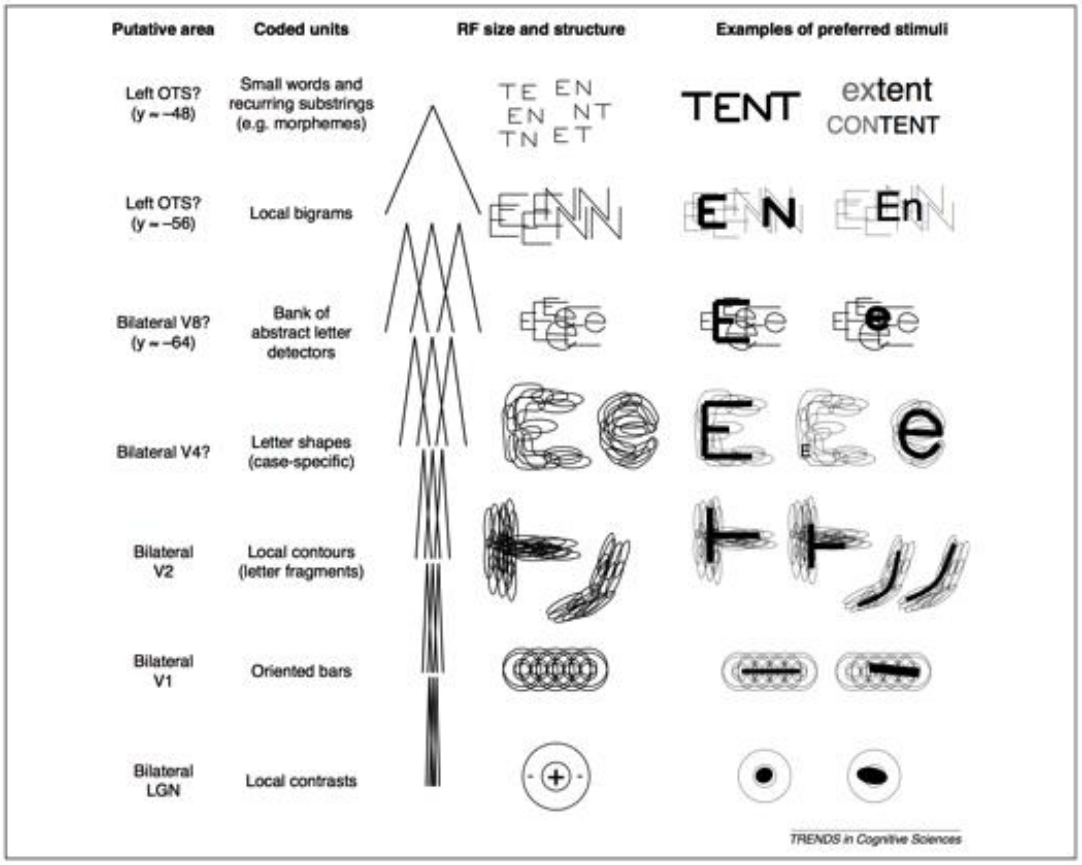

Figure 7 Diagram of the Local Combination Detector model. *From left to right, the columns depict: the suggested location of the neurons; the units coded by that region; the size of the receptive field and its structure; and some examples of stimuli that would be preferred by the neurons. The anatomical locations given in the left most column are tentative. OTS=occipito-temporal sulcus, LGN=Lateral Geniculate Nucleus and y co-ordinates refer to the approximate anterior-posterior coordinate relative to the human Montreal Neurological Institute template. From "The neural code for written words: a proposal." By S. Dehaene, L. Cohen, M. Sigman, and F. Vinckier, 2005, Trends in cognitive sciences, 9, p. 335-41. Copyright [2005] by Elsevier. Reprinted with permission.*

This model attempts to provide a detailed description of orthographic processing; specifically, how words are visually perceived. While it does acknowledge the numerous backwards and lateral connections observed within the visual system, and notes that these may shape processing as it moves along the ventral pathway, it does not document how this process might be achieved. In providing a largely feed-forward model, it implies that that semantic and phonological processing occurs after orthographic processing has finished, making it a bottom-up model of reading. This is largely in contrast to the previously described

computational models of reading, which allow for the spread of activation in a bidirectional manner.

1.3.2.2 Interactive Account of Reading

By contrast, the Interactive Account (IA; Price & Devlin, 2011) proposes that word recognition is achieved by a synthesis of learnt top-down predictions and bottom-up sensory input. IA applies the principles of predictive coding to reading.

In predictive coding, the brain can be considered as an inference machine, which predicts and explains incoming sensations. It tests these predictions against sensory samples (in this case visual stimuli) and updates its beliefs. The cortex is built within a hierarchy, in which the number of backwards connections outweighs forward connections ([Friston, 2008, 2010] see Methods section 2.16 for an example of hierarchal organisation of the brain). This allows for higher order levels of the brain to pass the predicted causes of a sensory input to a subordinate level through backward connections. The subordinate level assesses the accuracy of these sensory predictions and accordingly sends an error signal to the higher region through feed-forward connections. This allows for higher order representations to be updated with the new information about the world. If this error signal is minimal, the predictions imparted by the higher region were accurate. This account of the brain is drawn from principles of optimisation, in which the brain wishes to use the minimum energy to processes sensory inputs. The backwards connections inhibit the activity created by the excitatory sensory input, thus if it is maximally accurate, the brain will use less energy processing the sensory information. In order to increase to accuracy of these predictions, they need to be updated with exposure (and learning). This is achieved through the forward predictions.

It is argued that in skilled readers, the vOT serves as an interface between bottom-up sensory inputs from the visual system and top-down predictions (that are task dependent) from existing phonological and semantic representations. Partial activation of neurons encoding phonological and semantic representations occurs simultaneously with activation of neurons encoding shape information. Interaction between these representations then serves to supress incongruent candidates and support consistent candidates (see *Figure 8*).

The IA can be used as a framework to expand on how communication between the orthographic, semantic and phonological components of the triangle model may occur. Phonological and semantic representations may form the higher-level components predicting orthographic and visual representation. Orthographic representations may form an intermediate level above visual processing. The relative top-down contributions of the semantic and phonological domains may vary according to task demands or stimuli (e.g. semantic vs phonological decision tasks; irregular words vs. regular words) (Hoffman et al., 2015). In a group of PA participants with who reduced their word reading speed using an iReadMore prototype demonstrated increased feedback from the IFG to the vOT after training (Woodhead et al., 2013). The authors suggested that therapy effects were driven by increased support from higher-order regions (e.g. IFG), perhaps in the form of greater phonological and semantic influence on word reading. However, it is not clear what the model would predict when damage to the reading network occurs in CA patients, who typically have damage to higher-order areas of the language network.

The IA model was inspired by the apparently contradictory findings in the activation levels observed in the centre of vOT when visual stimuli were manipulated. Greater activity has been reported for pseudowords (e.g. GHOTS) over consonant letter strings (e.g. GHVST) and words (Price & Devlin, 2011). This cannot be explained only by familiarity due to the finding that low frequency words exhibit more activation than high frequency words. FRMI cannot differentiate between excitatory and inhibitory activity. Within the rubric of predictive coding, pseudowords are more word-like than consonant strings and thus benefit from top-down feed-back in their processing. In contrast, while both pseudowords and words activate top-down predictions, pseudowords are more surprising. This highlights the potential importance of considering how different parts of the reading network affect each other. This can be studied using dynamic causal modelling of neuroimaging data, detailed in the next section.

1.4 Interim summary: History of Models of Reading

It is hoped that we now are better equipped than Dejerine to investigate the relationship between reading and the brain. Scientists now have detailed connectionist models for which the reading profiles of patients and their response to therapy can be interpreted. For the first time, network level analyses of the

neural activity of CA patients when reading can be interpreted with neurophysiologically informed models. Having considered the models of reading in healthy controls, and how CA can be explained in terms of damage to those models, it is now necessary to understand how rehabilitation of CA might be possible through neural plasticity.

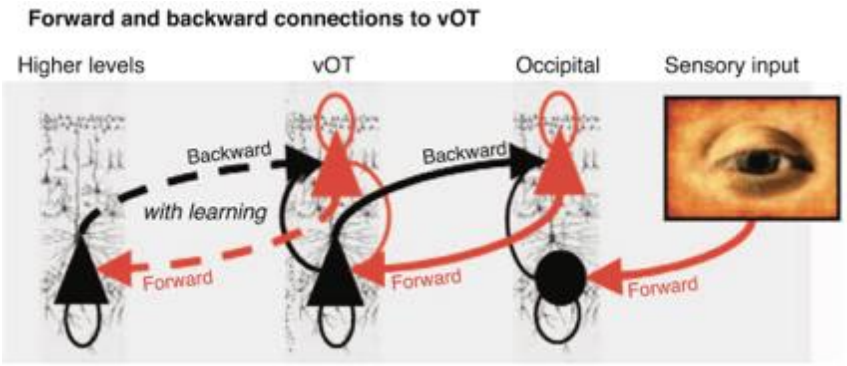

Figure 8 Interactive Account of reading. Sensory input enters the model to the Occipital regions and is fed forward (red arrows). Backwards connections (displayed in black) try to predict the response of a region to incoming sensory stimuli (in the form of forward connections). A minimal degree of difference is desired between the predicted response and the actual response. This differential is calculated within the region, and errors within the predictions are fed forwards (displayed by red dotted line between the vOT and IFG) so that future predictions can be updated (displayed via black dotted line between IFG and vOT). The processes reoccurs with learning, until the predictions from higher regions are optimised for the sensory inputs.

1.5 Rehabilitation

In this section I will discuss rehabilitation of reading after stroke. Part of this thesis is concerned with exploring the behavioural changes that occur after using iReadMore training. However, we know that when adults learn a new skill neuroplasticity underlies the observed behavioural changes (Draganski et al., 2004) and lesioned animals can form new synaptic connections with training (Kleim, 2011; Kleim et al., 2002; Nudo, 2013). Therefore, this thesis is concerned not only with changes in observable behaviour but also the neuroplasticity underlying these changes. I will start by providing an overview of neuroplasticity and why it is so important in the light of stroke rehabilitation. I will then evaluate previous post-stroke reading rehabilitation studies.

1.5.1 Neuroplasticity

Neuroplasticity refers to the reorganisation or regrowth of axons in response to brain damage or learning. In my thesis I explore neuroplasticity at the brain systems level in response to i) stroke damage, and ii) iReadMore reading training.

Improvements in language and reorganization can occur post-stroke in humans (Crosson et al., 2007; Saur et al., 2006). However, as I will detail below, the factors affecting post-stroke language reorganization and response to therapy are complex. This has resulted in varied hypotheses about the role of perilesional and contralesional brain regions in stroke recovery (Crosson et al., 2007; Hartwigsen & Saur, 2017; Turkeltaub et al., 2011).

One potential limitation of previous investigations into language reorganization post stroke is their focus on localized changes in functional activation patterns (either compared to healthy control participants or as a result of learning) rather than investigating how connections between the different nodes of the network have changed.

FMRI studies have highlighted the degree of individual differences when completing a reading task and how sensitive the brain is to different tasks and stimuli. Let's consider the vOT as an example. Historically, this region has been labelled the visual word form area (Cohen & Dehaene, 2004). This is in part due to the consistent observation of damage to this region in patients with pure alexia (Leff, Spitsyna, Plant, & Wise, 2006). However, as described in the section on the IA account of reading, the vOT shows a complex activation profile in response to words, pseudowords and consonant strings. The vOT also shows activation during non-orthographic tasks; greater vOT activation was observed when (i) participants made a decision about whether a pictorially presented non-object afforded to be twisted or poured, compared to when size judgements were made about the same objects (Phillips, Humphreys, Noppeney, & Price, 2002); or (ii) picture naming relative to saying "OK" (Moore & Price, 1999) . Finally, in patients with pure alexia, it has been argued that the deficit in word reading is due to a general disorder of complex visual processing, which can also be observed in patients with PA's mild deficit in face processing (Behrmann & Plaut, 2014). It is argued that if this area is specific to processing words, this variety of activation profiles should not be observed. Given what we now know with the use of

neuroimaging, it is unsurprising that 19th century neurologists such as Dejerine were challenged to identify pure structure-function brain relationships.

It appears that many neuronal regions may be involved in a cognitive task (as demonstrated in **Error! Reference source not found.**) and one part of the brain may be able to perform several cognitive functions, as demonstrated by the numerous potential roles of the vOT. That is not to say there is no functional specificity in the brain, merely that the exclusive nature of the brain structure-function relationship promoted in the 19th century is probably not the full story (Friston, 2002).

This is important with regards to language reorganisation after stroke. Due to these looser structure-function relationships revealed by fMRI, it appears plausible that functional recruitment of brain regions spared by the lesion may adapt to perform a cognitive task. However, identifying this reorganisation can be challenging from classical neuroimaging analyses e.g., fMRI or MEG task activation profiles alone. This is because modulation in the connections between regions cannot be identified. To examine reorganisation, it is beneficial to study word reading within the context of a reading network.

Additionally, it is important to study the influence of one region on another, rather than whether two regions are both important in task completion. Functional connectivity refers to the correlation in activation in two remote regions (Friston, 2002). In MEG, investigating oscillatory coupling between cortical areas may be used to assess functional connectivity (David, Cosmelli, & Friston, 2004). However, rather than each regions interacting, they may both be reacting to the input a different source. Therefore, it is beneficial to study connectivity between neural regions using effective connectivity measures. Effective connectivity refers to the influence one neural region exerts on another (Friston, 2002). As we are not only interested in parts of the brain that are engaged in task completion but the impact of these regions on each other, we will explore the effective connectivity between regions, rather than the functional connectivity.

1.5.2 Investigating neuroplasticity with Dynamic Causal Modelling

New tools, such as dynamic causal modelling for MEG data allowed me to investigate the language network of CA patients, and these results (in Chapters

3 and 5) can be interpreted with reference to neurophysiologically informed models of reading.

As word reading is a fast process, I used MEG data of reading analysed with DCM to investigate the early stages of word reading within a network. MEG has superior temporal resolution to fMRI as it measures the magnetic flow generated by neuronal firing, rather than the haemodynamic response to this activity, which is subject to an inherent time lag. DCM has been developed to explore connections between regions (Kiebel, Garrido, & Friston, 2007). An advantage of DCM is that it is able to identify the causal influence of one region over another. Previous studies have used the temporal profile of regional activity to infer the influence of one region on another (P. L. Cornelissen et al., 2009; Wheat, Cornelissen, Frost, & Hansen, 2010). As I am interested in neuroplasticity at the network level, and the causal influence of one region upon another, in this thesis I used DCM to explore this reorganisation following reading therapy, iReadMore, and tDCS.

DCM takes advantage of the stereotyped cortical layers within the brain and the connections between them to identify not only the different temporal activations between regions but the modulations in connection strengths that are most likely to have taken place to explain the activity in another region. This is calculated from the predictable pattern of influence neurons originating within a layer of one region have when they terminate on the layers of another region.

It is hypothesized that by understanding more about neuroplasticity at a network level, we will be better able to inform patients of their conditions and eventually, develop better therapies.

1.6 Neurological bases of reading in aphasia

As described above, models of reading have been informed by the ways in which the system fails when damaged. However, it is unclear how the system responds to damage (i.e. in the chronic stroke phase) or what the mechanisms of functional repair in the brain might be. There are three main hypothesised patterns of language reorganisation following stroke: 1) functional uptake by right hemisphere homologues of damaged left hemisphere regions, 2) functional uptake by perilesional regions within the left hemisphere, 3) a combination of both right and left hemisphere mechanisms. When active, each hemisphere mutually

inhibits activity in the opposite hemisphere's homologue. It has been suggested that following a lesion the damaged left hemisphere does not inhibit the right, resulting in maladaptive over activation of the right hemisphere. Below, I consider previous research into neuroplasticity in post-stroke CA and how it may respond to reading therapy. In the interest of brevity, I have only considered research directly investigating reading neuroplasticity, however, in interpreting the challenges of this research I consider studies from the neuroplasticity literature on aphasia in general.

1.6.1 Neuroplasticity in Central Alexia: Response to stroke damage

In one of the earliest neuroimaging studies of post-stroke language lateralisation and reorganisation, two deep dyslexia participants read concrete nouns aloud in a positron emission tomography (PET) scanner (Price et al., 1998). Normal or enhanced activation was observed in left perilesional regions, identified as involved in naming and semantics in healthy reading. In the right hemisphere, both participants showed increased activation in right IFG relative to controls and one participant showed increased activation in right inferior temporal cortex. The authors concluded that these results do not support the hypothesis that post-stroke language organisation is purely supported by right hemisphere regions (but see (Coltheart, 2000) for an alternative perspective on the results).

In a case study of a patient with phonological dyslexia, Small et al. (1998) showed pretreatment reading activity predominately in the left angular gyrus. Pillay and colleagues (2017) went one step further. They asked 21 aphasic participants with phonological deficits to read aloud nouns in an fMRI task. The brain activations for correct and incorrect trials were compared. Greater activation in the left angular gyrus was associated with correct trials, a region identified in the semantic network of healthy controls in a meta-analysis (Binder, Desai, Graves, & Conant, 2009). This suggests that perilesional left hemisphere regions may support word reading in participants with aphasia. In line with the triangle model of reading, the results here support the hypothesis that after damage to phonological representations, participants rely more on semantic support during word reading.

A bilateral reading network was observed when the reading related activation profiles of an aphasic participant were compared to that of healthy controls.

However, a shift in orthographic processing, over that of simply visual processing, was observed in the right vOT compared to healthy controls (Fischer-Baum, Jang, & Kajander, 2017).

In summary, the findings for post-stroke language lateralisation are mixed. A bilateral network has been indicated (Fischer-Baum et al., 2017; Price et al., 1998). This network may involve the right IFG to support post-stroke reading; however, there is little evidence to suggest deep-dyslexia reading is conducted predominately with the right hemisphere (Coltheart, 2000; Price et al., 1998). Perilesional regions have been indicated as supporting word reading, particularly those involved in semantic processing (e.g. angular gyrus) (Pillay et al., 2017; Price et al., 1998; Small, Flores, & Noll, 1998). These regions may provide damaged phonological representation (or their connections) with additional support from semantic representation for reading. A bilateral reading network after stroke may be predicted, and understanding the inter-hemispheric connections within this model may help in understanding the potential nature of the support offered by the right hemisphere.

1.6.2 Neuroplasticity in Central Alexia: Response to therapy

There are a limited number of studies focusing on response to reading therapy in CA. Richter et al., (2008) investigated the neural correlations of aphasia therapy in reading. They provided Constraint Induced Aphasia Therapy (CIAT) to 16 participants with chronic non-fluent aphasia. In CIAT, with the support of a therapist, patients are encouraged to attempt tasks that they find particularly challenging without the use of compensatory strategies (e.g. gesture). Participants completed a language assessment and fMRI scan in which they silently read words. No statistically significant changes in brain activation levels were observed over the study period. As a result, the authors identified pre-treatment peaks in activation (reading>rest), which correlated with change in behavioural performance. This indicated that the greater the pre-treatment reading activation in right IFG, precentral gyrus and middle temporal gyrus (MTG), the greater the participant's response to therapy. This suggests that recruitment of the right hemisphere might be beneficial in language recovery post-stroke. However, reading performance was not assessed either inside, or out of the scanner making it impossible to ascertain whether the therapy was effective

for the scanner task (silent reading). While CIAT was associated with improvements in spontaneous speech, auditory and semantic comprehension, aphasia therapy can result in positive changes to some areas of language while others do not improve (Brady, Godwin, Enderby, Kelly, & Campbell, 2016). This study did not find any significant differences in the task related activation levels before and after treatment, i.e. activation in the brain when reading words before and after therapy was not significantly different. This is concerning as the correlations between task related changes in activation and behavioural outcomes were completed on different tasks.

The neural changes associated with learning consolidation or over-learning in reading training has also been investigated. Immediately post treatment, an MEG case study of language comprehension showed increased activity in right hemisphere homologues, however, three months later, activity during the same task was bilateral (Breier, Maher, Schmadeke, Hasan, & Papanicolaou, 2007). Immediately following reading training, a participant with phonological dyslexia demonstrated increased right hemisphere activity in the inferior parietal and inferior frontal cortex. However, when training was continued on items that could be correctly read after training (i.e., these items were over-learnt), increased activation was observed in left hemisphere perilesional regions including the superior parietal lobe (Kurland et al., 2008).

There is limited research on the effect of reading rehabilitation on language lateralisation. It appears that right hemisphere homologues may support language relearning. However, with increased proficiency following training, reading may become increasingly reliant on left hemisphere structures.

1.6.3 Systems level neuroplasticity in Central Alexia: Challenges for interpretation

There are several reasons that might explain the variation in the degree to which the post-stroke language system relies on right and left hemisphere brain regions. Firstly, it may depend on the size and location of the lesion (Heiss & Thiel, 2006; Skipper-Kallal, Lacey, Xing, & Turkeltaub, 2017). Heiss and Thiel (2006) hypothesise that the right hemisphere may be able to adopt some language functions following left hemisphere damage, however, they found that right

hemisphere uptake was an ineffective in comparison to left perilesional regions (Heiss & Thiel, 2006). They argued that lesion size may impact upon the role of each hemisphere; large left hemisphere lesions were more likely to engage right hemisphere nodes, whereas smaller lesions resulted in functional take-over by perilesional regions. More recently, it was demonstrated that lesion size was positively correlated with the degree of activity observed in the right hemisphere during picture naming (Skipper-Kallal et al., 2017).

Parkinson (2005; reported in [Crosson et al., 2007]) found a high correlation between degree of left frontal lesion and naming improvement during treatment in 15 participants with aphasia. In other words, very large lesions were associated with large improvements in therapy, perhaps because of greater recruitment of right hemisphere homologues and less interference from surviving left hemisphere language areas. The role of lesion size in predicting recovery from stroke is complex (Lazar & Antoniello, 2008), so it follows that neuroimaging studies also find mixed results.

Hillis (2006) observed that different language functions may be more easily adapted to right hemisphere functions, for example, right hemisphere homologues may be able to subserve word meaning, but not others, for example translating orthography to phonology, which may instead rely on perilesional tissue. In line with this, the division of labour described by the triangle model of reading may explain the shift in activation between the hemispheres with recovery (Kurland et al., 2008; Saur et al., 2006). When the reading network is damaged, reading may be facilitated by semantic representations stored in the right hemisphere. As the perilesional connections between orthography and phonology are rebuilt this pathway becomes more reliable, leading to increased activation in the left hemisphere. Rather than a shifting of functionality between the hemispheres, the different activation patterns may reflect less reliance on semantic stores, supported by the right hemisphere. Accordingly, the activation results reported in therapy recovery studies may be due to type of therapy provided, which may, for example, put greater emphasis on retraining phonology or semantics (van Hees, McMahon, Angwin, de Zubicaray, & Copland, 2014).

It has also been argued that the processes in picture naming are different to those in sentence comprehension, or even between reading words aloud and word

reading silently. This will be reflected in different activation profiles of the participants (Price, 2012). Additionally, it is unclear whether decreased activation indicates more efficient task-specific processing, as suggested by priming studies, or whether it represents less involvement of a region in a process. It is also unclear if increased activation is facilitatory or maladaptive.

With these challenges in conducting functional recovery studies in participants with CA, I proposed to perform a group level network level analysis of my data. The complex nature of word reading means it involves interactions between several brain regions. Activation levels alone do not capture this. Therefore, I conducted functional network level analyses, to identify changes within regional activation, but also the strength of the connections between regions. One way to overcome challenges in lesion size and location variability has been to create activation profiles or network models for each participant. However, it can be challenging to draw concrete conclusions from this data (Kiran, Meier, Kapse, & Glynn, 2015; van Hees et al., 2014). Instead I look at the group level, but keep the therapy and dose consistent between participants and ensure that every participant has at least some tissue sparing in the core areas I wish to model.

1.7 Learning to read in Children

When a child learns to read, unfamiliar words may be read by mapping grapheme to phoneme correspondences, or by making an analogy to familiar words (e.g. “cat” read as in “bat”, “mat”, or “pat”). Once a word is familiar, it is reported to become a ‘sight word’ and the form and shape of the word are committed to memory (Ehri, 2014). However, others put forward the argument that sentence structure, the size of the words, or number of letters and context all pay an important part in learning to read (Ehri, 2014). According to Frith (1985) word recognition proceeds in three overlapping stages in the developing child. Firstly, familiar whole words are recognised (e.g. a child recognises their own name). In stage two, the analytic phase, the reader uses their developing knowledge of the alphabet letters and an analogy strategy to inspect the position of letters in unknown words and relate them to already known words. In the third stage, the reader can identify words from their spellings. At this stage, children can read unfamiliar text on the run, and no longer process words phoneme by phoneme. Overall, word reading in children is built up, through explicit learning of phoneme

awareness and its correspondence with orthography, but also through exposure to words in context during text reading.

In the developmental literature, a deficit in phonological skills has been highlighted as a potential cause for developmental dyslexia (Melby-Lervåg, Lyster, & Hulme, 2012; Pollatsek, Treiman, & Ehri, 2015), although it may also be influenced by memory and sensory-motor capabilities (Démonet, Taylor, & Chaix, 2004; Peterson & Pennington, 2015). In recent years, there has been an initiative to teach children to read and remediate reading difficulties using phonological awareness training (Castles, Rastle, & Nation, 2018; Rose, 2006; Snowling & Hulme, 2012). The following recommendations have been made for dyslexia interventions: training in small groups, supported reading of increasingly difficult connected text, writing exercises, and comprehension strategies (Démonet et al., 2004; Ramus et al., 2003).

A phonological deficit may underlie the reading impairments in central alexia, and targeting phonological awareness had been used effectively (see section; 1.7 Reading rehabilitation for Central Alexia). However, successful treatment of developmental dyslexia is associated with one-to-one sessions or small group work, which is not currently widely provided to post-stroke CA patients on the NHS. It should also be noted that in Central Alexia an established reading system has been damaged. While children learning to read do not have a relationship between orthography to phonology (with or without semantic influence), this relationship has been established in those with central alexia. This forces children to rely on a sub-lexical route to reading initially, however, in patients with central alexia the lexical route (or parts of this route) may be intact.

1.8 Reading rehabilitation for Central Alexia

1.8.1 Sub-lexical and lexical training for Central Alexia rehabilitation

Reading therapies for CA have focused on the retraining of GPC correspondences for patients with phonological or deep dyslexia, as both groups have a deficit in reading non-words compared to words. Often this training involves a number of steps including the production of a target word or phoneme, identification of a target phoneme's orthographic form and perhaps the reselection of the written word from a list of foils (Kieran et al., 2001; (Brookshire,

Conway, Hunting Pompon, Oelke, & Kendall, 2014; Conway et al., 1998; Kendall, Conway, Rosenbek, & Gonzalez-Rothi, 2003). This method is logical according to both the triangle and DRC model of reading; it aims to retrained the phonological or the mapping between O>P or the damaged non-lexical route.

In participants with severe deep dyslexia, individual phoneme retraining may be required prior to GPC rule learning. This can be achieved through the association of each letter of the alphabet with a word (e.g. A=*allo* in French*).* The patient is then taught to segment the initial phoneme in order to train the GPC correspondence. Once the G-P rules are mastered, phoneme blending is practiced (de Partz, Partz, & de Partz, 1986; Mitchum & Berndt, 1991).

Rather than training individual GPC rules some researchers have trained bigrams and syllable correspondences. Friedman and Lott (2002) trained a participant on three bigram syllable correspondences. In two subjects with deep dyslexia, participants were able to draw upon and blend the trained bigrams for both trained and untrained stimuli. Some generalisation for this technique has been observed in reading of low frequency words and paragraphs (M. Kim & Beaudoin-Parsons, 2007), and in reading untrained non-words when participants are trained using complex bigrams (Riley & Thompson, 2014).

Lexical training has aimed to retain the whole word. Training with pictorial cues to encourage the association between a picture and a written word has successfully retrained word reading (Kurland et al., 2008; Ska, Garneau-Beaumont, Chesneau, & Damien, 2003). These studies used a training method devised by Friedman et al., (2002). Verbs and functors were paired with pictorial noun homophones (e.g., not/knot) to retrain word reading in two phonological dyslexia patients. Their reading accuracy improved from 10% to 90%, immediately post-therapy but reading accuracy later stabilised at 60%. The authors claim that the improvements were driven by pairing low semantic value words with high semantic value words (nouns), (Friedman, Sample, & Lott, 2002). However, it is also possible that the picture provided an additional route by which phonological representations could be activated (Leff & Starrfelt, 2013). Additionally, when therapy focused on GPC retraining was compared to those focused on the whole word lexical semantic route (participants were presented

with a written semantically related word prior to the target word), results indicated a positive effect of both treatment strategies (Stadie & Rilling, 2006).

Multiple Oral Rereading (MOR) was first described by (Moyer, 1979), in which the reading speed of a PA patient improved. MOR involves the repeated rereading of text passages, with a clinician to provide online feedback on errors. Participants are often trained on one passage to criterion (e.g. 100 words per minute) before proceeding to the next passage. This has been shown to improve reading speed in cases of PA (Beeson, Magloire, & Robey, 2005; Moyer, 1979) and accuracy in patients with CA (Beeson & Insalaco, 1998) and has been shown to generalise to untrained passages. Additionally training effects have been observed on function words, which can be resistant to training. The proposed mechanism of rehabilitation in MOR is the synthesis of top-down and bottom-up information. Top-down information is provided by context and the grammatical structure of the sentence while bottom-up information could be provided by the individual words. However, one study manipulated the number of words and phrases that appeared in text to test for generalisation. It was revealed that mass exposure and repetition (i.e. bottom-up influences) were driving the therapy effects, rather than top-down influences (Lacey, Lott, Snider, Sperling, & Friedman, 2010).

1.8.2 Summary of reading rehabilitation for Central Alexia

There has been mixed success for the retraining of GPC rules and lexical reading in CA. Often the number of GPC rules trained are small. For example one study trained the ‘c rule’ and ‘g rule’ (Kendall, McNelil, & Small, 1998) or only ten G-P correspondences were targeted (Conway et al., 1998; Kiran, Thompson, & Hashimoto, 2001). Greater levels of generalisation to untrained items are associated with rule retaining in comparison to lexical retraining. However, the generalisation observed with GPC rule retraining is often limited to words that employ the rules or G>P correspondences as those trained (Kiran et al., 2001; Mitchum & Berndt, 1991). Some participants struggle to hold each phoneme in working memory to blend together as words (Biedermann & Nickels, 2008; Nickels, 2007). Lexical word reading avoids this difficulty, and tends to lean on intact resources, such as semantic representations to support reading of function words. Finally, the therapy dose provided by GPC training studies was often large

(e.g. Friedman and Lott (2002) provided 335 hours of training, Kim and Beaudoin-Parsons, 2007 provided aproximately 55 hours of therapy), consisting of one-to-one hour long sessions with a speech and language therapist, over multiple weeks (de Partz et al., 1986; M. Kim & Beaudoin-Parsons, 2007; Riley & Thompson, 2014). The additional challenge with training GPC rules is that a therapist is needed to decide when the patient can progress to the next stage of therapy, or to provide feedback (e.g. on phoneme production tasks).

1.8.3 Therapy dose in Central Alexia rehabilitation

It is unlikely that patients with aphasia in the UK will receive more than 10 hours of speech and language therapy through the NHS (Code & Petheram, 2011) despite evidence to suggest that the required dose to induce neuroplasticity is closer to 100 hours (Bhogal et al., 2003). Animal studies have also demonstrated that repetitive practice of a skill is necessary for long-term learning synaptic change (Kleim & Jones, 2008; Monfils & Teskey, 2004). GPC training and MOR involve mass repetition of therapy exercises that may not utilise therapists' time in the most efficient manner.

One way to alleviate pressure on therapists' time is to provide patients with scientifically proven computerised therapies that can be completed independently by the patient (Leff & Starrfelt, 2013). These can provide participants with the mass training exposure required for relearning, and allow therapists to use patient contact time more efficiently.

1.8.4 Computer based therapies for CA rehabilitation

I will now explore the feasibility of providing computerised reading therapy for CA patients (Cherney, 2015; Katz & Wertz, 1997; Zheng, Lynch, & Taylor, 2015). A review of seven studies investigating the use of computerised therapies for aphasia found positive results when compared to no therapy (Zheng et al., 2015). Within the realm of CA rehabilitation, one study provided patients with a series of computer based matching and reading comprehension tasks for 3 hours a week over 26 weeks. Measures of aphasia severity improved on two subtest of the Western Aphasia Battery (Katz & Wertz, 1997).

In another study, 25 participants with aphasia received MOR training with a virtual therapist (Cherney, 2015). No significant improvement was observed on reading measures, however tests of general aphasia impairment did improve. In summary, computerised therapy appears to be a viable option for increasing the therapy dose patient's with CA receive.

1.8.5 Rationale of iReadMore trial design

It is difficult to ascertain the impact of previous computerised therapies on word reading due to the use of general aphasia quotients as outcome measures. Therefore, in my thesis, the primary outcome measure adopted was single word reading, with test items divided into those that were treated, and those that were untreated.

As previously noted, patients rarely fall neatly into the three subcategories for CA; therefore, designing a computer-based therapy to retrain a specific impairment (e.g., a phonological deficit) seems unwise if the therapy is to be useful to a maximal number of patients. In my thesis I investigated iReadMore, a therapy developed by my colleague Dr Zoe Woodhead (Woodhead et al., 2013), which aims to strengthen the connections between semantics, phonology and orthography by repeatedly presenting patients with spoken, written and pictorial forms of a word. If we consider this in the context of the triangle model of reading, the training activates both the O-P and O-S-P routes. Patients with CA may have damage to one or both of these routes. Repetitive pairing of the written (O), spoken word (P) and pictures (S) should help strengthen the mappings between the three domains, in whatever way is possible according to the regions undamaged by the stroke. For example, if damage affects the O-P route, the O-S-P route would be trained.

It is expected that reading therapy will only improve treated items. Simultaneous activation of semantic, phonological and orthographic representations of trained words will strengthen the mapping between them. However, for untrained words, the weightings between these representations will not be modulated, and thus word reading improvements are not expected to generalise beyond treated items. This item-specificity is frequently observed for lexical reading therapies (Friedman & Robinson, 2007; Friedman et al., 2002; Kurland et al., 2008; Ska et

al., 2003) and in the anomia literature when a restitutive therapy approach is used (Nickels, 2002; Wisenburn & Mahoney, 2009).

1.9 Transcranial direct current stimulation

One challenge to therapy provision is the potential high dose needed to induce long-term behavioural change. tDCS provides a potential mechanism to exogenously induce neuroplasticity. When paired with behavioural therapy, it may result in a) greater therapy gains or b) longer lasting therapy effects. In Chapter 4 of this thesis, I explore whether A-tDCS paired with iReadMore enhanced therapy effects, in the form of greater improvements in word reading accuracy and speed. This has not previously been explored within CA patients. In the next section, I describe tDCS and its potential mechanisms for enhancing neuroplasticity. I then report previously conducted research into the use of tDCS with aphasia therapy, highlighting the potential limitations of this work and how in this thesis I tried to overcome them.

1.9.1 tDCS background and potential mechanisms

In tDCS a weak electrical current is passed between two electrodes. In the conventional bipolar set-up, one electrode is commonly referred to as active and the other as passive. The active electrode indicates the electrode over the brain area of interest to be stimulated while the reference electrode typically refers to the electrode over a region of no interest (Kuo & Nitsche, 2012). Depending on whether the active electrode is the anode (positive electrode) or the cathode (negative electrode) the stimulation method is referred to as anodal (A-tDCS) or cathodal (C-tDCS), respectively (please see Methods section 2.9 for further technical details). In studies investigating tDCS, a sham condition is often used to provide a placebo condition to compare with the stimulation condition of interest (i.e, anodal or cathodal). In the sham condition, electrical current is administered for a brief period of time (e.g. 30 seconds) at the beginning and end of the stimulation duration. In the intervening time, no electricity is administered. This induces the sensation of active tDCS (e.g. a sensation on the skin) without the associated neurophysiological effects. This allows for experimenter and participant blinding in tDCS trials.

Investigations into tDCS were ignited when Nitsche et al. (2000) demonstrated increased excitability in motor evoked response potentials after A-tDCS

stimulation of the motor region (Nitsche & Paulus, 2000). tDCS involves the delivery of sub-threshold current, typically between 1-2 mA. tDCS current is not sufficient to induce action potentials within neurons, and instead alters the resting membrane potential of the cell (Nitsche et al., 2008). In the case of anodal stimulation, the increase in the resting membrane potential of the cell is hypothesised to bring it closer to threshold and thus make it more likely that a neuron will produce an action potential (Bestmann, de Berker, & Bonaiuto, 2014; Kuo & Nitsche, 2012). One mechanism by which tDCS is thought to be effective is through the modulation of calcium and sodium channels, i.e., when drugs which block these chemicals are administered before A-tDCS, the excitatory effects are diminished (Nitsche et al., 2003).

In 1949 Hebb described the process of increased efficiency between neuronal firing between two neurons when one consistently induces the other to fire ('Hebbian' learning; Hebb, 1949). This change in connection strength can endure for days, weeks and months through mechanisms such as Long Term Potentiation (LTP). While the exact mechanisms of LTP are still being investigated, the glutaminergic system likely plays a key role; a reduction in GABAergic tone in slice preparations from rats has been shown to induce LTP (Castro-Alamancos & Borrell, 1995; Hess & Donoghue, 1996). Conversely, the introduction of GABA agonist prior to stimulation was shown to abolish LTP induction in rats (Trepel & Racine, 2000). The research into A-tDCS after-effects indicate that they are driven by activation of NMDA receptors in the context of a decreased GABAergic tone. Calcium channel blockers and NMDA receptor antagonists (which block the post-synaptic glutamate receptor) diminished the after-effects of A-tDCS (Liebetanz, 2002). As a result of activated NMDA receptors, there will be an increase in intracellular calcium in the postsynaptic neuron (Stagg & Nitsche, 2011). A large increase in intercellular calcium is associated with LTP-like changes (Lisman, 2001). Thus, the connections between the neurons are strengthened.

The mechanisms of tDCS have largely been studied in animal models and within the human M1 motor region. It should not be assumed that this will directly map onto cognitive functions (Jacobson, Koslowsky, & Lavidor, 2012). However, as discussed below, positive effects of A-tDCS on language task performance have been observed. My thesis adds to the literature regarding the interplay between

A-tDCS and cognitive tasks. Within the cognitive domain, it is hypothesised that by pairing A-tDCS with a relevant task, which requires engagement of the stimulation site, more neuronal firing will be induced (Miniussi, Harris, & Ruzzoli, 2013). Within (re)learning, long-term effects of tDCS are observed as this increase in successful firing will allow for Hebbian learning mechanisms to take place.

1.9.2 tDCS and aphasia therapy

Behavioural data collected in my thesis also explores the use of A-tDCS targeted to the left IFG when paired with reading training using iReadMore. This approach aimed to enhance neuroplasticity exogenously. This has not been tested in CA patients previously, although A-tDCS delivered to left IFG has shown positive effects on naming in participants with aphasia (Baker, Rorden, & Fridriksson, 2010; Marangolo et al., 2011). I will detail previous studies that have investigated tDCS in aphasia patients and the potential mechanisms by which it may be effective.

More behavioural training is generally deemed to have a greater long-term effect of language performance (Bhogal et al., 2003). In terms of tDCS, the hypothesis underlying multiple-session studies is that the short-lasting facilitation effects from a single session will accumulate with repeated sessions and eventually lead to longer-term consolidation of behaviour and a improvement in function (Crinion, 2016). Precisely how this approach might lead to a long-term improvement in language function in the aphasic population is not clear. One possibility is that by increasing the output from the damaged left hemisphere it will lead to more effective relearning of language. In other words, brain stimulation itself would not produce any lasting changes in language function; instead it would temporarily create a state that optimizes relearning and rehabilitation (Crinion, 2016; Holland & Crinion, 2012). This process would lead to an improvement in language function and reduction in aphasic deficits.

tDCS in speech and language therapy has predominately been investigated with picture naming as an outcome measure (for review please see [de Aguiar, Paolazzi, & Miceli, 2014; Crinion, 2016; Monti et al., 2013]). Stimulation of the left IFG has been successfully used to enhance short-term speech performance in

anomic patients. In cross-over designs, Marangolo and colleagues found positive effects for verb naming and repetition tasks in participants with chronic aphasia after A-tDCS compared with sham (Marangolo et al., 2011; Marangolo, Fiori, Calpagnano, et al., 2013). Five days of anomia training paired with twenty minutes of A-tDCS (1mA) targeted at the left frontal and precentral cortex resulted in an additive effect of 8% naming improvement above behavioural effects (sham tDCS) alone in 10 chronic aphasics (Baker et al., 2010).

Within the realm of reading rehabilitation, anodal stimulation of the left posterior temporal lobe paired with oral rereading training has been investigated in a pure alexia case study. This accelerated the rate of learning over the five-treatment sessions compared to sham. Training effects generalized to reduced reading duration for untrained passages (Lacey et al., 2015). A study by Tsapkiki and colleagues (2014) investigated the effects of spelling therapy paired with left IFG A-tDCS or sham in a cross-over design with six primary progressive aphasic patients. Spelling improved in both conditions but no significant effects of training were identified for reading. There was a clear test-retest effect from baseline to after training for all conditions, which makes the data challenging to interpret and highlights the need for multiple baseline measures (Tsapkini, Frangakis, Gomez, Davis, & Hillis, 2014).

There are a number of candidate sites for tDCS in reading rehabilitation. These include regions within the parietal lobes. In a matched-between-group study design, HD-tDCS was applied to the temporoparietal regions during novel language learning. Active HD-tDCS was associated with faster word retrieval times (Perceval, Martin, Copland, Laine, & Meinzer, 2017). In another study, anodal tDCS was applied to the left parietal region (cathode over the right hemisphere homologue) as a patient with CA underwent SLT (De Tommaso et al., 2017). In a cross-over design (with a 30 day wash-out period) 12 hour-long SLT sessions targeting the sublexical route to reading were accompanied for the first 20 minutes by tDCS. This case study demonstrated a significantly greater reduction in reading errors for non-words and words when SLT was accompanied by stimulation, compared to SLT administered alone.

A number of functions have been attributed parts of the parietal lobe such as the angular gyrus (Seghier, 2013). These include linguistic tasks, such as phoneme discrimination in speech processing (Turkeltaub & Coslett, 2010) and semantic processing (Vigneau et al., 2006) but also extend to number processing, memory (autobiographical and episodic) and inhibition on go/no go tasks (Seghier, 2013). The supramarginal gyrus is associated with phonological processing in reading in both fMRI studies (Oberhuber et al., 2016) and studies using high rate TMS to disturb the functioning of a region (Sliwinska, Khadilkar, Campbell-Ratcliffe, Quevenco, & Devlin, 2012). This may explain why it was so effective in improving word reading at the sublexical level in the study by De Tommaso et al., (2017).

A connectivity analysis revealed that iReadMore increased the feed-back from the IFG to OCC in participants with Pure Alexia (Woodhead et al., 2013). Early activation in the IFG has been demonstrated in healthy reading (P. L. Cornelissen et al., 2009; Wheat et al., 2010) and it is hypothesized that this activation constrains the visual processing of orthographic stimuli (Price & Devlin, 2011; Woodhead et al., 2014). In the current analysis, the left IFG was chosen as the stimulation target. The iReadMore training was designed to train word reading via both the O>P>S and O>P routes to reading, depending on the user. Therefore, we did not wish to choose a stimulation site that preferentially targeted the ventral or dorsal reading pathway. The role of the left IFG in reading is still unclear. However, it has been associated with both semantic and phonological processing in word and non-word reading tasks (Heim et al., 2005; Mechelli et al., 2005; Mechelli, Gorno-Tempini, & Price, 2003; Woollams et al., 2018). Given its association in both semantic processing and phonological processing, it seems well placed as the stimulation target site. While tDCS has the potential to accelerate the rate of learning over repeated sessions, my study is interested in simply whether it enhances the effect of iReadMore therapy, rather than the temporal pattern by which this is achieved. Thus, I measure A-tDCS effects only at start and end of each therapy block, rather than within blocks.

Two negative reviews of the effect of tDCS in speech and language therapy have been published (Elsner, Kugler, Pohl, & Mehrholz, 2013; Horvath, Carter, & Forte, 2014). These reviews were underpowered (A. R. Price & Hamilton, 2015) which is partly due to the restricted number of studies with adequate study design including condition blinding, randomisation and control conditions. The intra-

subject variability of tDCS is greater that the within subject variability (López-Alonso, Fernández-del-Olmo, Costantini, Gonzalez-Henriquez, & Cheeran, 2015). Additionally, participants with aphasia are highly variable in their response to treatment (Brady et al., 2016). Therefore, a cross-over study design is preferable to a between subject design. Blinding of both the experimenter administering the tDCS and the participant also reduces placebo effects (Brunoni et al., 2012). In light of this, in my thesis the effects of A-tDCS over left frontal regions paired with iReadMore training was tested using a multiple baseline, double-blind, cross-over design. Participants were randomised to receive either sham or A-tDCS stimulation in the first therapy block. Each participant then received the other stimulation condition in the second therapy block.

1.10 Aims and research questions

Chapter three focuses on the following research question:

1. How does the reading network of participants with CA differ from that of healthy readers?

It is unclear how the reading network of CA patients responds to stroke damage. This may be in the form of increased support from right hemisphere brain homologues (such as the IFG and vOT) or it may be the result of increased activation of perilesional regions. Alternatively, it may result from a combination of the two mechanisms. The participant group included in the iReadMore study are varied. As discussed, (see section 1.7.3) several factors may influence post-stroke reorganisation. As a result it is hypothesised that, at a group level, I will observe a bilateral reading network. Some participants employing both forms of reorganisation detailed above and other participants relying more or less on each hemisphere may drive this effect. As reading requires a network of interconnecting brain regions, the variability in functional reorganisation anticipated could be due to the variability in the ways to achieve word reading. Therefore, I investigated the functional connectivity of the reading network using DCM for MEG. This will also allow for the examination of whether post-stroke reading reorganisation increases reliance on a feed-forward or interacting reading network, which has not previously been conducted. I will discuss the results within the context of neural models of reading, such as the LCD and IA.

Providing a sufficient dose of speech and language therapy (SLT) to improve reading accuracy in CA patients is challenging within the NHS. One possible way to support the work of SLTs is through scientifically proven computerised training apps. The randomised controlled trial described in Chapter four investigated:

2. Does iReadMore improved word reading in patients with CA and does A-tDCS targeted at the left IFG enhance therapy effects?

As previous lexical therapies have found limited improvements in word reading beyond trained items, it is expected that iReadMore training will only improve word reading for trained items (Friedman & Robinson, 2007; Friedman et al., 2002; Kurland et al., 2008; Ska et al., 2003). Reading reaction time (RT) is also expected to improve, but again, only for trained items. This study will include trained items and matched untrained items in measures of therapy generalisation to the sentence or reading for meaning level. Reading at this level is usually assessed using standardised measures, which are not sensitive to improvements only observed for trained items. Therefore, I will not make a prediction regarding whether reading will generalise to this level.

Interpreting the effects of studies investigating tDCS as an adjunct for aphasia therapy is challenging due to poor study design and small sample sizes. Chapter four overcomes some of these challenges to add to the literature on the use of A-tDCS as an adjunct to reading therapy. A-tDCS to left IFG has enhance aphasia therapy effect in naming studies (Baker et al., 2010; Fridriksson, Richardson, Fillmore, & Cai, 2012), and the left IFG has been indicated as driving the therapy effects of iReadMore observed in PA patients (Woodhead et al., 2013). Therefore, it is predicted that A-tDCS will improve words reading performance.

Finally, Chapter five focuses on the following research question:

3. How does iReadMore reading training affect the reading network of CA participants?

As iReadMore induced a change in reading behaviour, I also wanted to explore the corresponding changes at the neuronal level. As reading requires a network of key regions, this analysis was performed using effective connectivity analysis of MEG data. Previous work using iReadMore for patients with PA revealed

therapy-induced changes in the feed-back connection from left IFG to OCC. In my thesis I wanted to identify if a similar mechanism took place in CA patients, or if the differences in the lesion locations between the two groups gave rise to different neuronal responses to iReadMore within the reading network.

2 Methods

2.1 Introduction

All chapters from this thesis are based on work completed within the iReadMore trial. The primary aims of this trial were to i) identify if iReadMore therapy improved single word reading aloud in CA participants and ii) investigate if A-tDCS delivered to the left IFG in conjunction with iReadMore training improved word reading performance. Additionally, this thesis explores i) the pre-training reading network of CA participants compared to a group of healthy control participants and ii) the changes in the reading network of CA participants with iReadMore training. Dynamic Causal Modelling (DCM) of Magnetoencephalography (MEG) data collected before and after the first therapy block was used to investigate the effective connectivity of CA participants' word reading network.

This section will consider the methods used in the thesis. I will first describe the iReadMore trial and iReadMore training app in detail. I will also outline the tDCS parameters used to target A-tDCS at the left IFG. Next, I will give an overview of the principles of MEG and DCM. I will then outline the specific MEG parameters used compare the pre-training reading network of CA participants to the reading network of a group of healthy controls. Finally, I will detail how DCM for MEG was used to investigate the changes that occurred within the reading network of CA participants after using iReadMore training.

2.2 iReadMore Study design

A repeated-measures cross-over design with six Time-Points (T1-T6) was used (*Figure 9*). T1-T5 were spaced by four-week intervals. Baseline language tests were spread over T1 and T2 and then combined. Dividing the baseline testing over two time-points, spaced 2 to 4 weeks apart, allowed for a comprehensive battery of cognitive and language assessments to be completed. A middle cerebral artery (MCA) territory stroke can result in impairment in varying domains and to varying degrees in different patients (Lazar & Antoniello, 2008). The test battery was designed to measure performance within the language and cognitive domains in order to capture this variation. This was the focus of my colleague Oscar Aguilar's thesis. In investigating how the connections in the brain changed in response to therapy, I also wanted to explore which connection modulations

were related to the degree of improvement seen in response to iReadMore therapy. However, as several factors have been argued to contribute to response to therapy, I wanted to explore whether a model including only connection strength modulation, or one including baseline behavioural variables, best explained the participant's response to therapy. Therefore, the baseline tests are detailed briefly in this section but were not the focus of this thesis.

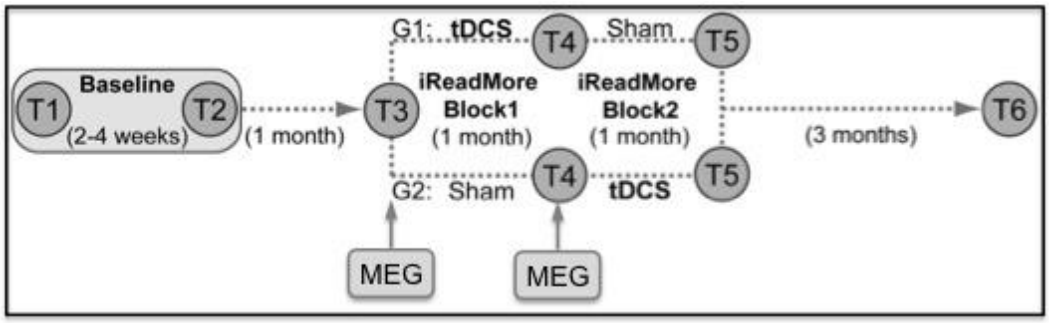

Figure 9 Study design. G1 = Group1: received tDCS in Block1 and Sham in Block2. G2 = Group2: received Sham in Block1 and tDCS in Block2. MEG scans were conducted at T3 and T4.

The interval between T2 and T3 was used to assess pre-therapy (test-retest) changes. By including a period with no therapy, which mirrors the duration of each therapy block (4 weeks), I was able to establish if the participant's word reading performance was stable and to control for test-retest effects. Two four-week therapy blocks followed: Block1 from T3-T4 and Block2 from T4-T5. A cross-over design was used so that the effect of A-tDCS could be explored using a within subject analysis. The effects of tDCS have demonstrated greater inter-individual variability in response to stimulation in comparison to intra-individual variability over repeated sessions (Chew, Ho, & Loo, 2015). Furthermore, aphasic stroke patients have demonstrated wide variability in their response to SLT (Bonilha, Gleichgerrcht, Nesland, Rorden, & Fridriksson, 2016; Lambon Ralph, Snell, Fillingham, Conroy, & Sage, 2010), therefore by using a repeated measures design, some of this variability is control for, which allows for the assessment of tDCS effects. T6 measured therapy maintenance three months after completion of training. At time-points T3 to T6 a core set of assessments (interval test) were completed to address the primary aims of the trial; to identify if iReadMore training and A-tDCS improved word reading ability.

During therapy blocks participants attended three 40-minute face-to-face sessions per week (Monday, Wednesday and Friday; a total of 11 session per block), where iReadMore was administered concurrently with A-tDCS or S-tDCS. Participants completed additional behavioural training using iReadmore independently at home to amass at least 35 hours total practice per block.

Half the participants (G1) received A-tDCS in Block1 and sham in Block2. The other half (G2), received sham then A-tDCS. Block randomisation with bias minimisation was used to allocate participants to G1 or G2 and ensure cross-over groups did not become unbalanced on severity (baseline word reading accuracy and speed). Numerical codes for A-tDCS and sham conditions were prepared independently in advance of the trial (JC) and executed by the researchers (SK, ZW). Participants and researchers collecting and analyzing the data were blinded to tDCS condition using the stimulator's study mode. Unblinding occurred after data acquisition and analysis ended.

MEG scans were conducted before and after the first therapy block (T3 and T4). At both time-points participants were asked to silently read words (in a pseudorandomised order) that were trained in Block1 and a matched list of untrained words. This allowed me to explore how the reading network of CA patients changed after using iReadMore training (Chapter 5).

Age and gender matched control participants took part in one testing session to provide normative data on the word and pseudoword reading tests (Table 1).

Testing and face-to-face therapy sessions were conducted at the Institute of Cognitive Neuroscience, University College London. I was involved in the data collection and analysis of the data at T3 to T6. This included performing the behavioural assessments and collecting the data from the MEG scans at T3 and T4 with my colleagues Drs Woodhead and Aguilar.

2.3 Structural MRI Acquisition and Lesion Identification

Structural whole brain MRI data were acquired for lesion identification using a multi-parameter mapping protocol with a 3.0T whole body MR system (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) and a 32-channel transmitter-receiver headcoil. Quantitative magnetisation transfer (MT) maps from a multi-parameter mapping protocol described by Callaghan and colleagues

(Callaghan et al., 2015) were calculated for each subject due to their excellent contrast and spatial resolution.

MT maps were created using the Voxel Based Quantification toolbox in SPM12 (http://www.fil.ion.ucl.ac.uk/Research/physics_info/QuantMRI_VBM.html; http://www.fil.ion.ucl.ac.uk/spm/). The ALI toolbox (Seghier *et al.*, 2008) was used for MT map normalization, segmentation and lesion identification.

2.4 Participants

2.4.1 Central Alexia Participants

Twenty-three participants with a diagnosis of Central Alexia (CA participants, 15 males, mean age 52 years, range 26-78 years, see Table 1 for demographic information), made by a Neurologist or Speech and Language therapist, were recruited from both the PLORAS stroke patients database held at the Wellcome Centre for Human Neuroimaging UCL (Seghier et al., 2016), and SLT services at the National Hospital for Neurology and Neurosurgery, University College London Hospitals. *Figure 10* displays a CONSORT diagram of recruitment. Two participants left the study at T4 (P03 and P18). Their data is included in the MEG analysis (Chapters 3 & 5), but could not be included in the behavioural analysis of iReadMore (Chapter 4), as they did not complete both blocks of the behavioural training. Twenty-two participants exhibited phonological (n = 13) or deep (n = 9) dyslexia and one exhibited surface alexia (P5). This incidence ratio is consistent with a study of 69 stroke patients with CA (Brookshire *et al.*, 2014); surface alexia is more commonly encountered in patients with semantic dementia (Woollams et al., 2007). For details of the sample size calculations please see Appendices 8.1.1 Sample size calculations.

The following inclusion criteria were used: i) left-hemisphere middle cerebral artery stroke with at least partial sparing of left IFG; ii) greater than 12 months post-stroke; iii) dominant English language use in activities of daily living; and iv) CA, operationalized as impaired word reading (CAT word reading T-score <61) and impaired spoken language (CAT naming <63 or picture description <61).

Exclusion criteria included: i) premorbid history of neurological or psychiatric illness; ii) history of developmental language disorder; iii) severe spoken output deficit and /or speech apraxia (CAT repetition <44); iv) seizures in the past 12

months; v) contraindications to MRI scanning; and vi) extensive damage to left IFG.

To identify if participants had partial sparing of the left IFG, participant's MRI scans from the PLORAS database were reviewed by a consultant neurologist. No formal constraints were placed on the amount of IFG tissue required to be eligible to take part in the study. The CONSORT diagram (Figure 10) in chapter 4 (pg. 76) shows that 35 participants were assed for eligibility but did not meet the inclusion criteria, however data regarding why they were not eligible was not kept. Potential reasons for not meeting the inclusion criteria would include, lesion location, speech severity, a non-dominant English speaker, or not meeting the inclusion criteria for a MRI scan. While the IFG is often damaged as a result of MCA stroke (Phan, Donnan, Wright, & Reutens, 2005) only partial sparing of this region was required for inclusion in the study.

The participant information sheet was provided in written and auditory forms. All participants gave informed written consent in accordance with the Declaration of Helsinki. The Queen Square Research Ethics Committee approved this project.

2.4.2 Central Alexia trial control participants

Control data for word and pseudoword reading tests (Table 1) were collected from 21 age and sex matched healthy participants. Control participants were matched to the 21 CA patients that completed both blocks of the iReadMore trial. Normative data was available for the standardised tests used elsewhere in the battery. There was no significant difference in age between CA and control groups ($P = 0.84$). Control participants spoke English as their dominant language, and had no history of neurological or psychiatric illness or developmental language disorder.

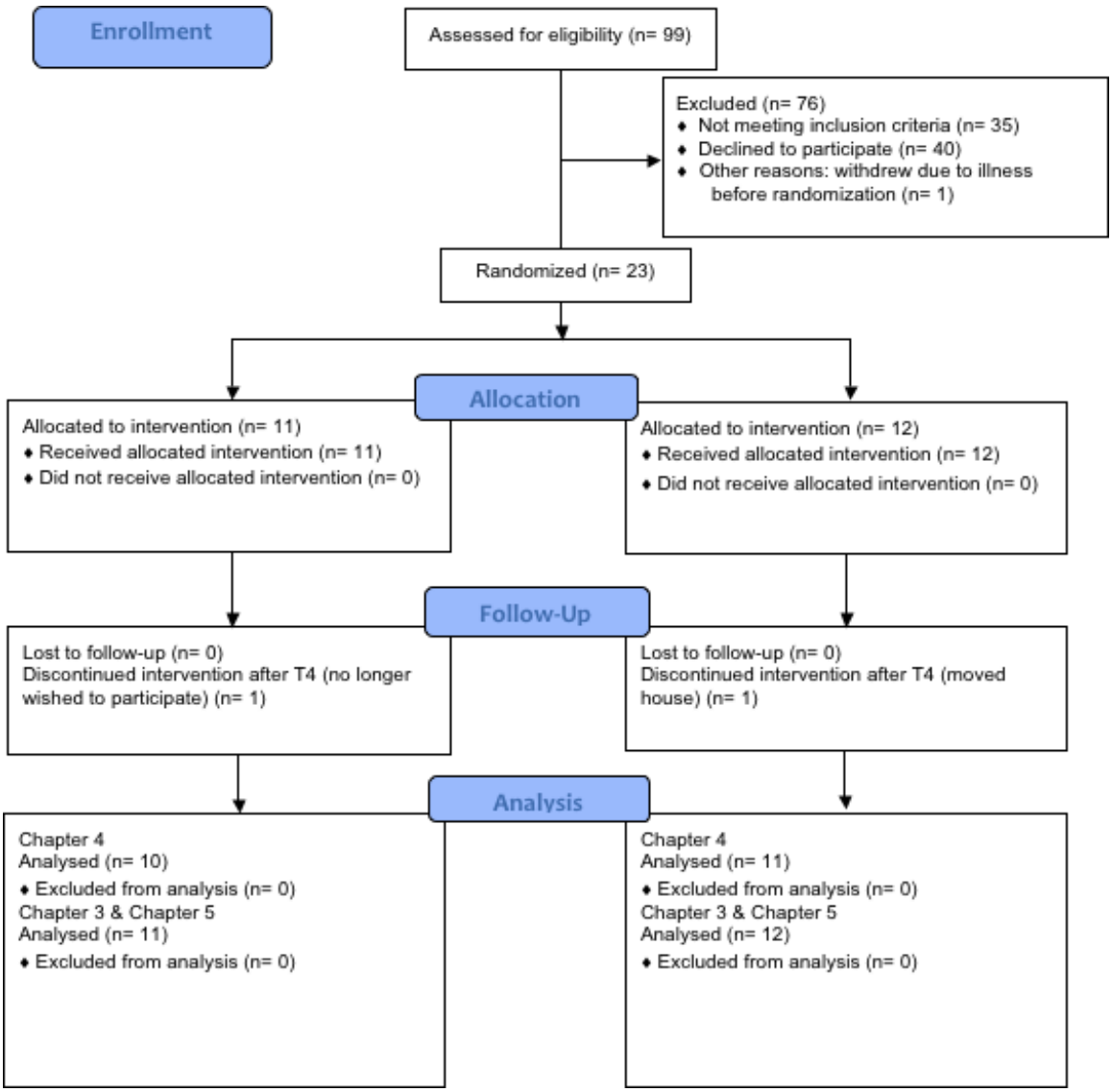

Figure 10 CONSORT flow diagram. This diagram shows the number of participants at the allocation, follow-up and analysis points of the iReadMore trial, arranged by tDCS group. The analysis boxes detail the number of CA participant's included in the analysis for each chapter of this thesis.

Table 1 Demographic characteristics and baseline assessment for 23 central alexia Participants. Central alexia subtype is also presented: Deep (D), Phonological (P) and Semantic (S).

ID	Age (yrs)	Gender	Time post-stroke (m)	Lesion Volume (cm^3)	Baseline Word Reading (%)	Naming (%)	Pseudo. Reading (%)	CA subtype
P01	44	Male	94	240.9	58.4	69.0	0	D
P02	50	Male	82	304.5	40.3	53.4	0	D
P03*	64	Male	25	102.7	96.7	81.0	70	P
P04	52	Male	66	122.7	71.1	65.5	0	P
P05	56	Female	93	149.8	63.8	5.2	75	S
P06	55	Female	75	151.2	91.9	93.1	30	P
P07	33	Female	59	181	90.1	94.8	2.5	P
P08	67	Male	107	11.7	12.5	72.4	2.5	D
P09	43	Female	55	399.2	58.2	81.0	0	D
P10	61	Male	19	195.6	3.4	39.6	0	D
P11	52	Male	12	31.2	96.3	87.9	75	P
P12	50	Female	14	59.4	90.6	82.8	25	P
P13	54	Male	24	149.3	91.5	86.2	65	P
P14	56	Male	23	45.1	80.4	72.4	0	P

P15	54	Male	39	189.7	47.3	13.8	2.5	P
P16	73	Male	158	205.2	20.0	70.7	0	D
P17	60	Male	16	102.6	28.1	32.8	10	D
P18*	78	Male	22	128.5	75.4	43.1	7.5	P
P19	50	Female	72	141.3	35.9	27.6	5	P
P20	72	Male	101	243.3	13.4	8.6	0	D
P21	58	Female	41	297.7	59.5	81.0	0	P
P22	42	Male	13	43.7	74.9	72.4	27.5	P
P23	26	Female	81	161.9	75.5	79.3	0	D
CA mean (SD)	54 (12)		56 (39)	159 (95)	59.8 (30)	62 (28)	17.3 (28)	
CA Range	26-78		12-158	12-399	3-97	95-5	0-75	
Control mean	53 (12)					100 (1)	93(11)	
Control Range	23-70					98-100	50-100	

* Indicates participants who left the study at T4

2.5 Training

Training was delivered using iReadMore on a tablet computer, which automatically recorded training duration. A large therapy dose is required for successful aphasia rehabilitation (Bhogal et al., 2003) but speech and language therapists' time is limited (Code & Petheram, 2011). Mass practice is one approach for reading training in CA patients. iReadMore aims to remove this from the speech and language therapists clinic. The software cycled through 'exposure' and 'challenge' phases. The training phase ensured that participants received adequate exposure to the correct pairings of the spoken and written word and the associated picture. This was hypothesised to strengthen the connections between the semantic, orthographic and phonological forms of the word, resulting in better word reading. The challenge phase allowed for the monitoring of participant performance and the automatic adaption of difficulty parameters. This ensured that participants continued to be challenged by the app, even over extended period of use.

2.5.1 Exposure phase

During exposure phases, participants were presented with 10 faced down cards. Upon the selection of each card, participants passively viewed a picture, symbol or visual mnemonic representing the target word, followed by simultaneous presentations of the written and spoken word-forms (See *Figure 11*). Participants could complete the exposure phase at their own pace.

In the first exposure phase, the first 10 items from the list were selected. The order of the word list then adjusted in response to the participants' performance in the challenge phase. The 10 words at the top of the list were selected for each subsequent exposure phase. Written word duration (the amount of time the written word was presented on the screen) initially matched the participant's baseline word reading speed, then adapted according to performance in the subsequent challenge phase (see 8.1.2 Difficulty Adaptation: Global Parameters in Appendices). Reducing the written word duration aimed to increase patients reading speed. Audio recordings from a female or a male speaker were randomly selected for each trial.

Figure 11 Screenshots of the training phase of iReadMore. Ten cards are presented. Upon selection, the reverse of the card reveals a picture associated with the word followed by the simultaneous presentation of the written and spoken word. The word is then backward masked using the pattern on the reverse of the card so that the exposure duration of the written word can be controlled. During this phase participants attend to the stimuli presented. This ensures they have mass exposure to congruent pairings of the written and spoken word form and an associated picture.

The pictures were colour photos or drawings representing the target word. The representations of low imageability target words were abstract – see Figure 12. Even if these representations were not immediately understood, they became learnt through repeated exposure to allow pictorial priming of written word recognition.

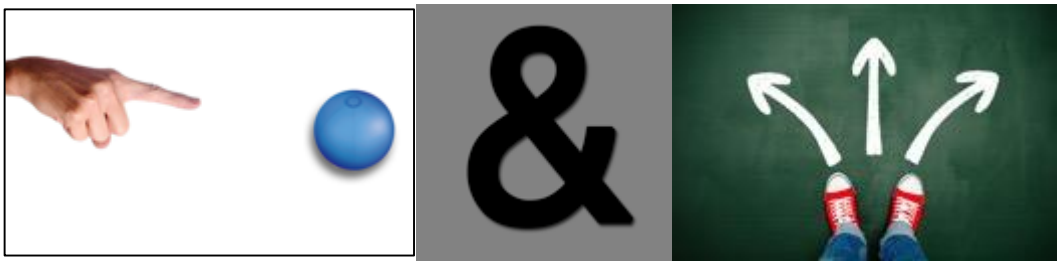

Figure 12 Examples of low imageability pictures used within the iReadMore software for 'that', 'and', and 'any'."

2.5.2 Challenge phase

Challenge phases comprised up to 30 trials. In each trial, a spoken word from the preceding exposure phase was presented with a written word. In half the trials the written and spoken stimuli were the same word, and in half they were different. Participants made a same/different response via button press and received immediate feedback (see

Figure 13). The challenge phase allowed the app to monitor task performance and amend the difficulty parameters within the app accordingly. Two points were awarded for a fast correct response; one for a slow correct response; and minus one for an incorrect response. The criterion duration for fast and slow responses adapted according to performance (see 8.1.2 Difficulty Adaptation: Global Parameters in

). Challenge phases comprised of up to 30 trials (3 repetitions of the 10 target words presented in the preceding exposure phase), but ended when the criterion score was reached. The criterion score adapted according to performance (see 8.1.2 Difficulty Adaptation: Global Parameters in Appendices).

For each training item there were up to 9 paired written words to use as easy, medium or hard distractor items in the challenge phase. All distractors shared the same length and first letter with the target word. Same/different task difficulty was adapted independently on a word-by-word basis. Each target word (e.g. 'hand') was paired with easy, medium or hard distractors varying in the number of letters shared with the target word (e.g. 'heap', 'hood', or 'hard'). The distractor selected for each trial started at the easy level and increased or decreased according to response accuracy. 'Easy' distractor words shared only the first letter in common with the target word. 'Medium' distractor words shared at least 2 letters in common. 'Hard' distractor words (for words > 3 letters only) shared more than 2 letters in common. For further details of the difficulty parameters used in the iReadMore training app, see 8.1.3 Difficulty Adaptation: Item-Specific Parameters in Appendices.

2.6 Training and testing stimuli

Words with high written frequency ($SUBTLEX_{WF}$ > 50) were selected from the SUBTLEX database (Brysbaert & New, 2009). High frequency words were chosen to maximise the ecological utility of the therapy. All words were three to six letters long so that they could easily be read in one fixation. Hyphenated or punctuated words were excluded, and an effort was made to avoid regular morphological variants of the same word (e.g. eat, eaten, eating). Words of all classes (nouns, verbs, functors etc.) were incorporated into the stimuli list, including words that have either high or low imageability ratings.

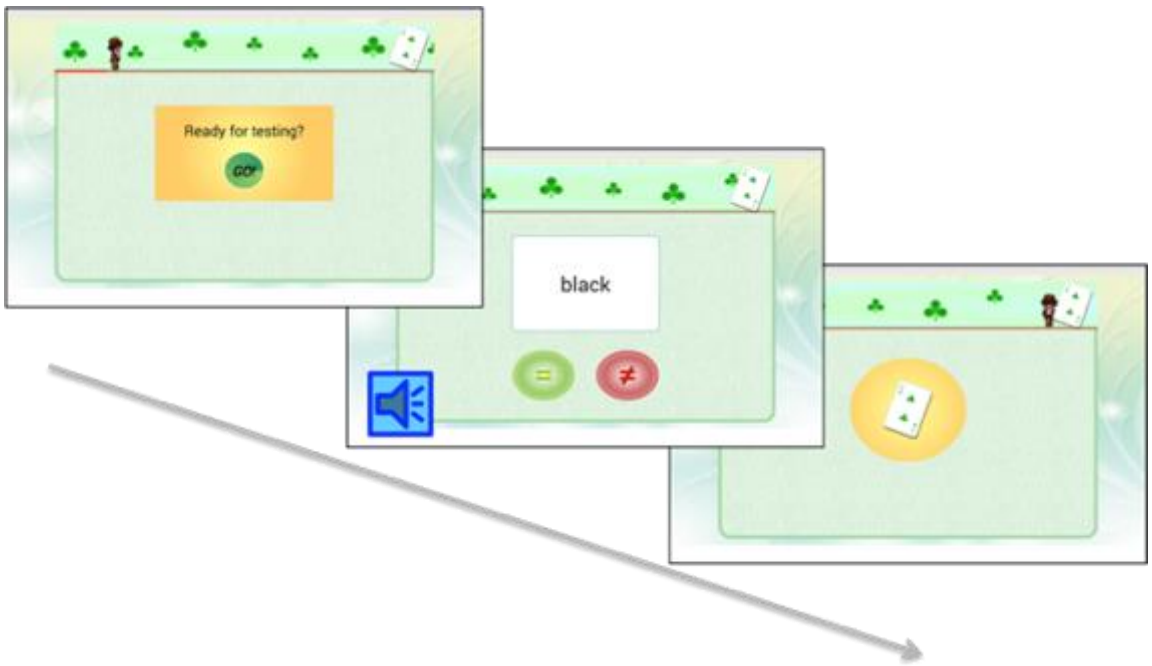

Figure 13 Screenshots from iReadMore training in the challenge phase. Participants were presented with a series of written and spoken word pairs. Participants made congruent/incongruent decisions of these word pairs via buttons responses. Points were awarded for correct responses and deducted for incorrect responses. As points were accrued, the character at the top of the screen moved toward the card on the right hand side of the screen. The level was passed if the participant reached a criterion score and collected the card. Participant performance during this phase of training was used to tailor the task difficulty for the user.

Three matched lists of 180 words were created (A, B and C). For each word on list A there was a corresponding word on lists B and C closely matched for letter length, syllable length, written frequency and imageability. Additionally, the 50 highest frequency words (mostly function words) were selected as a separate list of 'Core' words.

All 590 words were tested at baseline (split across T1 and T2 sessions). Results from this full corpus of testing items were used to establish the participants' profiles of reading impairment. Based on each participant's baseline performance, a customised set of 150 matched words from each of the A, B and C lists were selected to use in training. Thus this ensured the A, B and C lists selected for that participant were matched for baseline reading performance

(word reading accuracy and RT) and the lists remained matched for psycholinguistic variables. The aims of this word selection process were: to have no significant difference in the patient's baseline reading ability (accuracy or RT) between the selected A, B and C words; to have no significant difference in psycholinguistic variables (length, frequency, imageability, regularity or N-size) between the selected A, B and C words; and to have no significant difference in reading ability (accuracy or RT) between the selected word lists and the full list of words tested at baseline. The purpose of the final aim was to avoid the possibility of regression to the mean, which would have been an issue if we had only selected words that the participants read poorly at baseline. The A, B and C Word-Lists were assigned to be either trained in Block1, trained in Block2 or not to be trained (untrained words). List allocations were counterbalanced between participants. All 50 Core words were trained in both Block1 and Block2 due to their high utility.

From the customised 150-item A, B and C word lists, a subset of 90 items from each list were selected for use in all subsequent assessment time-points (T3-T6). These 90-item testing lists were matched for baseline performance and psycholinguistic variables. Importantly, the overall accuracy of the word lists selected for testing was matched to Baseline reading accuracy to avoid the risk of regression to the mean at future time-points (see Figure 14 for a diagram of derivation of word lists). A subset of 30 Core words were tested at T3-T6. Hence, in total 300 words were tested at T3-T6 sessions. Word reading accuracy and reaction time from this subset of testing items was used to report the change in reading performance from T1 to T6. A subset of words was tested at all interval testing points as reading all 500 words would have been time consuming and challenging for some of the participants. By selecting a representative subset of 90 words, we were able to ensure that the word reading interval tests were manageable, and to measure performance on each word list at every timepoint. The drawback of this approach is that there may have been change in

performance on some words within the lists that were not tested.

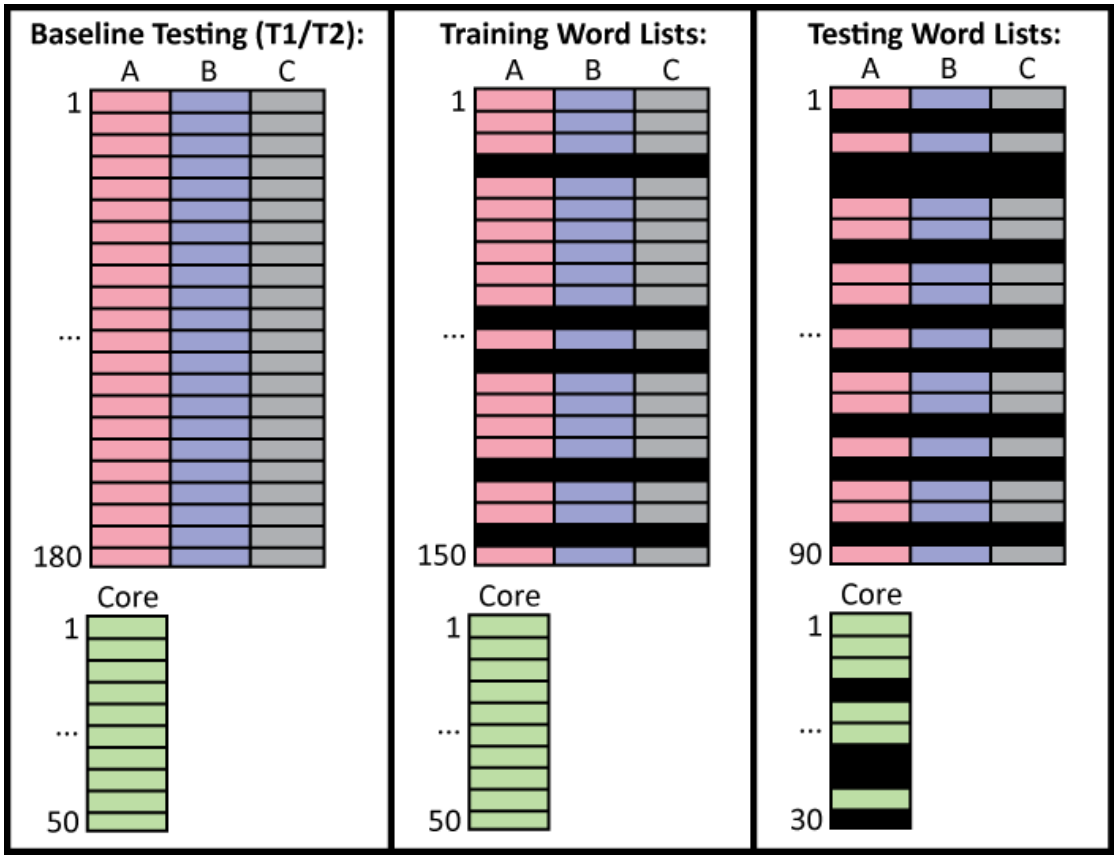

Figure 14 Graphic demonstrating the division of the full word corpus into the training word lists (central column) and testing word lists (right hand column) to ensure all word lists were matched for baseline performance. In the above figure, each row represents a word. The first column displays the 590 words (180 A, B and C words, plus 50 Core words) tested at Baseline (across T1 and T2 sessions). For every word in list A, there were words in lists B and C matched on linguistic variables (length, frequency and imageability). The middle column shows the subject-specific word lists selected for training from the full word corpus (150 A, B and C words, plus 50 Core words). Discarded words are displayed in back. The right hand column demonstrates the subject-specific word lists selected for testing from the training word lists (90 A, B and C words, and a set list of 30 Core words).

2.7 Behavioural assessment

A comprehensive battery of language and cognitive assessments were administered at baseline with the aim of creating a participant profile of each subject. Please see Table 2 for a list of the tests administered and the time-points.

My colleague, OA, used baseline measures to identify factors that predicted response to therapy. Within my thesis the results of the baseline assessment are used to provide background information about the participant's language profile and, within Chapter 5, to control for baseline characteristics when investigating the relationship between response to therapy and modulation of connectivity within the reading network. The baseline assessments were conducted by ZW and OA. Further details of these tests can be found in 8.1.4 Cognitive Tests in Appendices.

2.7.1 Baseline Tests

2.7.1.1 Baseline Single Word Reading Test

At the baseline assessments (T1 and T2), the full word corpus of 600 items were presented in a random order and split into six separate blocks, three at each testing session. The word corpus consisted of 150 words from each word list (A, B and C) and 50 Core Words. As described above, from T3-T6, the test used lists matched for individuals' reading performance at baseline. This consisted of 90 items from each word list (A, B and C), which were assigned to either trained in Block1, Trained in Block2 and untrained and a list of 30 core words.

Words were presented for up to four seconds in black, lower case, size 36pt Arial font on a grey background using E-Prime (Schneider, Eschman, & Zuccolotto, 2012). Participants were instructed to read the words aloud into a voice-key microphone as quickly and accurately as they could. Accuracy was recorded online by experimenter button press. One point was awarded for correct responses; 0.5 for self-corrections; and 0 for incorrect responses. Reading reaction times (RT) was recorded by the voice key. RTs were excluded for incorrect or self-corrected trials, voice-key failure and trial with RT > 2sd from the mean.

Word reading errors on the full corpus of words tested at baseline were coded as phonological (including purely phonological errors, SEW→'sue'; and visual and/or phonological errors, DOOR→ 'doom'); semantic errors, (including purely semantic errors, APE→'monkey' and visual and/or semantic errors, CLING→'clasp'); or 'other' errors (including morphological errors, LOVELY →'loving'; and unrelated errors)

2.7.1.2 Pseudo word reading

Wuggy software (Keuleers & Brysbaert, 2010) was used to generate 20 pseudowords of between 3-6 letters with plausible letter combinations. Psuedowords were presented and scored in the same format as the word-reading test, but without the four-second timeout.

2.7.1.3 Naming Objects and Naming actions from Comprehensive Aphasia Test

Anomia was assessed using the naming subsection of the CAT. In the naming objects test, participants were asked to name 24 black and white line drawings presented one at a time. In the naming actions section of the test, participants were asked to name the verb depicted in a five black and white line drawing. The test stimulus included both low and high frequency and imageability pictures. Two points were awarded for a timely and correct response, and one point for a correct response after a self-correction or a delay of more than four seconds before responding. A phonemic cue, followed by a semantic cue is provided if the participant is unable to name the item but the participant was not awarded any points after a cue was provided. A total maximal score of 58 could be obtained for the test.

2.7.2 Interval Tests

The interval tests formed the key outcome measures for the iReadMore trial and with the exception of the word-reading test, were conducted in the same format at every interval time point (Baseline-T6).

2.7.2.1 Single Word Reading Test

The word reading test (as described above) was the primary outcome measure for the trial. The outcomes from the test were word reading accuracy and RT (calculated using correct trials only, and excluding trials where the RT was more than 2 standard deviations from the subject's mean). A, B and C items were matched for baseline reading performance. Words were presented in a randomised order across three runs in the same format as the baseline word reading test.

2.7.2.2 Written Semantic Matching

This task assessed silent reading for meaning, and was based on the written version of the Pyramids and Palm Trees test (Howard & Patterson, 1992). In each trial (presented in E-Prime), participants silently read three words: a probe word at the top of the screen, a semantically-related target and an unrelated distractor below. Participants were instructed to identify the target as quickly as possible by button press. Percentage accuracy and mean RT (for correct trials only, excluding trials where RT >2sd from the mean) were calculated.

The three words for each trial were drawn from the same Word-List (A, B or C). 24 trials for each list were presented in a randomised order. The stimuli for each list were matched for number of letters, frequency, imageability and regularity.

2.7.2.3 Sentence Reading

This task assessed silent sentence reading. In each trial (presented in E-prime), participants silently read a sentence of five to eight words as quickly as possible, then pressed a button when finished. This response was used to calculate reading speed in words per minute (excluding trials with RT > 2sd from the mean). Next, a picture was displayed and the participant responded verbally whether the picture was congruent with the sentence or not. Percentage accuracy on the picture verification task was calculated.

Ten sentences for each Word-List (A, B or C) were created, each containing between two to four words from the list. For example, the sentence “He sold the broken camera” contained the words “sold”, “broken” and “camera” from list A. The sentences from each Word-List were matched for sentence structure, number of trained words, total number of words, and summed word imageability, regularity, frequency and letter length.

Assessment	Time-points completed	Group	Outcome
Single word reading	Interval (Bx – T6)	Language	Accuracy (%) Reaction time (ms)
Written semantic matching	Interval (Bx-T6)	Language	Accuracy (%) Reaction time (ms)
Sentence Reading	Interval (Bx–T6)	Language	Accuracy (%) Reaction time (ms)
Text Reading	Interval (Bx–T6)	Language	Word reading accuracy (%) Reading speed (msec) Words read per minute Comprehension accuracy (%)
cSART	Interval (Bx–T6)	Cognitive	RT for hits (ms) False negative hits (%) False positive hits (%)
Communication Disability Profile (CPD)	Interval (T1 & T5)	Language	Total change in perceived reading ability (max. 16)
Cattell: subtests 1 & 2	Baseline	Cognitive	Total correct trials for subtest 1 (max. 12) Total correct trials for subtest 2 (max. 14)
WAIS IV Digit span: forwards and backwards	Baseline	Cognitive	Total correct trials forwards (max. 16) Total correct trials backwards (max. 14)
Two armed bandit	Baseline	Cognitive	Correctly selected reward boxes (%)
Brixton	Baseline	Cognitive	Total number of errors (max. 55)
4 way Weigl	Baseline	Cognitive	Total score (max. 12)

Assessment	Time-points completed	Group	Outcome
Visual short term memory test	Baseline	Cognitive	Score (max. 7)
Auditory phonological discrimination task	Baseline	Language	Score (max .14, min. 1)
Pyramid and palm trees (pictorial)	Baseline	Language	Accuracy (%)
Non-word reading test	Baseline	Language	Accuracy (%)
CAT: naming objects and actions	Baseline	Language	Naming objects score (max. 48) Naming actions score (max. 10)

Table 2 Details of the behavioural assessments used, at which time point and whether they are primarily concerned with functions in the language or cognitive domain. The final column details the outcomes given by each test which were then entered into the automatic linear modelling in chapter 5. Interval tests were conducted at every time point. Baseline tests were administered once, either at T1 or T2.

2.7.2.4 Text Reading

Passages from level one and two from the Neale Analysis of Reading ability (Neale, McKay, & Barnard, 1999) were used to measure participants' text reading ability. Participants were asked to read aloud two passages before being asked comprehension questions on each passage. If a participant took longer than four seconds to read a word, the researcher provided it. This test resulted in four outcome measures; i) accuracy: the percentage of correctly read words ii) correctly read words per minute and iii) time taken to read the passage and iv) comprehension: the percentage of correctly answered questions relating to the text. The Neale test has two different forms for each text level. To minimise the amount that participants learned the texts over repeated testing, the form used alternated at each sequential time point. The order of forms (i.e. starting with form A or form B) was counterbalanced across participants.

2.7.2.5 Children's Test of Sustained Attention (cSART)

A domain general test of sustained attention (Manly, Davison, Heutink, Galloway, & Robertson, 2000) was used to assess each participant's ability to concentrate. This Go/No-Go task contained pictures of two different people, one of which was revealed in each trial. Participants were instructed to press a button whenever one person appeared (go trial), but withhold their response for the other (no-go trial). 192 go trials and 24 no-go trials were presented in a pseudorandomised order. Outcome measures were the number of false negative and false positive responses and the mean RTs on correct go trials.

2.7.2.6 Communication Disability Profile

This test was completed at baseline (T2) and after completion of the second training block (T5). This test aimed to assess changes in the participant's perceived reading ability. Using a pictorial scale form 0 (bad) to good (4), participants were asked to rate their ability to silently read i) a word, ii) a sentence, iii) text, and iv) an official letter. The summed score, out of a maximum of 16, was used as the outcome measure.

2.7.3 Exit Questionnaire

Upon completion of the therapy (T5), participants completed an exit questionnaire where they judged whether their word reading had improved (No / A little / A lot); whether they wished to continue using iReadMore; and whether they had noticed any difference in stimulation effects in Blocks 1 and 2.

2.8 Central Alexia Classifications

Participants were classified into CA a subtypes (Surface dyslexia, Phonological dyslexia and Deep dyslexia) using classification criteria described by Whitworth et al., (2014):

- Surface dyslexia (Marshall & Newcombe, 1973) was defined according to the presence of a regularity effect (better reading of regular compared to irregular words) and relatively preserved pseudoword reading. Word reading errors in surface dyslexia include regularisation errors (SEW>"Sue") and visual errors (SUBTLE>"Sublet").

- Phonological dyslexia was defined according to the presence of a lexicality effect (better word reading than pseudoword reading) and an imageability effect (better reading of high than low imageability words). Word reading errors include visual and/or semantic errors.
- Deep dyslexia was defined according to the presence of lexicality and imageability effects. Word reading errors include purely semantic errors as well as visual and/or semantic errors.

Regularity, imageability and length effects on word reading ability were identified using binary logistic regression on each participant's baseline word reading accuracy data. Only regression models that were significant were used for classification purposes: for some participants (P11, P12, P13 and P16) accuracy was very high and there was insufficient variance in the dependent variable to produce a significant model overall. In these cases, a linear regression analysis on word reading RT data was attempted, but none were significant.

Finally, the lexicality effect was determined according to significantly worse accuracy on pseudoword reading than word reading, using Pearson's chi squared tests.

2.9 Transcranial Direct Current Stimulation

Participants received either anodal or S-tDCS three times a week over both therapy blocks. The electrode montage was identical in the two conditions, and the researcher administering the stimulation was blinded to the stimulation type. Participants were randomised with bias minimisation to two groups (G1 and G2) to receive anodal stimulation in either the first or second therapy block. G1 comprised 10 participants (alexia subtypes: 7 phonological, 3 deep, 1 surface) and G2 comprised 11 participants (alexia subtypes: 4 phonological, 6 deep). There were no between-group differences in age, time since stroke, lesion volume, training dose or baseline word reading performance (independent-samples t-tests, $P > 0.3$ in all cases); the number of male and female participants (Fisher's exact test, $P = 0.18$); or the number of participants showing a phonological or deep dyslexia subtype (Fisher's exact test, $P = 0.37$).

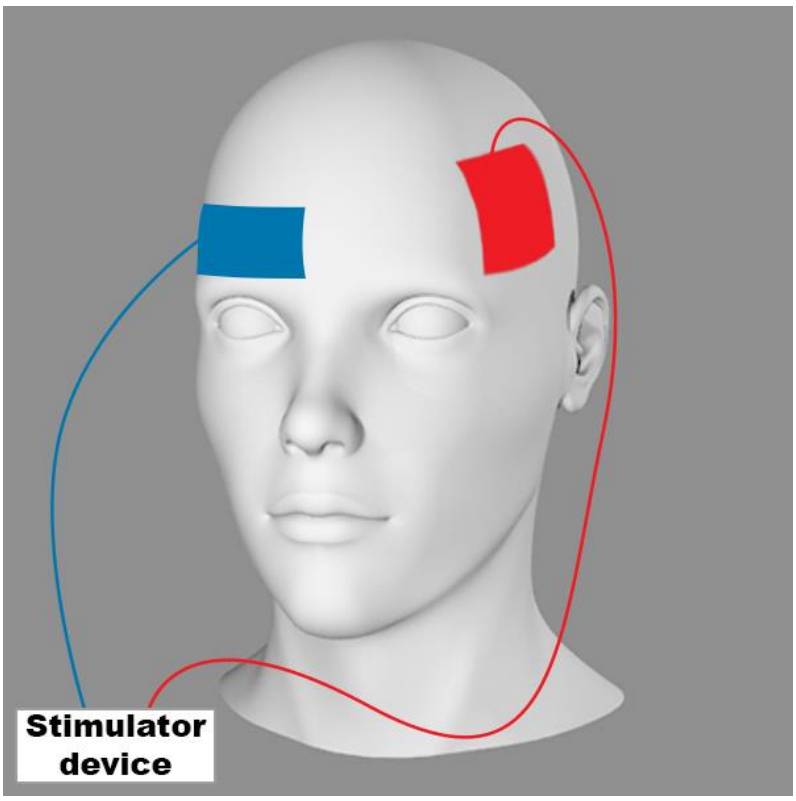

Figure 15 Diagram of the tDCS electrode placement used in the iReadMore trial. A 5 x7 cm anodal electrode (red) was placed in a saline soaked sponge and positioned over the left inferior frontal gyrus (Point FC5 in 10-20 EEG convention). The cathodal reference electrode was placed over the right supra-orbital ridge. A continuous current of 2mA was delivered for 20 minutes in the A-tDCS condition whereas in the sham condition stimulation was delivered for 30 seconds and thereafter ramped down. Both the participant and the researcher administering the stimulation were blinded to the stimulation condition (anodal or sham).

The stimulation site corresponded to F5 on the international 10-20 measuring system (Jasper, 1958) and was identified for each participant at each session. The vertex of each participant's head (the location that the midpoints of the intraocular distance and nasion to idiom distance intersect) was established and a measurement 10% of the total distance between the nasion and idiom was identified from the vertex anteriorly. From that point, 30% of the intraocular distance was measured laterally to the left. The anode was placed over the resulting location, and the reference electrode was placed of the right fronto-orbital ridge. Both electrodes used 5 x 7 cm rubber pads in saline soaked sponges and were attached to the participant's scalp using two rubber bandages (see *Figure 15* for a diagram of the electrode montage). The use of these electrode

sizes has been deemed appropriate given the focality of the tDCS current (Brunoni, Boggio, Ferrucci, Priori, & Fregni, 2013).

A constant current of 2mA was provided using the battery driven NeuroConn stimulator for 20 minutes (http://www.neuroconn.de/dc-stimulator_plus_en/). This intensity of stimulation has been deemed safe (Nitsche et al., 2008). iReadMore training was completed for 40 minutes commencing with the stimulation (participants completed 20 minutes of online iReadMore training and 20 minutes of iReadMore therapy immediately after the stimulation had ceased). Investigation using tDCS in the motor region have demonstrated post-stimulation tDCS effects for same length of time as the duration of the stimulation (Nitsche & Paulus, 2001). It is hypothesised that by providing training with online tDCS, the focality of the stimulation is improved (Halko et al., 2011; Holland et al., 2011).

The active sham stimulation used 15 seconds fade-in, 30 seconds 2mA direct current, 15 seconds fade-out and 20 minutes without any stimulation, but with continuous impedance control. In the anodal condition, the 15 second fade-in was followed by the application of 2mA of constant dc current for 20 minutes, before the 15 second fade-out period.

In line with best practice, certain exclusion criteria were employed to ensure that it was safe to administer tDCS (Bikson et al., 2016). For example, participants could not enter the study if they had experienced a seizure in the preceding year. To monitor any adverse effects, a safety questionnaire was completed at the start of each stimulation session. Participants were asked if they were experiencing greater than usual levels of fatigue, had consumed excessive amounts of alcohol the previous night or if they had experienced any adverse events since the last stimulation session. In order to monitor the immediate effects of tDCS, participants were asked to rate their comfort level on a ten-point picture scale (0 – very comfortable, 10- very uncomfortable) before and after stimulation.

2.10 Analysis of the iReadMore trial

2.10.1 Behavioural data analysis: Planned Analysis

Planned analyses were conducted as stated in the clinical trials registration (www.clinicaltrials.gov NCT02062619).

For each task, an 'Omnibus' analysis was applied to investigate overall changes in performance across all time-points. A more focused 'Therapy' analysis investigated immediate therapy effects of iReadMore and A-tDCS in Block1 and Block2.

Where multiple outcome variables were produced from a single test (e.g. accuracy and RT measures from the Word Reading Test), the Omnibus analysis used a multivariate ANOVA (MANOVA). If not, a univariate ANOVA was used.

The Omnibus (M)ANOVA had the following factors:

- Within-subjects effect of Time-Point (Baseline, T3, T4, T5 and T6)
- Within-subjects effect of Word-List (where appropriate: Trained in Block1, Trained in Block2 and Untrained)
- Between-subjects effect of tDCS Group (G1 [A-tDCS in Block1], G2 [A-tDCS in Block2])

The Therapy analysis used a repeated-measures ANOVA with factors:

- Within-subjects effect of Block (change in Block1 [T3-T4], change in Block2 [T4-T5]. Change was simply calculated as the difference from one time-point to the other).
- Within-subjects effect of Word-List
- Between-subjects effect of tDCS Group

For the CDP (administered at T3 and T5), scores were compared using Wilcoxon Signed Rank tests.

Cohen's *d* standardised effect sizes were calculated for changes in the primary outcome measure, word reading accuracy and RT.

2.10.2 Behavioural data analysis: Exploratory Analyses

Post-hoc exploratory analyses were conducted to explore additional aspects of the results.

I tested whether changes in word reading ability during Block1 and Block2 were larger than the test-retest effects between Baseline and T3. This was done using

paired t-tests, comparing change in trained word reading accuracy and RT over Block1 and Block2 to changes in the same measures between baseline and T3.

Maintenance of therapy effects on word reading ability were assessed with paired t-tests comparing scores immediately before treatment (T3) to the follow-up testing session at T6.

I tested whether word imageability or regularity influenced the efficacy of reading therapy. To do this, the full word corpus (180 words from each of 3 different lists) was ranked in order of imageability. Words in the lowest 40th percentile were labeled as low imageability; words in the highest 60th percentile were labeled as high imageability. For the regularity analysis, words were classified as either regular or irregular. I then calculated each subject's improvements in trained word reading over Block1 and Block2 for words with high/low imageability, and for regular/irregular words. The results were then averaged over the two blocks. Finally, four paired t-tests were computed, testing the effect of word imageability and regularity on change in trained word reading accuracy and RT.

2.11 Magnetoencephalography

2.11.1 Magnetoencephalography scanning procedures

The current thesis was interested in the early stages of word processing. This is because in healthy readers, word reading is a fast, almost automatic process (Leff & Starrfelt, 2013). MEG was deemed a suitable neuroimaging tool due to its high temporal resolution. This is because MEG measures the magnetic flow generated from neuronal firing. In contrast, fMRI measures the haemodynamic response to neuronal firing and as such it has an inherent time lag of up to four seconds. Additionally, I had a strong hypothesis about important regions for word reading due to existing neuroimaging literature (Carreiras et al., 2014; Taylor et al., 2013). Thus, high spatial resolution (for which fMRI is superior to MEG) was deemed less important than high temporal resolution.

Specifically we were interested in the first 300ms of reading. The start and end of visual word recognition is still debated, as is the role of various brain regions within the reading network. However, three key time points have been identified within visual word recognition; the N170, N250 and N400. I will now discuss these in turn.

Within the 150-170ms time period, a left lateralised peak in the occipitotemporal cortex has been identified which differentiates orthographic stimuli from pseudowords and symbol strings (Bentin, Mouchetant-Rostaing, Giard, Echallier, & Pernier, 1999; Duñabeitia, Dimitropoulou, Grainger, Hernández, & Carreiras, 2012; Nobre, Allison, & McCarthy, 1994; A. Tarkiainen, Cornelissen, & Salmelin, 2002). This has led to the suggestion that the N170 peak represents an automatic response in typical word recognition, as it is not observed within the reading profiles of dyslexic children (Simos et al., 2007). However, the exact nature of this peak is still debated. It may correspond to visual feature letter identification and has led to the suggestion that word reading prior to 170ms only responds to letter frequency (Grainger & Holcomb, 2009; Petit, Midgley, Holcomb, & Grainger, 2006). However, lexical effects and an early influence of phonology and semantics have been observed in the 100-200ms window (Assadollahi & Pulvermüller, 2003; Carreiras, Vergara, & Barber, 2005).

The N250 peak is sensitive to the phonological status of letters such as whether the letter is a constant or a vowel (Assadollahi & Pulvermüller, 2003; Carreiras et al., 2005). It has been suggested that as consonants constrain word processing more than vowels, these studies indicate a lexically driven top-down effect in early word reading (Carreiras et al., 2014). It is believed that the accumulation of lexical information and lexical competition has taken place at N250 as a similar response pattern in masked priming paradigms are revealed in the N400 and in behavioural reaction time studies (Duñabeitia, Molinaro, Laka, Estévez, & Carreiras, 2009).

The subsequent N400 peak is associated with whole word representations and semantics. In mis-match negativity tasks this peak has been shown to be larger for words unrelated to a prime, while this is not the case for pseudowords (Holcomb & Grainger, 2006; Kiyonaga, Grainger, Midgley, & Holcomb, 2007). Therefore, in this research, we are mainly interested in visual word recognition, rather than the effects of word meaning.

MEG measures the magnetic flow that runs orthogonally to the electric flow generated with neuronal firing. MEG signal is believed to reflect the post-synaptic potentials of pyramidal cells because i) pyramidal cells are orientated radially to the cortical surface, which when active would result in a magnetic field optimal to MEG pick up ii) as pyramidal cells are arranged in a generally parallel formation,

when multiple cells are simultaneously active they generate a magnetic signal strong enough to be measurable. For further details, please see 8.1.5 Magnetoencephalography in Appendices.

Scans were acquired using a VSM MegTech Omega 275 MEG scanner with 274 axial gradiometers in software third gradient-mode at a sampling rate of 480Hz. Fiducial markers on the nasion and left and right pre-auricular points were used to determine head location in the scanner.

2.12 MEG Experimental design and stimuli

Participants were seated upright in the scanner with a screen approximately 50cm in front of them. Stimuli consisting of words (n=300 for CA participants; n=200 for controls), 'False Font' symbol strings (n=150 for CA participants; n=200 for controls) and common names (Name trials; e.g. "Jenny", "Bob", n=40) were projected onto the screen (See *Figure 16*). The stimuli types were evenly distributed in a pseudorandom order across 4 runs and presented using cogent software (http://www.vislab.ucl.ac.uk/cogent.php). The disparity in the number of presentations of Word and False Font stimuli between the two participant groups was due to the CA participants' involvement in the iReadMore study in which Word stimuli were formed of 150 words trained in Block1 of the iReadMore trial and a matched list of 150 control words which were not trained (untrained words) (see **Error! Reference source not found. Error! Reference source not found.**). Participants were instructed to silently read the Words, look at the False Fonts and to press a button on a button pad when they read a name. Participants practiced the task in the MEG scanner with the experimenter in the room. Trials containing Names served as catch trials. This meant that the participant was required to attend to every trial to identify if it was a name, but the catch trials were later removed from analysis.

Carian script was used to generate the False Font stimuli. This script developed by Jane Warren consists of a 26-item script based on an obsolete Anatonlian language. It uses similar curves and straight line as roman script to create similar visual stimuli to words, however without the associated meaning. The False Font stimuli were directly translated from the words, and were therefore matched for stimulus length. The names used for the catch trials had a distribution of stimulus length matched to the word stimuli.

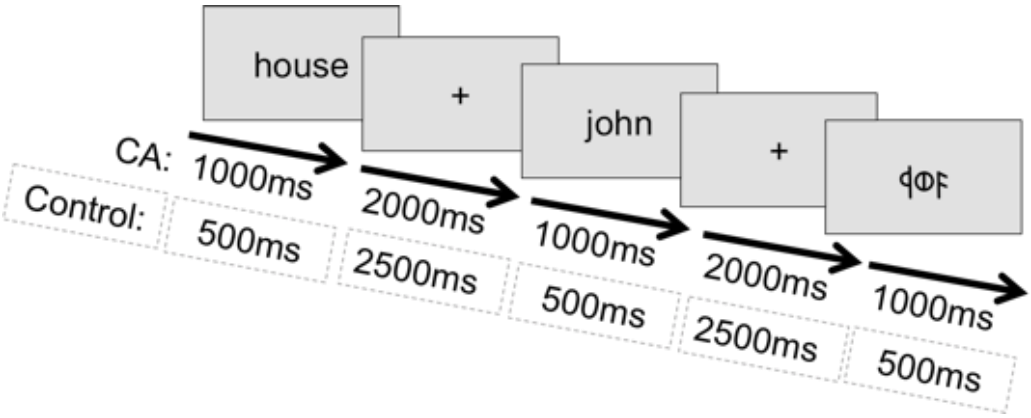

Figure 16 Stimulus presentation procedure for the MEG scans. Participants were scanned before and after training. Examples of the three stimuli types are displayed; Words; Names and False Fonts. The duration of presentation is written under the stimuli. Different exposure durations were used for the two participant groups, due to the faster reading speed of healthy control participants in contrast to CA patients. The same inter-stimulus-interval was preserved between groups.

For the CA participants each stimulus was presented for 1000ms followed by a crosshair for 2000ms, while for control participants stimuli were presented for 500ms followed by a crosshair for 2500ms. Different timings were used between the two participant groups because healthy word reading occurs more quickly than impaired reading in CA but it was important to preserve the inter stimulus interval between participant groups. In both cases the total inter stimulus interval was 3000ms. The stimuli were presented lower case Arial font of size 50.

2.13 MEG pre-processing

In order to analyse MEG data it first needs to be pre-processed. This process gets the MEG data ready for analysis, and tends to include a reduction in the noise in the data. MEG data can be analysed in a number of ways, and the pre-processing steps reflect the eventual analysis. The data presented in this thesis were pre-processed for dynamic causal modelling of evoked response potentials. Data was pre-processed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) mounted on Matlab 14a (https://uk.mathworks.com/products/matlab.html)

The pre-processing steps were as follows:

- Initially, data was converted to SPM 12 format for pre-processing.
- All sensors were highpass filtered at 1Hz, to remove low frequency noise (slow drifts). This type of noise is most likely introduced by the participant's head moving relative to the sensors over time.
- Another source of unwanted noise is the signal is caused by eye movements and blinking. Removing each trial containing this artefact could result in a lot of data loss, so the Berg method of topographic artefact detection was used (Berg & Scherg, 1994). The spatial confounds were defined as three orthogonal dipoles at each eye and a forward model was used to convert this into topographic artefact maps. These artefact maps were compared to representative cortical topographies and the identified artefacts were removed.
- The data were then epoched. Each MEG run forms one continuous recording. Epoching slices this recording into single trials relative to stimulus presentation. This was suitable for this analysis as I was interested in evoked neural responses to different experimental stimuli. Each epoch was then defined as containing one of the different experimental stimuli (Block1 Trained words, Untrained words, False Fonts or Names).
- A low pass filter was then applied. This removed oscillations greater than 30 cycles per second. Data at these frequencies were unlikely to be caused by the neuronal sources of interest but could be introduced by muscle action potential or nearby mains electricity (>50Hz).
- The four runs were then merged together.
- Artefact detection was performed to remove any residual artefact from data that could have been introduced by eye movements or muscle activity. This process detects trials in which the signal recorded at any channel exceeds the predefined threshold (2500fT). If a specific channel had greater than 20% of trials rejected, the channel was removed.
- All trials for each of the different stimuli types (Block1 Trained words, Untrained words, False Fonts or Names) were averaged. MEG data contains white noise from various sources including the sensors themselves and environmental noise. It is hypothesised that this occurs randomly across the MEG recording, but the signals of interest (the evoked

responses) are time locked to the stimulus presentations. By averaging across epochs, this noise is cancelled out, allowing the signal in response to the stimuli to be identified. Robust averaging was applied. This method down weighs outlier trials and removes noise from the data (Litvak et al., 2011) .

2.14 The forward model

The forward problem refers to estimating the data that would be observed by the MEG sensors if certain regions of the cortex were active. To solve the forward problem, a cortical mesh is created. In SPM, a template boundary element model mesh (Mosher, Leahy, & Lewis, 1999) simulates the geometry of the cortex. Given that MEG signal is assumed to arise from pyramidal neuron activity that occurs perpendicular to the cortical surface, the orientation and location of dipolar sources can be fixed to this mesh. Secondly, a representation of the 275 sensors is produced. This informs the model of the location and orientation of each of the sensors. Three fiducial markers, placed on the nasion, and at the left and right pre-auricular points, give the location of the participant's head relative to the sensors. Thirdly, the conductivity of the head tissues are specified. In MEG a single shell model of the head is deemed appropriate for most analyses as the magnetic flow is largely unaffected by the material type between the source and the sensors (Henson, Mattout, Phillips, & Friston, 2009). A lead-field matrix is then generated which specifies how current flow at any vertex in the cortical mesh will translate to magnetic field strength at each of the sensors. This matrix is of size N x M where N is the number of sensors and M is the number of mesh vertices. So, for each mesh vertex there is a corresponding lead field.

2.15 Source localisation

Generating a lead field matrix to solve the forward problem is a relatively simple. The inverse of this, identifying the source of the activity from the data collected in the sensor data is a much more difficult question to answer. It is an ill-posed question - there are infinite possible solutions that could give rise to the observed data. There are a number of methods available for source localisation, and the choice of methods depends on the research question. In the current thesis, the functional connectivity between sources was of interest. In order to compare between groups (controls vs CA participants) and time-points (pre-treatment vs

post treatment) and to average across participants within each group, these models needed to contain the same nodes. Variational Bayes Equivalent Current Dipole (VB-ECD) source localisation is suitable for these purposes for three main reasons. Firstly, VB-ECD is a form of data reduction. By reducing the data to six sources I was able to better understand the interactions between these sources that would not be possible if all the data were preserved. Secondly, the literature on the functional neuroanatomy of reading is relatively mature (from fMRI data), resulting in strong priors to enter into the model. Finally, VB-ECD allows for the comparison of different number of sources. By estimating different source I was able to test which source configuration best fits the data. For example, the model fits of a four-source model, containing left and right OCC and vOTs can be compared to a six-source model containing left and right OCC, vOT and IFGs. This means that the DCM models estimated to identify the reading network and training related modulations in this network, can be estimated using the model that best fits the data.

2.15.1 Variational Bayes Equivalent Current Dipole Modelling

The VB-ECD source localisation method requires a single time point from which to model the dipole location. The M170 is known to represent orthographic processing (Marinkovic et al., 2003; Pylkkänen & McElree, 2007; Rossion, Joyce, Cottrell, & Tarr, 2003; Antti Tarkiainen, 1999; Vartiainen et al., 2009; Zweig & Pylkkänen, 2009) and thus is a suitable candidate time point from which to conduct the VB-ECD analysis. This peak was identified for each participant in a semi-automated fashion. Root mean square graphs (plotted against time) were created for all participants. This displayed the peak of the signal averaged across all the trials of interest. Within Chapter 3, which investigated the reading therapy before training, the M170 peak was identified for averaged data across all Word and False Font trials. In Chapter 5, where I investigated the modulation in the reading network with training, the peak was identified for the averaged signal for Block 1 Trained and Untrained words,

before and after therapy. This ensured the chosen time point was not biased to any particular condition (see

Figure 17 for example plots).

In multiple dipole model fitting, the source parameters are manipulated to minimise the error between the model and the measured activity. The expected locations of the dipoles based on previous research ('location priors') were chosen as starting points. In the current study, the location priors for each source were defined with prior variance of 6mm, i.e. a random Gaussian distribution of 6mm in each direction from the starting coordinate. For each iteration of the VB-ECD search, a starting point was selected at random from the Gaussian area for each source, and from here the dipoles were allowed to move until they reached locations that generated the least error when the outputs from the model were compared to the sensor data. The point at which moving the dipole locations could not remove more error is called convergence. This process was then repeated with different starting points for each dipole. In the current analysis, 100 iterations were performed, and the iteration with the highest model evidence was selected as the winning dipole locations. I chose to estimate a 6 source model based on the findings of experiments completed by this group (Woodhead et al., 2014). In this previous work, data from the control participants was used to compare 4 dipole configurations:

- C1: bilateral OCC only
- C2: bilateral OCC and vOT sources
- C3: bilateraly OCC, vOT and IFG sources
- C4: bilateral OCC, vOT, STS sources.

The six source configuration C3 (including the left and right, OCC, IFG, vOT) was the winning model with a log-evidence value of F=2011 (model posterior probability of >0.99) compared to the second best model (C4). In the current thesis, models C2 and C3 were fitted for the CA participant data collected before and after therapy. Model C3 was the winning model with a log-evidence value of F=153.1 (model posterior probability of >0.99). Therefore, in the current analysis a six source model was used with the following spatial priors; OCC ±15 -95 2 (MNI coordinates), vOT ±44 -58-15 and IFG ±48 28 0.

In a final step, dipole locations were checked manually. This is because the VB-ECD places no restrictions on where the dipoles can move. Sources estimated by VB-ECD were only accepted if they met the following criteria: 1) were within the anatomically defined regions of interest; 2) were more than 2cm apart, 3) were outside of the lesion (for CA participants only).

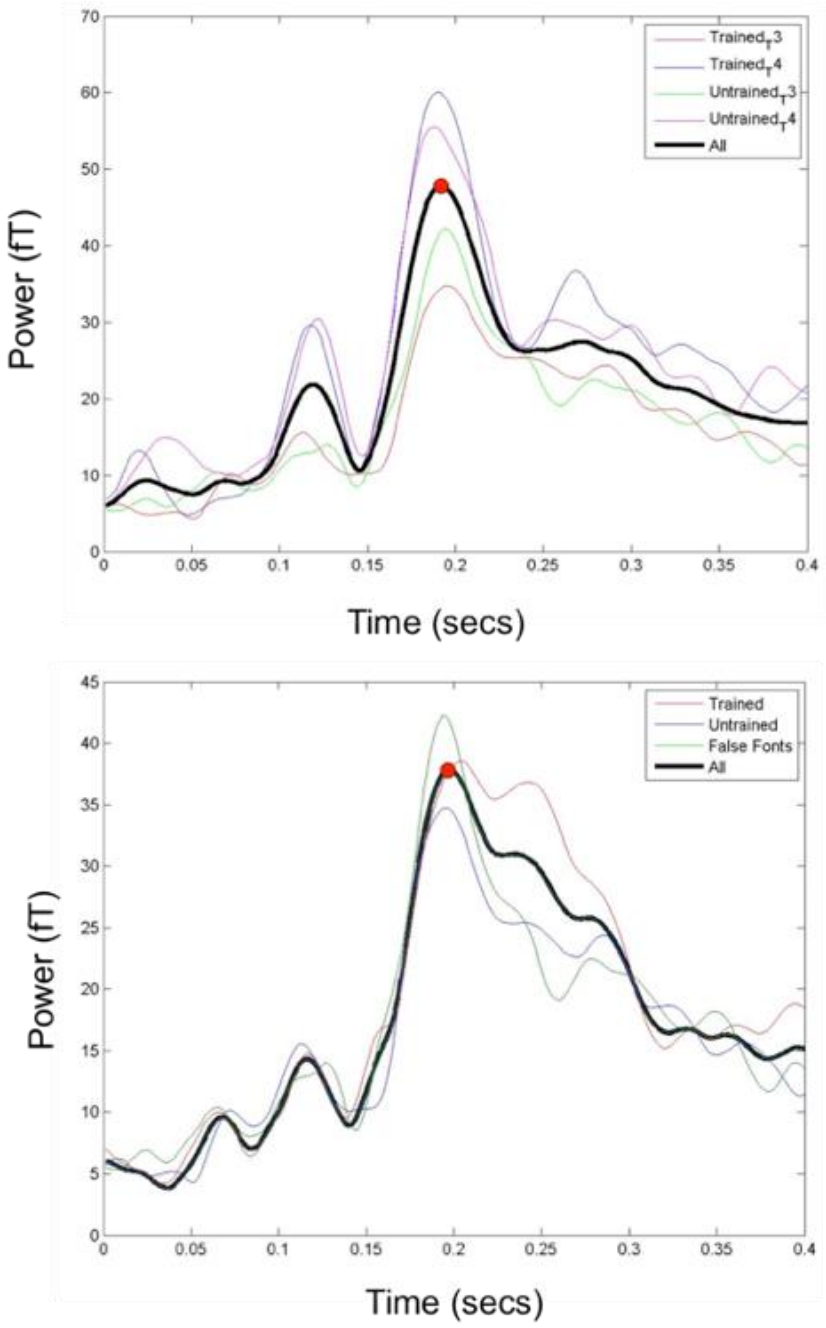

Figure 17 Examples of M170 peak plots in the 0-400 ms time window (x-axis) and power (fT, y-axis). The top panel displays an example peak used in Chapter 3 of this thesis. Word trials (red=trained and blue=untrained), false font (green) trials and the average of the two conditions (black) are displayed. The peak, indicated

by a red dot, is identified using a semi-supervised method for each participant. The bottom panel displays an example M170 plot for Chapter 5. To-be-trained words (red), to-be-untrained words (green), trained words (blue) and untrained words (pink) are plotted and the M170 peak (red dot) is identified using the average (black) power from all trials.

2.16 Dynamic Causal Modelling

Dynamic causal modelling was used to identify effective connectivity within the reading network. I was interested in modelling the reading network for the evoked response potentials for different types of visual stimuli, either Words (which were comprised of Block1 Trained and Untrained words) or False Fonts. The influence of different regions within the reading network has previously been investigated with a focus on the timings (Carreiras et al., 2014; P. L. Cornelissen et al., 2009; Pammer et al., 2004; Wheat et al., 2010). For example, if activation in the left IFG precedes processing in earlier parts of the reading hierarchy (i.e. the left vOT), it might be suggested that there is an early influence of frontal regions on word processing. However, this association lacks evidence of causality. This is overcome in DCM, which investigates the causal impact of activation in one region on another. This is what makes using DCM appealing over exploring functional connectivity alone. Functional connectivity could include correlations in fMRI signal in different brain regions. It suggests a relationship between those regions, but it's not causal (Friston, 2011).

Dynamic causal modelling is fundamentally different in its use of time-series to forms of functional connectivity analysis. This is best outlined in the following quote from David et al. (2006), p.1256.

"These approaches [functional connectivity] generally entail a two-stage procedure. First an electromagnetic forward model is inverted to estimate the activity of sources in the brain. Then, a post hoc analysis is used to establish statistical dependencies (i.e., functional connectivity) using coherence, phase-synchronization, Granger influences or related analyses such as (linear) directed transfer functions and (nonlinear) generalized synchrony. DCM takes a very different approach and uses a forward model that explicitly includes long-range connections among neuronal subpopulations underlying measured sources. A single Bayesian inversion allows one to infer on parameters of the model (i.e.,

effective connectivity) that mediate functional connectivity. This is like performing a biological informed source reconstruction with the added constraint that the activity in one source has to be caused by activity in other, in a biologically plausible fashion."

It may be best explained if the steps used in DCM are considered:

- The averaged ERP responses are used as the 'observed' data. They are simplified using principal component analysis, and the components this produces become the data features that the DCM is trying to explain or fit.

- DCM's generative model is then built up to try and provide the best fit to this observed data. The generative model produces a set of 'predicted' data, i.e. the response that would be expected in each sensor based on the parameters provided in the model.

- The generative model is comprised of the Forward Model (based on the source localisation and head geometry) and the Neural Model (based on the neural mass model, which describes the dynamics of each different layer of neurons and how they interact within and between regions).

- The Neural Model contains the elements of 'causality'. By varying the (directional) connections in the model, how the data would look if Region A had a causal influence on Region B, or vice versa, can be predicted.

- Finally, by comparing all of the models that are generated, the one that best fits the data is selected. In the current set of experiments Bayesian Model Averaging is used. This looks at the evidence for each connection separately, summed across all models.

It is by estimating several different version of a perturbed neural model, and using Bayesian statistics to evaluate which of these models best fits the data that causal connectivity within the model can be inferred.

DCM for ERP takes advantage of stereotyped connectivity patterns (detailed below) to estimate a generative model that can be compared to the observed data (See *Figure 18*). Bayesian statistics then provide an estimate of how well

the generative model fits the observed data. The generative model is comprised of a neural model, which describes the dynamics of the brain, and the forward model, which maps brain activity to data features.

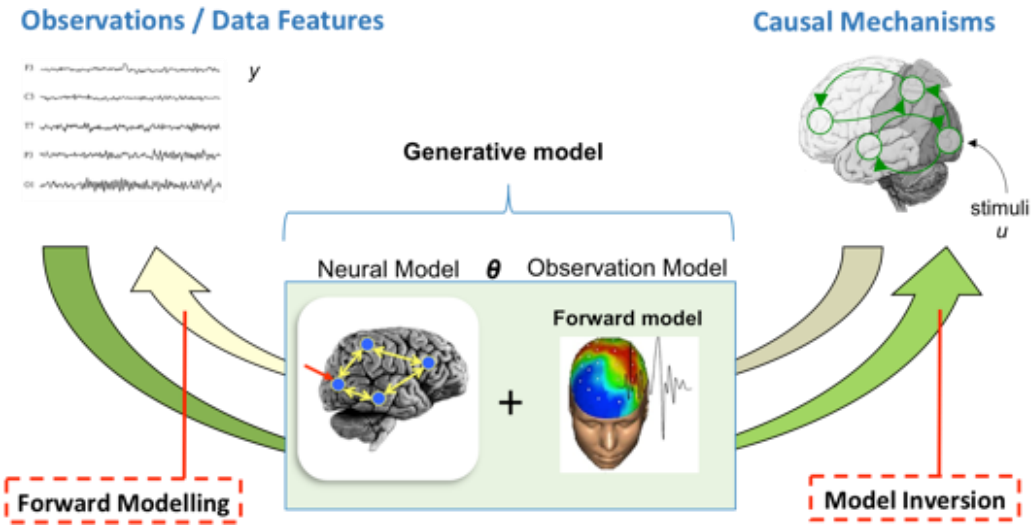

Figure 18 Diagram of the modelling that take place in DCM. The yellow arrow indicates the direction of the forward model. This allows me to predict what brain activity data would be observed if those neural model parameter values were used. The Green arrow indicates model inversion. This is concerned with identifying how the model parameters (θ) within the model can be altered to make the model best fit the observed data (y) when that stimuli is entered into the model (u). Taken form van Wijk, B, "Principles of Dynamic Causal Modelling (DCM)" from SPM course for MEG & EEG 2017 available at http://www.fil.ion.ucl.ac.uk/spm/course/slides17-meeg/. Reproduced with permission via email from van Wijk, B.

The cortical columns are categorised into three distinct layers of neurons, oriented perpendicular to the cortical surface (see Figure 19). Essentially, DCM for ERPs employs a biologically informed neural mass model that uses the characteristic response rates and patterns of connectivity (Felleman & Van Essen, 1991) of three neuronal subpopulations (pyramidal cells, spiny stellate cells and inhibitory interneurons) within the layers of the cortical column (Jansen & Rit, 1995) to model the connections between different sources (the neuronal

model). For example, forward connections innervate spiny stellate cells in the granular layer which results in an excitatory effect (see Figure 20), backward connections synapse pyramidal cells and inhibitory interneurons in the supra- and infra granular layers and hence can be excitatory or inhibitory, lateral connections can innervate all three layers of the cortical column and thus can also have an inhibitory or excitatory influence on the target region (see 8.1.6 Dynamic Causal Modelling within MEG in Appendices for further information on DCM model estimation).

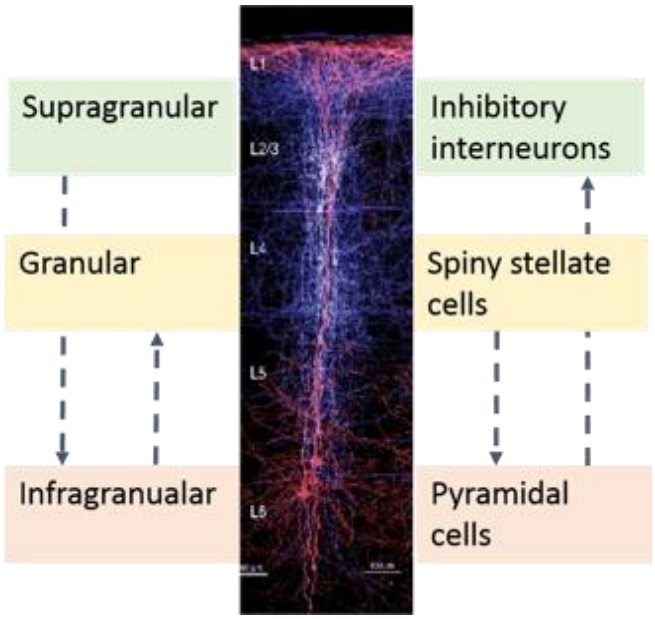

Figure 19 Schematic diagram of the cortical columns composed of three cortical layers (on the left) and the predominant cells contained within those layers (displayed on the right). An image of a mammalian neocortex, the different layers than make up the three cortical layers are labelled (L1-L6). The dotted arrows represent the connections that run between the neuronal subpopulations of the column. From "Dynamic causal modelling for EEG and MEG" by S.J. Kiebel, M. I. Garrido, R. J. Moran, and K. J. Friston, 2008, Cognitive Neurodynamics, 2, p. 121-136. Copyright [2008] by Springer Nature. Adapted with permission.

Self-connections are also modelled within the DCM. These quantify the maximal amplitude of the post-synaptic response in each cell population in that region (Kiebel et al., 2007). These maximal responses are modulated by gain parameters. Gain parameters greater than one increase the maximal response that can be elicited from a neuronal region. As such, the gain parameters are a measure of a region's sensitivity to an input. Like VB-ECD, the estimation of DCM

models is an iterative process, whereby free model parameters are varied in each iteration, and the fit of generative model to the observed data is assessed. This is then repeated until the modulation of the parameters does not result in a more accurate generative model. This is performed using an Expectation-Maximisation Algorithm. The outputs of the Expectation-Maximisation Algorithm are the posterior distribution of the parameters (this is what is used to identify the modulation in connectivity with different stimuli types) and the model evidence (how well the generative model fits the observed data). For a detailed description of the methodology of DCM the reader is directed elsewhere (David, Harrison, & Friston, 2005; Garrido, Kilner, Kiebel, Stephan, & Friston, 2007; Kiebel, David, & Friston, 2006; Kiebel et al., 2007; Kiebel, Garrido, Moran, & Friston, 2008; Reato, Rahman, Bikson, & Parra, 2013).

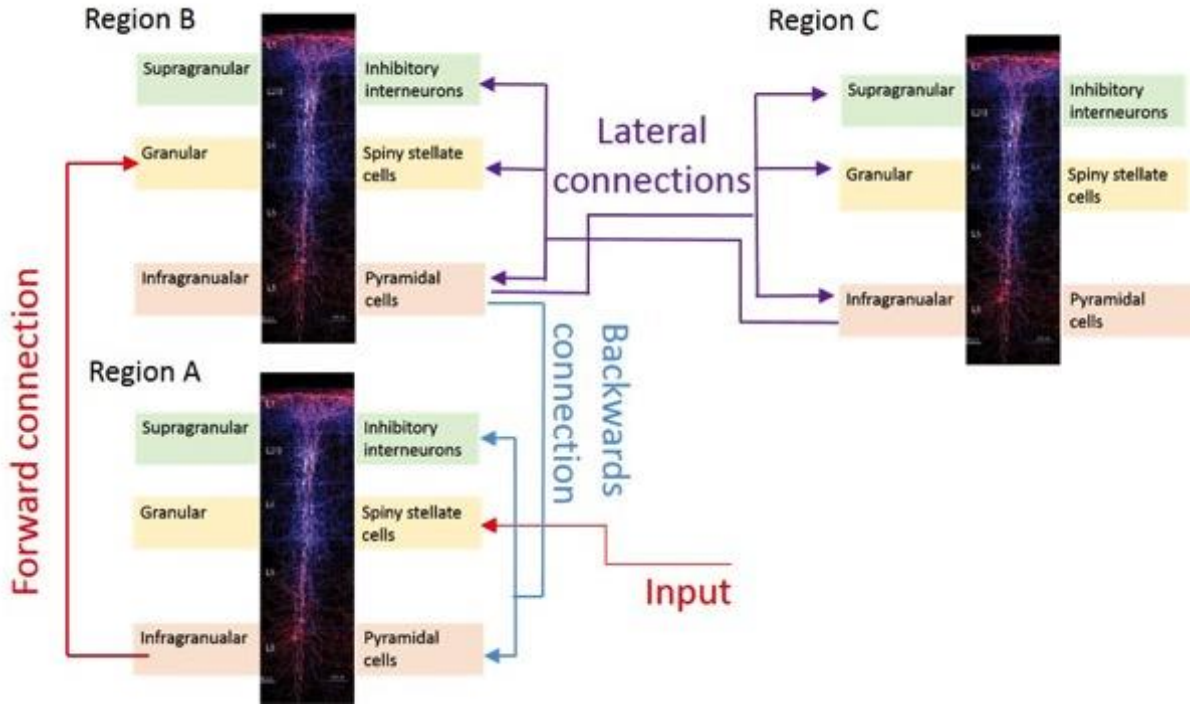

Figure 20 Schematic diagram of the connection between different regions involved in a network. The three types of connections modelled in dynamic causal modelling are displayed; forward (red), backwards (blue) and lateral (purple). The cortical columns are composed of three cortical layers (on the left) and the predominant cells contained within those layers (displayed on the right). An image of a mammalian neocortex, the different layers than make up the three cortical layers are labelled (L1-L6). Adapted from "Dynamic causal modeling of evoked

responses in EEG and MEG" by O. David, NeuroImage, 30, p. 1255-1272. Copyright [2006] by Elsevier. Adapted with permission.

Activity in the 0-300 ms time window was estimated in the DCM. This time window was chosen due to my interest in the early stages of word processing. In order to estimate the effective connectivity of the reading network three matrices were specified. The C matrix specified the location of the sensory input to the network. In the present thesis this was identified as the left and right OCCs (see *Figure 21*). The A matrix specified the endogenous connections and served as a baseline measure of effective connectivity. The B matrix specified how connection strengths were modulated by task.

Similar to other studies (Woodhead et al., 2013, 2014), and in order to reduce the model space to a manageable computational level, I placed the following constraints on how network connections varied between models: i) lateral connections were only allowed within the same level of the cortical hierarchy (e.g left OCC to right OCC) and not between levels (e.g. left OCC to right vOT); ii) lateral connections were reciprocal (e.g. a connection from the left vOT to right vOT was mirrored by a connection from the right vOT to the left vOT); and iii) forward and backward connections were symmetrical between hemispheres. This resulted in nine independently varying types of connections leading to 512 models (2^9) per subject, all of which were fitted to their individual MEG data.

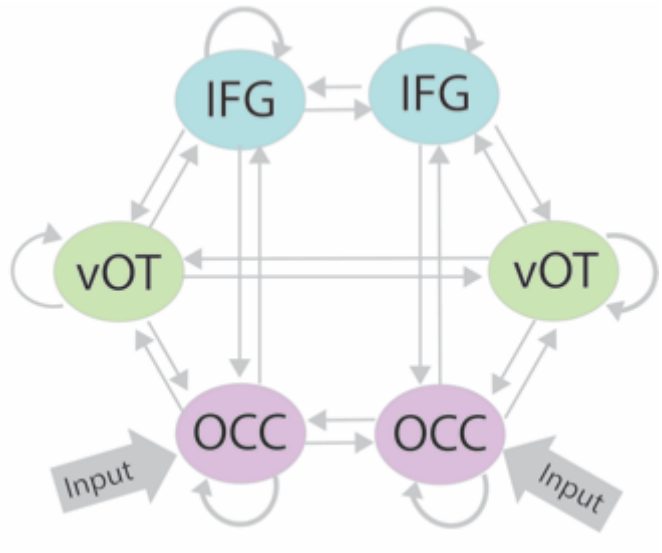

Figure 21 Diagram of the six-source model estimated in dynamic causal modelling. Inputs are specified in the left and right occipital regions. Bidirectional

connections were specified. Occ= Occipital region, vOT=ventral Occipitotemporal region, IFG=Inferior Frontal Gyrus

2.17 Bayesian model averaging

Random effects Bayesian Model Averaging (BMA) (Penny et al., 2010) was used to identify the average change in each connection strength across the sample. BMA was chosen for a number of reasons. Firstly, Bayesian Model Selection (where only the winning model out of all models tested – the 'model space' – is selected) becomes brittle when the model space is large, as is the case here. BMA considers the entire model space and computes weighted averages according to the posterior probability for each model. BMA is deemed suitable when investigating cognitive processes that could be performed in a number of ways by different subjects (Penny et al., 2010).

After performing BMA, I determined if each connection in the B-matrix was significantly modulated (stronger or weaker) than would be expected by chance. This was done using a non-parametric proportion test in which connection gains, measured in log space, were compared to one. A Gaussian distribution based on the posterior mean and standard deviation was generated for each connection from which 10,000 samples were obtained. As the exponentiation of zero is one, gains equal to one indicate no modulation of that connection strength. A connection was deemed to be significantly stronger in the B matrix compared to the A matrix if >90% of samples that were greater than 1 (Richardson, Seghier, Leff, Thomas, & Price, 2011; Seghier, 2013; Woodhead et al., 2013). If >90% if samples were less than 1 then the connection was judged to be significantly weaker.

2.18 Comparing the reading network of CA patients with healthy controls

I will now specify the methods used for study one (chapter 3), which aimed to investigate the reading network of CA patients and how it differs from healthy controls. Participants in both groups completed an MEG scan during which they viewed Words and False Fonts. The False Fonts provided a baseline of complex visual stimuli processing, upon which to identify the processes specific for word reading. The functional connectivity when viewing False Fonts was estimated to

provide a baseline visual processing network. How these connections were modulated when viewing Words was then estimated, to give the connection strengths specific to Word processing within the reading network of the two participant groups. While most of the chapter is based on the generic methods outline above, there are some study-specific methods that are outlined below.

2.19 MEG control data

A full description of the CA participants is given within the section on the iReadMore trial above (see 2.4.1 Central Alexia Participants, above). Normative MEG data was also acquired from ten healthy controls subjects (5 males, mean age 57 years, range 30-82 years). The CA participants were not significantly different in age from the MEG controls $t(31)=0.90$, $p=0.38$.

2.20 MEG source plots

The power of activation at each of the sources modelled in the DCM was plotted for each of the stimulus conditions. This allowed for the inspection of the data away from the DCM, and allowed for the investigation of the time courses of stimulus processing within each group. Signal from each participant's six dipole locations were extracted for Word and False Font trials. Within subject, the data is averaged across Word and False Font trials at each dipole. The data is then averaged and normalised at the group level for each dipole. The power at each dipole source was plotted against time for the averaged Word and False Font trials in the two participant groups.

2.21 Identification of the structural integrity of White Matter Tracts using MRI

Functional connectivity suggests a relationship between regions, but does not indicate a causal relationship between regions. Effective connectivity refers to the causal influence of one region on another (Friston, 2011). DCM identifies the degree of effective connectivity between nodes and this is why I used it over correlating activity (used in functional connectivity studies). However structural connectivity is not considered in DCM this analysis. In reality the effective connectivity identified within DCM would require some structural architecture upon which to communicate. A commonly used method to investigate white

matter tract quality is diffusion tensor imaging. However, this requires a specific set of sequence acquisitions during the MRI scan. Instead of this, I quantified the amount of damage to key white matter tracts (identified using probabilistic atlases) that were likely to provide the structural basis for the effective connectivity estimated within the DCM. The key tracts were identified as the inferior occipitofrontal fasciculus, the inferior longitudinal fasciculus, the superior longitudinal fasciculus and the uncinate fasiculus. The degree of damage was estimated by comparing each participant's binary lesion image (see 2.3 Structural MRI Acquisition and Lesion Identification, above) to anatomical masks of the tracts. The masks were created within FSL software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) using the 2mm masks from the John Hopkins University White Matter Tracts Atlas (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases; (Hua et al., 2008)) thresholded at 10% probability.

2.22 Dynamic Causal Modelling

The A matrix specified the endogenous connections when participants observed False Fonts, which served as a baseline measure of effective connectivity for visual processing. The B matrix specified how connection strengths were modulated by task, or more explicitly, how the connection strengths estimated in the A matrix (for False Fonts) were modulated when the participant observed Words. Through comparing the estimated B matrices for CA and control participants, I was able to test whether effective connectivity for Words vs False Fonts differed between groups.

As described above, the results of the DCM analysis were tested for significance using BMA and non-parametric proportion tests. Within each group, BMA with random effects was conducted, and non-parametric proportion tests was administered for each connection. This allowed for the identification of significantly modulated connections for reading within each participant group. In order to compare the groups, a non-parametric proportion test was conducted, akin to the one described above. However, this test considered if <10% of the sample with the mean and standard deviation taken from each participant group overlapped.

2.23 The effect of iReadMore on the reading network of patients with CA

Using the MEG data collected before and after the first training block, I investigated the effects of iReadMore therapy on the early stages of word processing. The MEG scans conducted before and after iReadMore training were merged after pre-processing. This enabled source localisation (VB-ECD) to be conducted without biasing the sources to one time point and it allowed me to ensure that the DCM estimates were obtained using data from the same sources at both time-points. The data needed to be combined into one file in order to compare change in connectivity strengths for to-be-trained words before therapy (Tr_Before; these are the same words described as Block1 Trained words above) to the same words after therapy (Tr_After) and Untrained words before therapy (Un_Before). VB-ECD was conducted as described above on the merged dataset.

Activity was estimated in the 0-300 ms time window from the four conditions of interest; words to-be-trained words before therapy (Tr_Before), the same words after therapy (Tr_After), to-be-untrained words before therapy (Un_Before) and the same words after therapy (Un_After). These conditions were specified in the DCM modelling as follows:

- Inputs to the model were specified as the left and right OCC.
- The A matrix estimated the connection strengths when participants observed to-be-trained words (Tr_Before)
- The two B matrices specified how connection strengths were modulated by task.
    - Matrix B1 estimated the modulation for trained words over time (Tr_Before vs Tr_After).
    - To ensure the modulation observed in the first B matrix did not represent a simple effect of time, rather than training per-se, the modulation of connectivity strengths for untrained items after therapy compared to-be-trained items prior to therapy was estimated in matrix B2 (Tr_Before vs Un_After).

The aim was to capture any test-retest effects that consistently played out in the reading network but were not modulated by therapy and subtract any of these connections away from the first B matrix.

2.23.1 MEG DCM training effects statistical analysis

2.23.2 Analysis 1: Group-level effects of iReadMore therapy on the reading network

Analysis 1 identified the training-related modulation in effective connectivity between regions at the group level. I defined whether connections showed training-related modulation according to two criteria: i) there was significant modulation in Matrix B1 (Tr_Before vs Tr_After); and ii) the therapy-specific modulation in Matrix B1 was significantly different to the non-specific change over time in Matrix B2 (Tr_Before vs Un_After).

For the first criteria, a non-parametric proportion test (as described above) was used for each connection to test whether modulation in Matrix B1 (Tr_Before vs Tr_After) was significant.

To identify therapy specific training effects, rather than a simple effect of time, I then compared the B1 and B2 matrices. The B1 matrix provides the modulation of connections for training over time whereas the B2 matrix encapsulates the main effect of time in the absence of any training. If the experiment only induced a simple effect of time, the modulation observed in matrix B1 and B2 would be very similar, and therefore, not significantly different. If, on the other hand, there were an additional effect of therapy over time, I would expect the modulation in the two B matrices to be different. Using a fixed effect within subject Bayesian Model Comparison (BMC), I compared the two models; i) Matrix B1 ≠ Matrix B2; and ii) Matrix B1 = Matrix B2. Log Bayes Factors > 3 indicate that connections in B1 were significantly different to those in B2 (i.e. the effect of therapy could not be simply explained as an effect of time). If both criteria are satisfied then the connection is significantly modulated by reading therapy (criterion 1) and is not simply explained as an effect of time (criterion 2).

2.23.3 *Analysis 2: Testing whether therapy-related modulation of connection strength predicts improvement in reading accuracy*

The aim here was to relate the strength of modulation of individual connections to the percentage change in reading accuracy caused by the iReadMore therapy. This utilized a multivariate statistical test called Automatic Linear Modelling (ALM) in SPSS version 22.0 software (IBM, 2013; https://www-01.ibm.com/support/docview.wss?uid=swg21646821). The benefits of ALM analyses are that this method automatically normalises variables and removes outliers before applying a forward regression. To deal with outliers ALM determines the influence of outliers on the model by calculating a Cook's distance value in cases that are three standard deviations (SD) away from the mean. This is performed because in some cases outliers do not necessarily influence the fitted model (contrary to cases in which non-outliers strongly bias the model). A Cook's distance value close to 1 is considered problematic and this outlier would be removed (Field, 2013). This allowed me to identify whether modulations of connection strengths were better able to explain patients' response to therapy than behavioural factors alone. Secondly, I was able to explore whether changes in individual connections contributed to explaining the therapy effects over and above those already explained by demographic and behavioural measures. ALM uses a stepwise, forward feature selection process to optimise the model that best explains the dependent variable (in my case, an individual's percentage change in reading accuracy for trained items after therapy: Tr_After - Tr_Before / Tr_Before * 100). This is indicated by a minimised Akaike Information Criterion (AIC; Akaike, 2011) which is generated by the ALM procedure within SPSS. The ALM process starts with an empty model, and adds a single predictor whose addition optimises the model (reduces the AIC). This continues in iterations, adding the best new predictor to those already selected, until no new feature's addition improves the quality of the model to a degree that outweighs the expense of increased model complexity. It should be noted that this was an exploratory analysis, and the findings of this analysis should be interpreted with caution. The current study is underpowered for such an analysis as shown by a series of leave-one-out cross validation tests, which revealed the model to be unstable. However,

in the current thesis, I wished to explore this technique as a potential approach to future analysis with larger sample sizes.

Models containing different combinations of variables can be formally compared using the Akaike Information Criterion. I assessed three models: i). ‘Behavioural’, comprising 41 behavioural and demographic variables; ii.) ‘Neuroimaging’, comprising of the normalised, log values of connection strength modulation from Matrix B1 for 13 connections that showed a significant therapy effect in Analysis 1; and iii.) ‘Combined’, comprising all behavioural, demographic and neuroimaging variables (54 in total). See Appendix 8.1.6.3 Automatic linear modelling for details of all the variables entered into the models.

3 Chapter 3: How does the reading network of Central Alexia participants differ from that of healthy control participants?

3.1 Abstract

This was the first analysis of the effective connectivity in the reading network of Central Alexia (CA) participants using magnetoencephalography. It aimed to explore the reading network of CA participants and how this network differed to that of healthy controls

The reading network of 23 patients with CA was compared to that of 10 healthy controls. Participants were presented with written stimuli consisting of Words, meaningless symbol strings (False Fonts) and common Names. Name trials served as catch trials and were removed prior to analysis. Evoked response potentials within the first 300ms post stimulus onset were modelled. The effective connectivity between left and right occipital (OCC), ventral occipitotemporal (vOT) and inferior frontal (IFG) sources were estimated using Dynamic Causal Modeling.

As expected, the reading network of control participants was left-lateralised. In contrast, CA participants demonstrated a bilateral reading network. In CA patients stronger feed-back connections within the left hemisphere from IFG to vOT and from vOT to OCC for Words over False Fonts were observed. Contrary to control participants, within the right hemisphere, a stronger self-connection for Words was observed in the right IFG and stronger forward connections for Words were observed between right OCC to vOT and IFG in CA patients. This supports literature suggesting a bilateral model of language processing following aphasic stroke damage.

3.2 Introduction

It is hoped that a greater understanding of the neural network that supports the residual reading ability of patients with Central Alexia (CA) will help us provide better information for patients and design more effective therapies. I aimed to investigate this network by comparing MEG data collected while reading, from patients with CA and healthy, age-matched control subjects (data collected by

Woodhead et al. [2014]). This was the first study to explore reading in CA patients using a causal network analysis.

Healthy word reading involves a number of brain regions that interact as a network, including: left and right frontal gyri (IFG); left and right supramarginal gyri; left ventral occipitotemporal region (vOT); and left occipital region (OCC; P. L. Cornelissen et al., 2009; Dehaene et al., 2001; Dehaene, Cohen, Morais, & Kolinsky, 2015; Oberhuber et al., 2016; Price, 2012; Richter, Miltner, & Straube, 2008; Wheat et al., 2010). A dorsal contribution has also been identified (Hoffman et al., 2015; Levy et al., 2009; Oberhuber et al., 2016; Price, 2012; Seghier, 2013; Taylor et al., 2013), however, this could not be considered in the current research as imaging nodes for this location (e.g. the angular gyrus or posterior superior temporal sulcus) could not be identified for all participants.

In recovery from aphasia, the roles of the left and right inferior frontal regions have been debated. While some studies have identified the perilesional (i.e., left hemisphere) frontal regions as supporting reading recovery following stroke (Abel, Weiller, Huber, & Willmes, 2014; Abel, Weiller, Huber, Willmes, & Specht, 2015; Bonilha et al., 2016; Jobard et al., 2003; Pillay et al., 2017; van Hees et al., 2014), others have found that signals from perilesional regions may interfere with functional adaptation of reading offered by right hemisphere homologues (Crosson et al., 2007). In the present study I aimed to further illuminate the role of the left and right IFG, vOT and OCC regions in reading following aphasic stroke.

Successful reading aloud requires the effective processing of visual information and relating it to existing semantic and phonological knowledge (Price, 2018). Accordingly, it involves the interaction of a number of different cortical regions within a network to transform print to sound and/or meaning. In the Interactive Account of reading (Price & Devlin, 2011), existing phonological and semantic representations (stored or accessed by higher regions of the cortical hierarchy) interact with early processing of orthographic stimuli along the ventral visual stream. These top-down predictions, which are instantiated via backwards connections, constrain the processing of (bottom up) sensory information. If the predictions are inaccurate, the lower order region (e.g. the ventral occipitotemptoral or occipital regions) send a prediction error signal to the higher

order region (e.g. inferior frontal gyrus), in order for it to update its ‘knowledge’ of the world and make more accurate future predictions (Friston, 2010).

In contrast to the Interactive Account, the Local Combination Detector (LCD) model proposes a largely feed-forward model of reading. Inspired by direct neuronal recordings obtained in non-human primates, it suggests that neurons are tuned to progressively larger fragments of the word according to their locations along the ventral visual pathway (Cohen & Dehaene, 2004; Dehaene & Cohen, 2011). For example, neurons in bilateral V1 may be sensitive oriented bars, whereas neurons in the left occipital temporal sulcus may be tuned to local bigrams. This model of reading primarily explains the ‘front end’ of visual word recognition, and does not detail the top-down influence of semantic and phonological knowledge. Given that the role of semantics and phonology is not detailed, it is assumed that their influence occurs later on and is largely separable from word recognition.

The potential role of left IFG, and its influence on the rest of the reading network within CA patients, is poorly understood. While increased IFG activation has been associated with improved aphasia recovery following stroke (Kiran et al., 2015; van Hees et al., 2014), it has also been associated with generating unreliable top-down signals (Cope et al., 2017). Woodhead et al., 2013 demonstrated that iReadMore resulted in stronger feed-back connections from the left IFG to left vOT in participants with Pure Alexia (PA). Although lesions in the PA participant group are more posterior, a similar mechanism for functional recovery may occur in the CA participants.

This study investigated the roles of right and left hemisphere IFGs, vOT and OCC in the early stages of word reading in CA patients. This was performed using effective connectivity analysis of MEG data when participants viewed Words and False Fonts (visual stimuli matched for visual complexity, but devoid of orthographic, phonological or semantic content). The results are explored within the IA and LCD models. Neither model makes explicit predictions regarding how the reading network would respond to CA damage, but I would tentatively hypothesise the following:

Local Combination Detector Model

- This model provides a feed-forward account of word recognition. Primary visual areas and the vOT will be spared in the CA participant group; thus it is expected that activity in the OCCs and between the OCCs and vOTs will mirror that of controls.

Interactive Account of Reading

- Deviations from the healthy reading network could be observed at any level within the CA network, due to the interactive nature of this account of reading. Patients with CA have damage to central semantic or phonological representations (or their connections to the orthographic system), so we might expect to see differences between patients and controls in the self-connection strengths in the left IFG or right IFG (or their top-down connections to the OCC or vOT). However, the long-term interactive effects of this damage in chronic aphasia may be to change the functioning of the OCC and vOT areas as well.

3.3 Methods

I have briefly outlined the main methods used in this investigation, but for full details please see the Methods chapter of this thesis (p. 73). Twenty-three CA participants and ten healthy controls subjects participated in the MEG component of the study. The groups did not differ significantly in age, $t(31)=0.90$, $p=0.38$.

CA participants completed an MEG scan before their first block of iReadMore training. The control group data was collected previously at a single time point by Dr Woodhead (Woodhead et al., 2014). Control subjects did not undergo any subsequent training. All participants were seated in an MEG scanner and asked to silently read Words, symbol strings (henceforth referred to as False Fonts), and common names (e.g. John, Sarah). Participants were asked to press a button when they saw a name. These catch trials ensured that participants were attending to all the stimuli, and were removed from the analysis.

Variation Bayesian Equivalent Current Dipole modelling source localisation was used to individually identify the left and right OCC, vOT and IFG source solutions for each participant. Please see *Figure 22* for dipole locations.

To investigate the effective connectivity within the two groups, a six source model was estimated (left and right OCC, vOT and IFGs) using Dynamic Causal Modelling (DCM). Input was specified through the right and left OCCs. Effective connectivity for False Fonts formed the A matrix (the endogenous connections strength for visual stimuli resembling letters). The estimated modulation of this model for Words formed the B matrix.

In Analysis 1, Bayesian model averaging was performed on the two groups separately. A proportion test then identified connections that were significantly modulated by stimulus type (Words vs False Fonts) within each group. In Analysis 2, I compared connections that were significantly modulated by Words vs False Fonts in both groups to see if this modulation was significantly different across the groups.

A post-hoc correlational analysis was performed on significantly modulated connections within the CA group with the aim of further investigating the relationship between changes in connection strengths in the brain and reading performance post-stroke (Analysis 3). This is a simple way of investigating between-subject variability, rather than treating all patients as the same, which the preceding group analysis does. The connection strengths for Word stimuli (B matrix posterior means) were extracted for each participant with CA. The normalised log values for each connection were correlated against each participant's baseline word reading accuracy and reaction time using Spearman's correlations.

The DCM assesses connectivity between regions. I assessed the structural integrity of four potential white matter tracts that could correspond with the connections involved in the DCM (Table 4); the SLF, ILF, IFOF and Uncinate. The exact anatomical connections of each tract are still being uncovered (Ashtari, 2012; Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Forkel, Thiebaut de Schotten, Kawadler, Dell'Acqua, & Danek, 2014; Martino & De Lucas, 2014). These tracts may be involved in the ventral reading stream that is estimated using the DCM. It is for this reason that I wanted to investigate their integrity.

The IFOF connects the OCC, vOT and IFG and may correspond to the connection between OCC and IFG or vOT and IFG, as well as OCC and vOT. An indirect reading route may be provided by the ILF and the Uncinate. The ILF runs

along the ventral reading route, connecting the OCC, vOT and vATL (Bajada, Lambon Ralph, & Cloutman, 2015), this would correspond to the connection between the OCC and vOT. The uncinate fasciculus connects the temporal pole with the inferior portion of the IFG. This may serve to connect the vOT with the IFG. Finally, the SLF would form a key part of the dorsal reading pathway, connecting temporal, parietal and frontal regions. This would correspond to a connection from the vOT to IFG through a dorsal pathway.

3.4 Results

3.4.1 Task results

All participants completed the in scanner name detection task. The median hit accuracy for CA participants and healthy control participants was 90.00% (, IQR=83.12-95.0) and 100% (IQR=89.13-100), respectively. The median number of false alarms per participant was 8.97% for CA patients (SD=19.96, IQR=4.77-11.04) and 0.00% for healthy control participants (IQR=0-2.7).

3.4.2 MEG results

The M170 peak was found in CA participants with an average latency of 188ms (range: 158 – 231 ms) and in control participants at 166ms (range; 153 - 193ms). The average peak amplitude for each group was 36.75fT (range: 15.02 -58.43fT) and 48.65fT (range 20.88- 96.70fT) respectively. There was a significant difference between groups in peak latency ($t(27)=3.80$, $p<0.01$ but not amplitude ($t(27)=1.47$, $p=0.17$; 95. There was a significant correlation between the latency of the M170 peak and participants' baseline word reading test reaction time $r=415$, $p<0.05$.

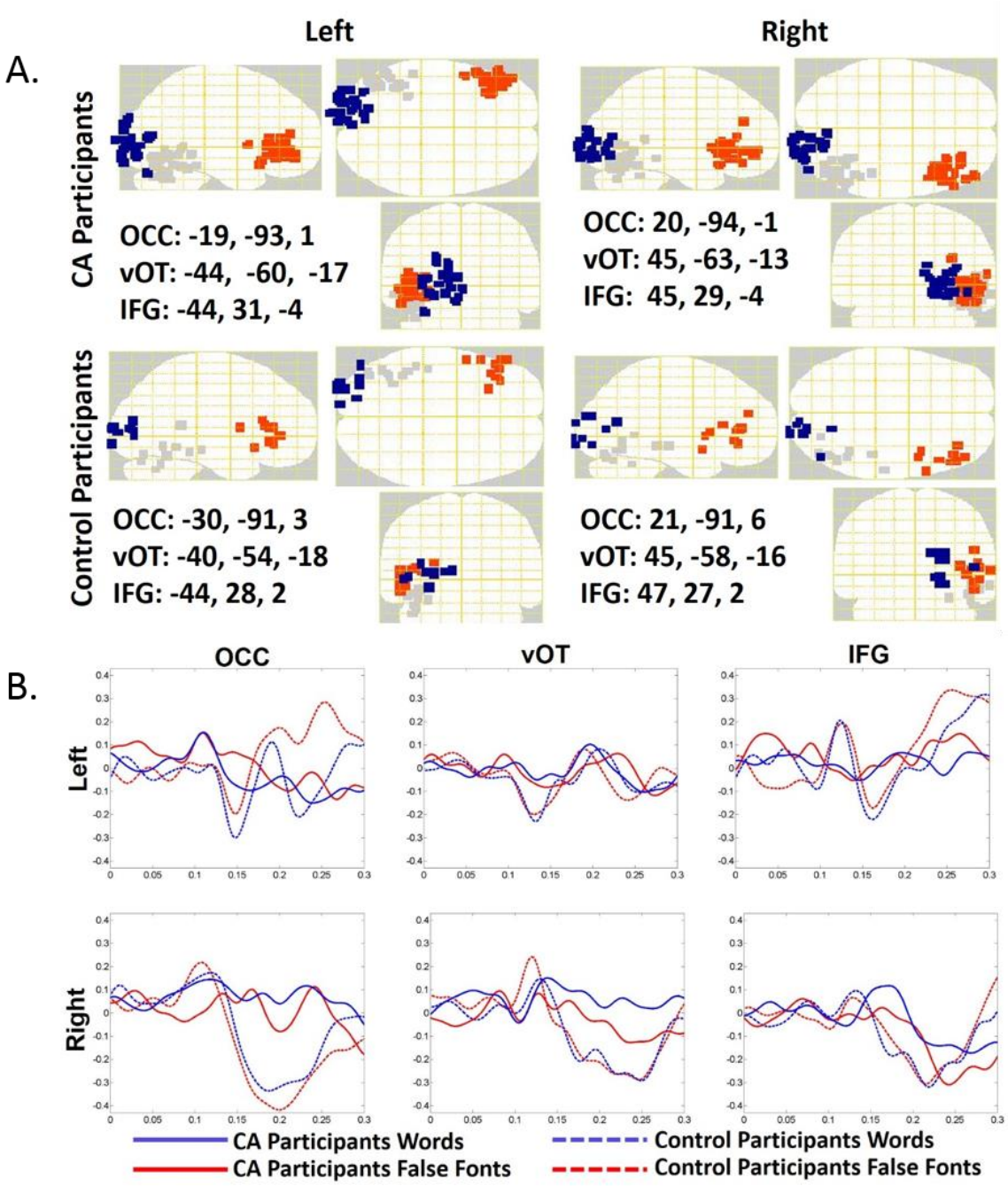

Figure 22 A. Winning dipole locations for Central Alexia (CA) participants (top row) and Control participants plotted on a glass brain in MNI space. Each point represents a subject, with winning dipole locations for the right and left occipital (OCC; blue), ventral occipitotemporal (vOT; grey) and inferior frontal gyrus (IFG; red). Group means of the winning coordinate locations are given. B. Normalised group mean power (fT), plotted against time (0-300ms) for each of the dipole location. Mean power when CA (solid line) and control (dashed line) participants were viewing words (blue) and False Fonts (red).

The average ERP data is reported in Figure 22b and ERP data for each participant, at each source, for each condition is overlaid in Figure 32 of the appendix. Figure 32 shows a high degree of variability between False Fonts and Words in control participants within left OCC and left IFG within the 200-300ms time window. Overall, it could be argued that the plots in Figure 22 appear to show less activity for CA patients compared to controls, especially in left IFG. This finding would be at odds within the DCM analysis, which showed greater levels of modulation for Words compared to False Fonts within the reading network of the CA patients compared to controls. However, as shown by Figure 32, there is a high degree of variability in the patient data that is not captured within the ERP plots displayed in Fig 22. The DCM relies on a within subject contrast between Words and False Fonts, which is then averaged across participants at the group level BMAs. The data presented in the source plots shows the average activity across subjects for each condition. This may hide some of the variation in responses between Words and False Fonts within participants.

3.4.2.1 Analysis 1: Control group reading network

Figure 23 displays the results of the effective connectivity strength modulations for Words compared to False Fonts in control participants. The colours indicate if the posterior means are significantly different from 1, indicating a significant difference in the modulation of connectivity strength. The posterior means of significantly modulated connections are displayed in Table 3.

3.4.2.2 Control group: Connections that were stronger for Words than False Fonts

The reciprocal connections (forwards and backward) between the left OCC and left vOT were stronger for Words than False Fonts. The connection from the right OCC to left OCC was also stronger for Words compared to False Fonts.

3.4.2.3 Control group: Connections that were stronger for False Fonts than Words

The self-connections at the left and right occipital and the right vOT sources demonstrated significantly stronger connections for False Fonts compared to Words. The self-connection parameters model the within-region connectivity

between the three cell sub-populations, and therefore reflect the gain or sensitivity of that region to an input. A stronger self-connection represents increased neuronal firing in response to postsynaptic stimulation than a weaker self-connection with the same level of stimulation. The connections from the left IFG to left vOT showed stronger connections for False Fonts than Words.

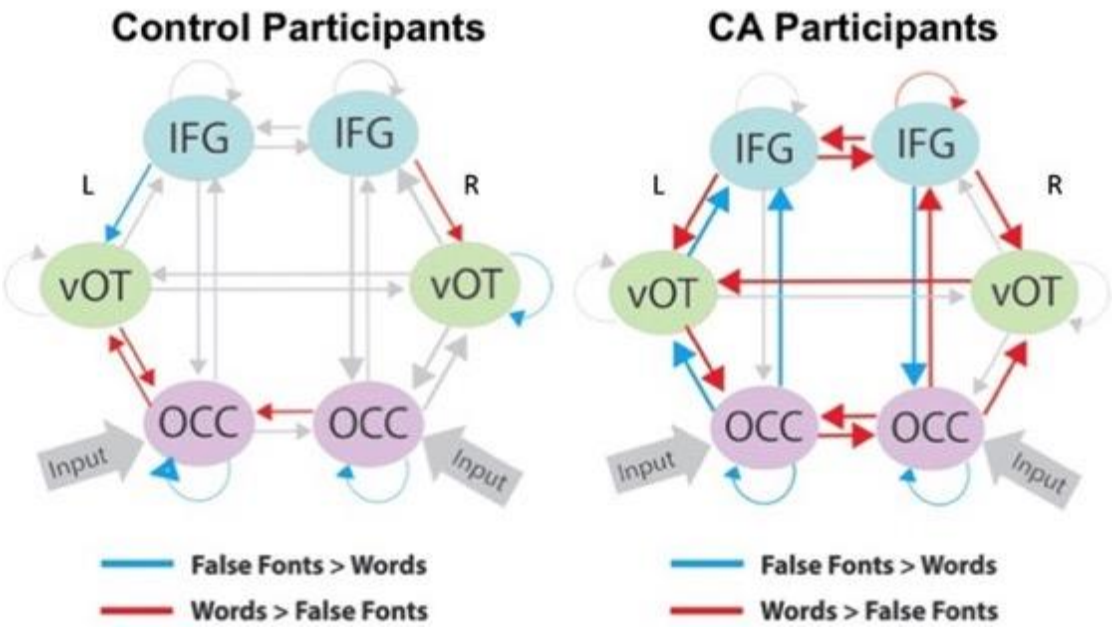

Figure 23 The effects of stimulus type on connection strength for Control participants (left, N=10) and Central Alexia participants (right, N=23). Results of the DCM analysis in time-window 1-300ms. Red arrows represent stronger modulation of connections for Words compared to the baseline stimuli (False Fonts) (P>0.9). Blue arrows represent a weaker modulation for Words compared to False Fonts (P>0.9). Grey arrows indicate a non-significant modulatory effect. See Table 3 for connection strength values.

Table 3 Posterior means and exceedance probabilities for the connections that were significantly stronger for words (posterior mean>1) or weaker for words (posterior mean <1) that would be expected by chance.

	Posterior Mean	Exceedance Probability
Control participant		
Words>False Fonts		
Left OCC to left vOT	1.12	0.995
Right OCC to left OCC	1.22	>0.999
Left vOT to left OCC	1.09	0.983
Right IFG to right vOT	1.12	0.994
False Fonts>Words		
Left OCC self-connection	0.92	<0.001
Right vOT self-connection	0.92	<0.001
Left IFG to left vOT	0.92	0.058
CA participants		
Words>False Fonts		
Left OCC to right OCC	1.06	0.942
Right OCC to left OCC	1.14	>0.999
Right OCC to right vOT	1.04	0.930
Right OCC to right IFG	1.10	>0.999
Left vOT to left OCC	1.12	>0.999
Right vOT to left vOT	1.20	>0.999
Left IFG to left vOT	1.07	0.978
Left IFG to right IFG	1.06	0.942
Right IFG to right vOT	1.06	0.952
Right IFG self-connection	1.02	0.912
False Fonts>Words		
Left OCC self-connection	0.98	<0.001
Left OCC to left vOT	0.88	<0.001
Left OCC to left IFG	0.96	0.062
Right OCC self-connection	0.91	<0.001
Left vOT to left IFG	0.87	<0.001
Right vOT to right OCC	0.90	0.003
Right IFG to right OCC	0.92	0.006

3.4.3 Analysis 1: CA participants reading network

3.4.3.1 CA participants: Connections that were stronger for Words than False Fonts

A distributed set of connections were significantly stronger for Words compared to False Fonts. In the left hemisphere, these included the backward connections from IFG to vOT and from vOT to OCC. In the right hemisphere, the following connections were significantly stronger for Words compared to False Fonts: from OCC to IFG, from OCC to vOT and the backwards connections from IFG to vOT. The self-connection within the right OCC was also stronger for Words. Five of the inter-hemispheric connections were stronger for Words than False Fonts, these included the reciprocal connections between the OCCs and IFGs and from the right vOT to left vOT.

3.4.3.2 CA participants: Connections that were stronger for False Fonts than Words

Similarly to the control participants, the self-connections of the left and right occipital regions were stronger for False Fonts than Words (see *Figure 23*). The forwards connections between the left OCC and left vOT and between left OCC and left IFG were negatively modulated for Words; that is, the connection strength was stronger for False Fonts than Words. The connection from left vOT to left OCC was stronger for False Fonts than Words. In the right hemisphere, only the backward connection from right IFG to right OCC was significantly modulated in favour of False Fonts.

3.4.4 Analysis 2: Between-group analysis of the reading networks

3.4.4.1 Significant between group differences in within-group significantly modulated connections

Two connections showed significant modulation in opposing directions in the two participant groups. Firstly, the forward connection from left OCC to left vOT was significantly stronger for Words than False Fonts in control participants, while the opposite was true in the CA participants (see **Error! Reference source not found.**). Secondly, the backwards connection rom left IFG to left vOT was

significantly stronger for Words than False Fonts in CA participants and significantly stronger for False Fonts in control participants.

In both groups the self-connections within left and right OCC was stronger for False Fonts than Words. However, this was to a significantly greater extent in controls compared to CA participants in the left hemisphere and to a significantly greater extent for CA participant then controls in the right OCC.

3.4.5 Analysis 3: Correlations between significantly modulated connections and word reading accuracy

The aim of this analysis was use word reading performance obtained outside the scanner to indicate if each significantly modulated connection was adaptive or maladaptive. As the data was not normally distributed a Spearman's correlation was conducted. No significant correlations were identified even at an uncorrected, $p < 0.05$ threshold.

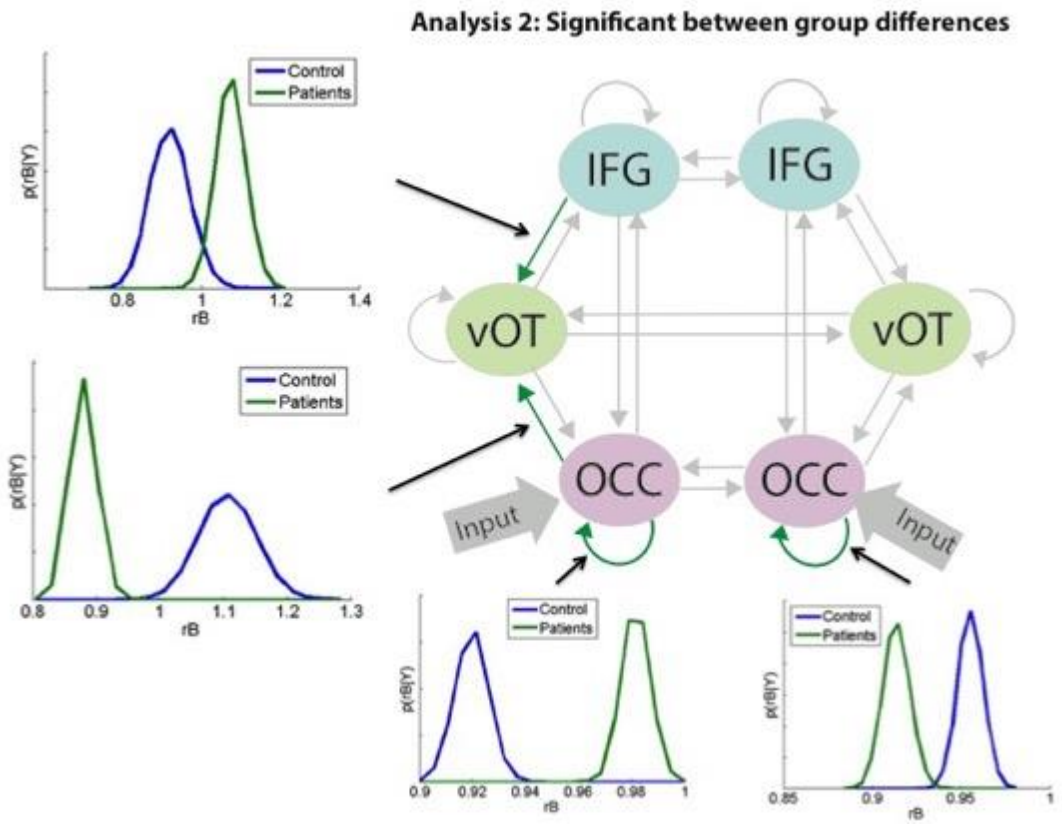

Figure 24 Highlighted connections that show a significant within group and between group difference. Line graphs of the distribution made of the posterior mean and standard deviation for each connection indicate the direction of the connection modulation in the CA (green) and control (blue) participant groups. Modulation values on the x-axis >1 indicates a stronger connection for Words compared to False Fonts, whereas values <1 indicate weaker connections strengths for words compared to False Fonts. *Table 4 Percentage of damaged voxels in four major white matter tracts for each participant*. White matter tracts identified using the John Hopkins University White Matter tracts Atlas. IFOF=Inferior fronto-occipital fasciculus; ILF= Inferior longditudinal fasciculus; SLF=Superior longditudinal fasciculus; Unc= uncinate fasciculus.

	Damaged to voxels (%)			
	IFOF	ILF	SLF	Unc
P01	57.79	38.56	97.02	43.47
P02	60.49	50.55	95.08	62.59
P03	28.56	38.16	39.53	0
P04	10.85	12.76	73.99	0
P05	48.97	90.04	48.21	37.88
P06	41.71	36.53	80.81	12.03
P07	44.49	45.1	57.58	73.30
P08	0.82	0	0.08	0.28
P09	74.93	90.53	99.67	61.93
P10	41.89	60.99	49.04	0
P11	21.73	28.00	21.72	0
P12	19.88	13.21	35.10	5.49
P13	16.64	13.33	73.96	1.99
P14	0.07	0	19.42	0
P15	51.39	61.97	71.15	69.13
P16	39.90	47.18	89.51	4.17
P17	11.34	11.30	44.78	0.95
P18	36.59	43.36	54.49	0
P19	25.68	52.58	64.17	24.43
P20	72.23	41.45	97.66	64.3
P21	67.53	73.99	98.11	18.94
P22	3.52	4.02	21.17	0
P23	46.34	32.26	91.99	37.03
Mean (SD)	35.8 (22.2)	38.52 (25.7)	61.92 (29.2)	22.52 (26.6)
Range	0.07 – 74.9	0 – 90.53	0.08 – 99.7	0 – 73.3

3.5 Discussion

This study aimed to investigate the early stages of visual word processing in a group of chronic CA participants, and how they deviated from those of control participants. Differences between Word and False Font processing were more widely distributed in CA participants than in control participants. CA participants demonstrated increased top-down influence for Words over False Fonts via the

vOT in both left and right hemispheres. Additionally, the self-connection within the right IFG was stronger for Words compared to False Fonts, as were the feed-forward connections from right OCC to vOT and IFG. These results are discussed within the context of the IA and LCD models of reading.

3.5.1 Central Alexia reading network: LCD account

I will first explore the reading network of CA participants within the rubric of the LCD reading model. According to the LCD model of reading, orthographic stimuli is processed in a feed-forward direction along the ventral visual stream (Dehaene et al., 2005). Semantic and phonological processing is assumed to occur later. Specific predictions regarding the changes to this reading network with CA stroke damage are not explicitly detailed. Stroke damage in CA participants occurs anterior to the ventral visual stream. Therefore, it would be expected that the feed-forward processing of orthographic stimuli would be preserved.

The connection strengths within the ventral visual regions, from right OCC to left OCC and from left vOT to OCC mirrored that of those observed in healthy controls and thus were in line with LCD predictions. However, unlike control participants the connection from left OCC to vOT was stronger for False Fonts compared to Words. This finding could be contrary to the LCD prediction.

According to the LCD account, it would be expected that disruption within the reading network of CA participants would occur upstream, after orthographic processing, potentially between vOT and IFG or within the IFG. The connection from left vOT to left IFG was weaker for Words. If the nature of processing along the visual ventral stream were feed-forward, weaker connection strengths for Words may be expected, due to the potential damage to this connection. However, given that the feed-forward connection from OCC to vOT was also weaker for Words than False Fonts, this suggests that there is less activation from the ventral visual regions to pass forward to the more anterior regions.

3.5.2 Central Alexia reading network: IA account

The results described above indicate that CA is a network disorder (Hartwigsen & Saur, 2017). Word reading was interrupted in regions distal to the lesion including the connection between OCC and vOT. All but three participants had

damage to the left inferior fronto-occipital fasciculus and inferior longitudinal fasciculus (Table 3). I would argue that network level damage is easier to interpret within the IA of reading, which predicts the influence of higher order regions on visual word processing.

The IA details word reading in the context of the cortical hierarchy. It stipulates that word reading is an outcome of predictions from higher-order regions (e.g. IFG) constraining the processing of visual sensory inputs in the lower-order regions of the ventral pathway (e.g. OCC and vOT). It does not explicitly predict what would happen to the model after CA damage. Research into post-stroke language reorganisation has suggested that that the damaged word reading network would be supported by either increased activation within the perilesional left IFG or the right hemisphere homologue (Crosson et al., 2007; Hartwigsen & Saur, 2017; Turkeltaub et al., 2011). Due to its view of reading as a network disorder, compensatory changes in connections distal to the lesion are more readily interpretable with this model.

Greater left hemisphere feed-back was observed from left IFG to vOT for Words over False Fonts in CA participants. As word reading aloud is slower in participants with CA this may reflect the early top-down feed-back observed in control participants within the 0-200ms window of Woodhead et al., (2014). Early IFG involvement in visual word recognition been demonstrated within the first 200 ms of word reading in healthy readers (P. L. Cornelissen et al., 2009; Wheat et al., 2010). It is surprising that in the current analysis control participants did not show a stronger connection from left IFG to vOT in for Words in comparison to False Fonts. In the Woodhead et al. (2014) analysis, increased feed-back was observed in the 0-200ms time window, but was not significant in the 0-300ms time window. The constraints placed on the vOT from the IFG may have been eclipsed in this larger time window, as this is relatively late in the word processing for healthy controls (see *Figure 22*).

Feed-back from left IFG has been associated with improved aphasia recovery following stroke (Kiran et al., 2015; van Hees et al., 2014). Others have argued that the IFG could be providing unreliable top-down signals (Cope et al., 2017). If this were the case, it would be expected that the error signal from vOT to IFG

would be stronger for Words, however, the opposite is observed within the current data.

Both controls and CA participants demonstrated a stronger top-down signal was observed for Words over False Fonts between the left vOT and OCC. However, the feed-forward signal from left OCC to vOT is significantly different between groups; False Fonts>Words in CA participants and Word>False Fonts in control participants. This effect in CA patients is compatible with a version of the LCD if one allows it to be modified by the IA model. If top-down influences are reduced due to damage further upstream of vOT, then one would expect greater error signals being passed forward from OCC to vOT. While the LCD model predicts no changes in connectivity at this level, if some effect of higher-regions in CA word reading were allowed for, then it would probably look like this. The stronger feed-forward connection from left OCC to vOT for Words compared to False Fonts in healthy readers may be an influence of semantic and phonological representations (P. L. Cornelissen et al., 2009; Hauk, Coutout, Holden, & Chen, 2012; Munding, Dubarry, & Alario, 2015; Wheat et al., 2010), as the time window (0-300ms) used in this experiment includes late processing for healthy readers. This allows for Word stimuli to activate a number of possible candidate representations due to neighbourhood effects whereas these relationships are not established between meaningless False Fonts (Perea & Pollatsek, 1998). These neighbourhood effects cause identity conflict that would results in an increased feed-forward error signal.

Increased right IFG involvement after stroke has been reported elsewhere in the aphasia literature (Crosson et al., 2007; Hope et al., 2017; Skipper-Kallal et al., 2017; Turkeltaub et al., 2011) and is observed here in the stronger self-connection for Words over False Fonts (in CA participants). Along with the increased inter-hemispheric connections, at all levels of the hierarchy, this suggests an increased role of the right hemisphere in reading in CA participants. Price and colleagues (Price et al., 1998) observed bilateral patterns of activation in the inferior frontal regions of two patients with deep dyslexia during word reading aloud. An MEG connectivity study investigating the effects of auditory comprehension training in a group of chronic aphasia participants (Woodhead et al., 2017) revealed increased inter-hemispheric connectivity between higher levels of the auditory cortex for more severe participants. The bilateral reading

network observed here may reflect the variability in the CA sample. Larger lesions have been associated with increased use of the right IFG in post-stroke aphasia (Skipper-Kallal et al., 2017). However, others have argued that use of perilesional left hemisphere regions is more effective (Heiss & Thiel, 2006). This is a potential explanation of the bilateral reading model observed here at the group level.

The IA model does not specify the role of the right hemisphere. However, the IA model and predictive coding models of the brain in general (Friston, 2008, 2010), do describe how the network may be adaptive. This is through the transmission of a feed-forward prediction error signal, which serves to update long-term representations upon which future predictions are made. The stronger feed-forward connections from right OCC to vOT and IFG for Words indicate plasticity for orthographic stimuli processing within the right hemisphere, which has been demonstrated elsewhere (Fischer-Baum et al., 2017). According to the IA account the modulation of the forward connections from right OCC to vOT and IFG would represent prediction errors for Words (Kiebel et al., 2006), which may lead to an update of the representation of words within the right IFG. These findings are incompatible with the LCD model. If orthographic processing is achieved by specifically tuned neurons along the left ventral visual stream it would not be expected that the right hemisphere would be able to support this function.

The feed-back from right IFG to OCC was weaker for Words. Healthy controls have demonstrated increased use of the right hemisphere for processing non-orthographic stimuli (Bokde, Tagamets, Friedman, & Horwitz, 2001; Maurer, Blau, Yoncheva, & McCandliss, 2010; Tagamets, Novick, Chalmers, & Friedman, 2000). This finding, with the increased prediction error for Words within the right hemisphere, and self-connection strength in right IFG, may represent a reading network in flux, with the right hemisphere taking an increased role in processing orthographic stimuli, with less processing of non-orthographic stimuli.

3.5.3 White matter connections

The SLF demonstrated the largest degree of damage (6 participants had over 90% damage to this connection). This corresponds to the posterior lesions observed within the sample, and the difficulties I experienced in finding a suitable dorsal dipole for all the participants. The Uncinate is the shortest of the tract

measured, and also demonstrated the least damage, with over half of the participants demonstrating less than 10% damage in this tract. This might also be because an inclusion criteria for the study was at least partial sparing of the IFG. The degree of damage to the IFOF corresponded to the degree of damage observed in the ILF; six of the participants had over 50% damage to the IFOF, of those four also had greater than 50% damage to the ILF. This is reflected in the mean damage to the IFOF (mean=35.2) and the ILF (mean= 38.52). However, these are long tracts and the precise location and degree of damage at any one point is unclear. Additionally, damage distal to one region may still affect its ability to pass information through the damaged area. Without individual DCM is it difficult to assess how well the DCM data and the results of the damaged voxels complement one another. However, this is something to consider for future research to ensure that the results of the DCM are plausible.

3.5.4 Between group differences

As well as identifying the reading networks within participant groups, I also sought to identify connections for which both group demonstrated significant within group modulation, but for which there was a significant between group differences (see **Error! Reference source not found.**). This is particularly important for connections which are modulated in the same direction in both groups, but to a lesser or greater extent between groups. This analysis identified the following connections: the backward connection from left IFG to vOT, the forwards connection from left OCC to vOT and both OCC self-connections. I have explored the between group connections from left IFG to vOT and from left OCC to left vOT with an interpretation of the connection strength modulation in opposing directions above. However, the self-connections within the right and left OCCs were weaker for Words in both groups, but to a significantly greater extent for CA participants in the right IFG and to a significantly greater extent for control participants within the left IFG.

Self-connections are a measure of gain control. This means for the same level of input, the neural output from the OCCs will be weaker for Words than False Fonts (Kiebel et al., 2007). In accordance with the IA model of reading, this may reflect the familiar nature of Words to the visual system, in comparison to False Fonts. As a consequence, Words require less sustained visual processing. The group

differences between the right and left OCC are challenging to explain. Within the left OCC, the healthy control participants may be better able to identify Words quickly in comparison to CA participants, leading to greater activation for the unusual False Fonts described above. The right OCC may have an increased role in orthographic processing in CA participants. In a fMRI case study of a CA participant, representational similarity analysis showed increased use of the right vOT region specifically for processing orthographic visual stimuli compared to healthy controls (Fischer-Baum et al., 2017). If a similar process took place within the CA participants, it may develop a preference for processing word stimuli as opposed to unfamiliar False Fonts in the right OCC, and thus shows greater processing for False Fonts.

There is a possibility that the differences in the reading networks between the CA patient group and the control group were driven by pre-morbid individual differences. As reading is a taught learnt skill, there is variability in the proficiency of readers, which may affect how reading is organised in the brain. Lesions in similar locations affect individual stroke patients differently (Hillis & Tippett, 2014; Watila & Balarabe, 2015). Premorbid reading ability may also impact the involvement of the vOT: cases of pure alexia with and without prosopragnosia may be due to pre-morbid variation in language lateralisation (Behrmann & Plaut, 2014). Individual differences are particularly apparent when reading exception words (via O>S>P pathway). These individual differences have been cited as the reason that some participants with semantic dementia may demonstrate surface dyslexia when a similar degree of semantic impairment is present in both patients (Woollams et al., 2007). The triangle model of reading predicts there will be individual variability in the reliance on the O>P and O>S>P routes to reading (Hoffman et al., 2015). In a study with 24 healthy adults, semantic reliance (difference in performance between reading low imageabiltiy with consistent vs inconsistent spelling to sound correspondences) correlated with activation in the ATL (Halai, Woollams, & Lambon Ralph, 2017). However, while it cannot be ruled out that individual differences may play a role in the between group differences observed between the CA and control participant's it seems unlikely that the two groups would differ significantly in their pre-morbid reading networks by chance. It would be expected that individual differences would be present in both groups, and would be overcome by the group level analysis. It is possible

that by selecting CA patients with posterior MCA lesions, they may have been pre-morbidly more reliant on the dorsal stream to reading (as this is now damaged) and rely less on the ventral stream modelled in this analysis. If this were the case, it could be predicted that these participant's would use less of their ventral reading network, and thus we would expect to see more modulation in left hemisphere connections within the control group, however, this is not observed.

There is a possibility that the apparent between group differences in the reading network were driven by the task, rather than a fundamental abnormality within the reading network of CA participants. The CA patients are likely to have been slower or unable to read the words, hence the type of processing within the 1-300ms time window may have been different between the CA and the control group. The catch trial design was used to ensure that participants did read the words, but the results showed between group differences in task performance. The IFG forms part of the domain-general network (Duncan, 2010; Fedorenko, Duncan, & Kanwisher, 2012; Geranmayeh, Brownsett, & Wise, 2014). This network is sensitive to task demands. There is a possibility that CA patients found the MEG task more challenging and this is driving the differences between groups, rather than differences in the neurological processes associated with word reading. While this might be true, efforts were made to make the task required of participants low in terms of cognitive demand.

3.6 Conclusion

A bilateral reading network was identified for CA participants. This is in contrast to the predominately left lateralised network observed within Control participants. The reading network of CA participants indicated that the right hemisphere might be supporting the left hemisphere-reading network. Connections at the bottom of the CA reading network (from OCC to vOT) were different from healthy control participants. However, I do not know whether these changes in connection were due to damage or compensations as none of the connection strengths were correlated with reading ability. My findings could be contrary to the predictions of the LCD model of reading, which provides a feed-forward account of orthographic processing. Further work is required to explore how the LCD and IA models of reading would respond to CA damage and to validate which model is most supported.

4 Chapter 4: The effects of iReadMore training and A-tDCS on word reading accuracy and speed in CA participants

4.1 Abstract

Central alexia (CA) is an acquired reading disorder co-occurring with a generalised language deficit (aphasia). I tested the impact of a novel training app, 'iReadMore', and anodal transcranial direct current stimulation of the left inferior frontal gyrus, on word reading ability in CA. The trial was registered on www.clinicaltrials.gov (NCT02062619).

21 chronic stroke patients with CA participated. A baseline-controlled, repeated-measures, cross-over design was used. Participants completed two 4-week blocks of iReadMore training, one with anodal stimulation and one with sham stimulation (order counterbalanced between participants). Each block comprised 34 hours of iReadMore training and 11 stimulation sessions.

Outcome measures were assessed before, between and after the two blocks. The primary outcome measures were reading ability for trained and untrained words. Secondary outcome measures included semantic word matching, sentence reading, text reading and a self-report measure.

iReadMore training resulted in an 8.7% improvement in reading accuracy for trained words (95% CI [6.0, 11.4]; Cohen's d = 1.38) but did not generalise to untrained words. Reaction times also improved. Reading accuracy gains were still significant (but reduced) three-months after training cessation.

Anodal transcranial Direct Current Stimulation (compared to sham), delivered concurrently with iReadMore, resulted in a 2.6% (CI[-0.1,5.3]; d=0.41) facilitation for reading accuracy, both for trained and untrained words.

iReadMore also improved performance on the semantic word-matching test. There was a non-significant trend towards improved self-reported reading ability. However, no significant changes were seen at the sentence or text reading level.

In summary, iReadMore training in post-stroke CA improved reading ability for trained words, with good maintenance of the therapy effect. Anodal stimulation

resulted in a small facilitation (d=0.41) of learning and also generalised to untrained items.

4.2 Introduction

Acquired disorders of reading may be a consequence of generalised language impairment. I refer to these disorders as CA (but see, e.g., Warrington & Shallice (1988; Ellis & Young, 2013) for a slightly different use of this term). CA encompasses phonological, deep and surface alexia (Leff & Behrmann, 2008). Patients with CA are slow to read, make frequent errors and have additional problems with spoken language. I tested two concurrent therapies aiming to improve word reading in patients with CA after left hemisphere stroke: (1) 'iReadMore', a novel reading therapy app, and (2) anodal transcranial direct current stimulation (A-tDCS) delivered to left inferior frontal gyrus.

According to the primary systems hypothesis and connectionist triangle model of reading (Plaut et al., 1996) CA may be due to damage to the phonological (P), semantic (S) or orthographic (O) system, or the connections between them; but see Coltheart and colleagues (Coltheart, 2006c; Coltheart et al., 2001) for a different theory of reading and the causes of phonological and surface dyslexia (also outlined in the introduction to this thesis, see Introduction section 1.1.3. Damage affecting phonology or the direct O-P mappings primarily impairs pseudoword reading (phonological dyslexia) (Crisp & Lambon Ralph, 2006; Patterson & Lambon Ralph, 1999) and causes semantic errors in more severe cases (deep dyslexia) (Crisp et al., 2011). Damage to the semantic system or the semantically (S) mediated O-S-P route impairs irregular word reading (surface alexia) (Patterson & Lambon Ralph, 1999; Woollams et al., 2007).

A number of therapies for CA have been tested, mostly in single case experimental designs (n=1). Attempts to retrain GPC rules or phonomotor processing have met with mixed success in phonological and deep dyslexia (Adair et al., 2000; Brookshire, Wilson, Nadeau, Gonzalez-Rothi, & Kendall, 2014; Conway et al., 1998; de Partz et al., 1986; Friedman et al., 2002; Kendall et al., 2003, 1998; M. Kim & Beaudoin-Parsons, 2007; Kiran et al., 2001; Mitchum & Berndt, 1991; Riley & Thompson, 2014; Stadie & Rilling, 2006; Yampolsky & Waters, 2002). Such sublexical approaches can be painstaking slow, but may

demonstrate some generalisation to untrained words. Conversely, lexical approaches, e.g. crossmodal paired associate learning, priming or semantic remediation, have proven effective in phonological, deep and surface alexia, but tend not to generalise (Friedman & Robinson, 2007; Friedman et al., 2002; Kurland et al., 2008; Ska et al., 2003).

iReadMore uses a crossmodal, lexical approach, pairing written (O), spoken (P) and pictorial (S) representations of words over multiple trials with adaptive difficulty. It aims to strengthen connections between O, P and S domains, hence has the potential to benefit all types of CA. If the word reading training is effective by improving the O-S-P representations of a word, then it is expected that this will be item-specific (improvements in reading accuracy and RT will not generalise to other, untrained words). Item specific effects are commonly observed within the anomia therapy literature (Webster et al., 2013). As the mappings between semantics and phonology are largely arbitrary a generalisation effect would not be expected (Howard, 2000; Marshall, Pound, Whitethomson, & Pring, 1990). For example, knowing that one furry domestic animal is called a CAT is no help to knowing that another is a DOG (Miceli, Amitrano, Capasso, & Caramazza, 1996). I hypothesised that iReadMore would improve reading accuracy for trained words, but like other lexical therapies, would not generalise to untrained words.

iReadMore is based on a prototype reported by Woodhead and colleagues (Woodhead et al. 2013). In that trial (in participants with pure alexia [PA]) functional imaging data indicated that training strengthened feed-back connections from left IFG to visual cortex. Hence, I hypothesised that A-tDCS delivered to left IFG during training may enhance feed-back and facilitate therapy effects. This tDCS montage delivered concurrently with language therapy has been shown to improve speech production in chronic post-stroke aphasia (Baker et al., 2010; Campana, Caltagirone, & Marangolo, 2015; Marangolo et al., 2011; Marangolo, Fiori, Calpagnano, et al., 2013); reading in pure alexia (Lacey et al., 2015); and spelling in primary progressive aphasia (Tsapkini et al., 2014). There have been no studies of tDCS in CA to date.

The effects of iReadMore and A-tDCS were tested in a repeated-measures cross-over design. Each participant received two four-week blocks of iReadMore

therapy, accompanied with either real (anodal) or S-tDCS. Change in reading ability for trained and untrained words after iReadMore training was assessed, and compared for real versus sham stimulation. A subset of the 50 most frequent English words ('Core' words), mostly low imageability function words, were trained in both blocks due to their importance for reading, and to test the hypothesis that words with low semantic content could also be trained using iReadMore.

4.3 Materials and methods

For full details of the iReadMore study see Methods section (pg. 73). A repeated-measures cross-over design with six Time-Points (T1-T6) was used (*Figure 9*). This included two four-week therapy blocks: Block1 from T3-T4 and Block2 from T4-T5. In a double blind design, half the participants (G1) received A-tDCS in Block1 and sham in Block2. Twenty-one patients (13 male; Table 1) with CA (subtypes; phonological (n = 11), deep (n = 9) and surface alexia (n=1).

During therapy blocks participants aimed to amass 35 hours of practice per block through independent use at home and three 40-minute face-to-face sessions per week (Monday, Wednesday and Friday), where iReadMore was administered concurrently with A-tDCS or S-tDCS. In each therapy block participants were trained on 150 words. A list of 50 high-frequency Core words was trained in both blocks.

At time-points T3-T6 participant's were tested on a subset of 90 from each of the following word lists; trained in Block 1, trained in Block 2 and a list of untrained words matched for linguistic properties. A subset of 30 Core words was tested at each time-point.

At time-points T3 to T6 the following tests were administered; a Written semantic matching test which aimed to assess changes in reading for meaning; a sentence reading task which aimed to capture potential generalisation of iReadMore training to the sentence level; the Neale test assessed generalisation of training to the text passage level and a test of sustained attention (cSART) measured changes in sustained attention. The written semantic matching task and sentence reading task contained stimuli from the following word lists; Trained in Block1, Trained in Block2 and Untrained.

4.4 Results

4.4.1 Lesion Overlay Mapping

The lesion overlay map (*Figure 25*) showed group damage throughout left perisylvian MCA territory. All patients had some anatomically spared tissue in left IFG. Adjacent pars opercularis and/or premotor cortex were damaged in 14 patients.

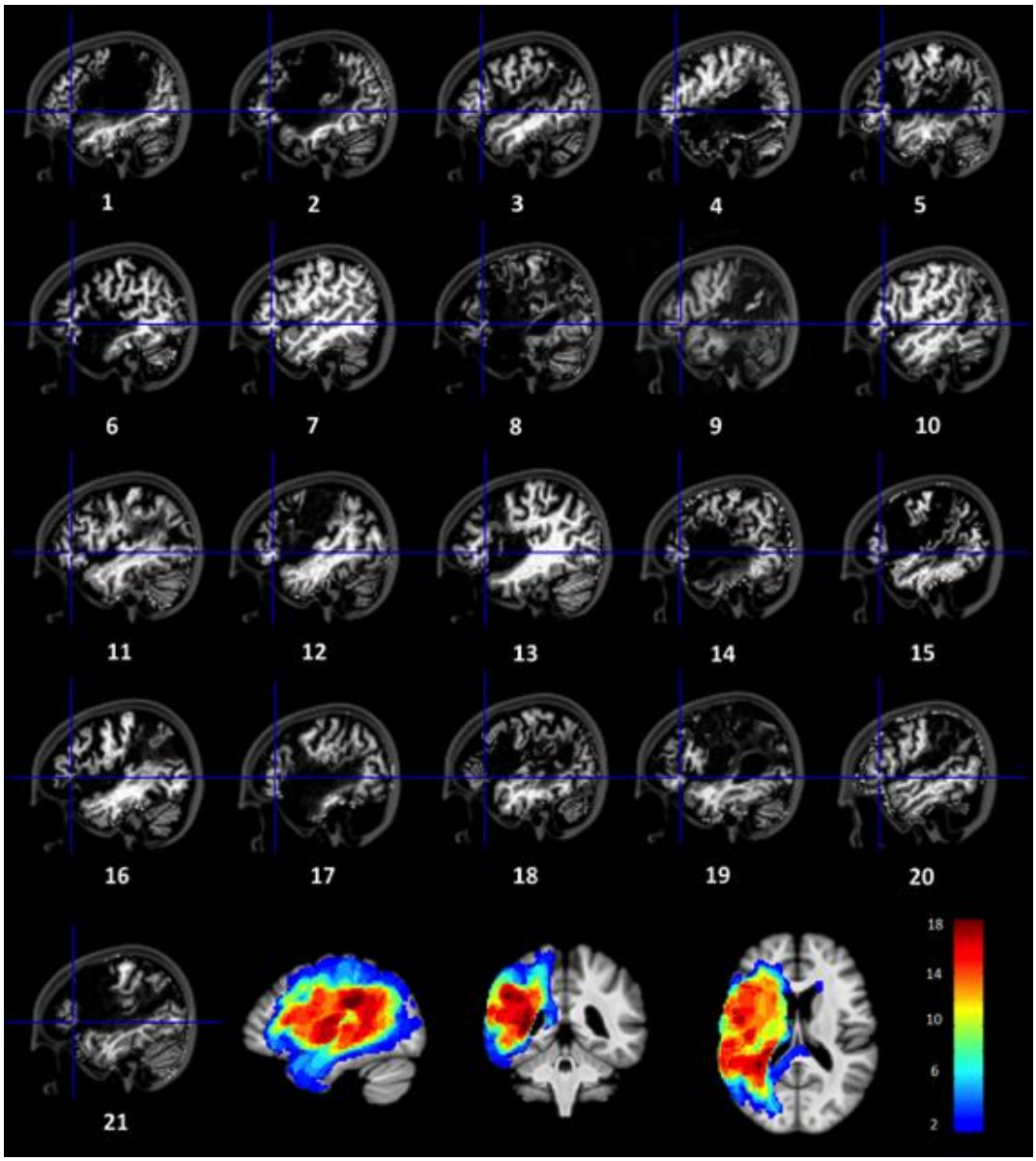

Figure 25 Participant structural MRI images and lesion overlap map. Crosshairs indicate the approximate location of the stimulation site. Bottom right tiles show the lesion overlay map with voxels where at least 2 patients had damage. The highest lesion overlap (n = 20) was seen in two areas: 1) the superior longitudinal fasciculus underlying the supramarginal gyrus; and 2) the junction of the superior

longitudinal, inferior longitudinal and inferior fronto-occipital fasciculi underlying the posterior superior temporal sulcus.

4.4.2 tDCS Adverse Events

Patients reported only mild adverse events, including fatigue, headaches and skin irritation. No adverse event was severe enough to warrant cessation of stimulation. Adverse event frequency did not differ during A-tDCS versus sham ($t(20) = 2.3$, $P = 0.82$).

The effect of stimulation on comfort ratings was calculated as rating before stimulation minus rating after stimulation, with a maximum possible change of 10. The average change was small: -0.05 for A-tDCS (range: -0.8 to +0.9) and -0.18 for sham (-1.47 to 0.45). There was no significant difference between A-tDCS and sham blocks ($t(20) = 1.6$, $P = 0.12$).

In the exit Questionnaire 10/21 participants said stimulation felt different in the two blocks. Of those, 6/10 commented on which block contained real tDCS stimulation: unblinding revealed that 4/6 were correct. All participants reported that they found tDCS tolerable and would be willing to continue receiving it if it were available in future.

4.4.3 Behavioural Effects of Therapy

Average outcome measures for each tDCS Group and results from the Omnibus and Therapy (M)ANOVAs are reported in Appendices Table 1s.

4.4.4 Primary Outcomes

4.4.4.1 Word Reading Accuracy

Overall change in word reading accuracy is shown in *Figure 26*. All Word-Lists showed a test-retest effect between Baseline and T3. Between T3, T4 and T5, therapy effects specific to trained words were observed. Between T5 and the follow-up test at T6 reading ability diminished, but stayed above baseline levels.

The item-specific therapy effects of iReadMore training on word reading accuracy were observed in the Therapy ANOVAs as a significant Block by Word-List

interaction (P<.0005). Unstandardised and standardised effect sizes for changes in word reading accuracy are shown in Table 5. Combining data from both blocks, the average improvement in trained word reading accuracy was 8.7% (CI [6.0, 11.4]; d=1.38). Exploratory post-hoc paired t-tests showed that the improvement in trained word reading accuracy (during Block1 and Block2) was significantly greater than the test-retest effects observed between Baseline and T3 (Block1: t(20) = 3.3, P<.005; Block2: t(20) = 3.5, P<.005).

As shown in *Figure 27*, A-tDCS also had a beneficial effect on word reading accuracy (Block by tDCS interaction, P<.05), an effect which generalised to untrained words. Collapsing data from both Word-Lists and Blocks, accuracy improved by 2.6% more during A-tDCS than sham (CI [-0.1, 5.3]; d = 0.41).

Maintenance of the iReadMore training effects were tested using post-hoc paired t-tests to compare accuracy at T3 (immediately before training) and T6 (3 months after training cessation). Accuracy for all trained words were significantly better at T6 than T3 (Trained in Block1: t(20) = 3.6, P<.005; Trained in Block2: t(20)=3.9, P<.005). The improvement in untrained items was not significant (t(20)=1.7, P=0.10). At T6, accuracy for trained words was significantly greater than for untrained words (Trained in Block1: t(20) = 2.3, P<.05; Trained in Block2: t(20)=3.3, P<.005).

Maintenance of the tDCS effects were harder to assess due to the cross-over design, but reading accuracy at T6 was assessed with an ANOVA with within-subjects factor Word-List (Trained in Block1 versus Trained in Block2) and between-subjects factor tDCS Group; if the facilitatory effects of tDCS had persisted until T6, the interaction between word list and group should be significant. The interaction was not significant (F(1,19)=0.4, p = 0.55).

Exploratory post-hoc paired t-tests tested the hypothesis that the therapy may have been more effective for more imageable or more regular words. Neither factor had a significant effect on change in trained word reading accuracy (imageability: t(20)=1.84, P = 0.081; regularity: t(20=1.18, P=0.251); in fact, for imagability, there was a trend for larger improvements for low imageability words (mean improvement=9.76%, sd=10.85) than high imageability words (mean improvement=5.07%, sd=5.90).

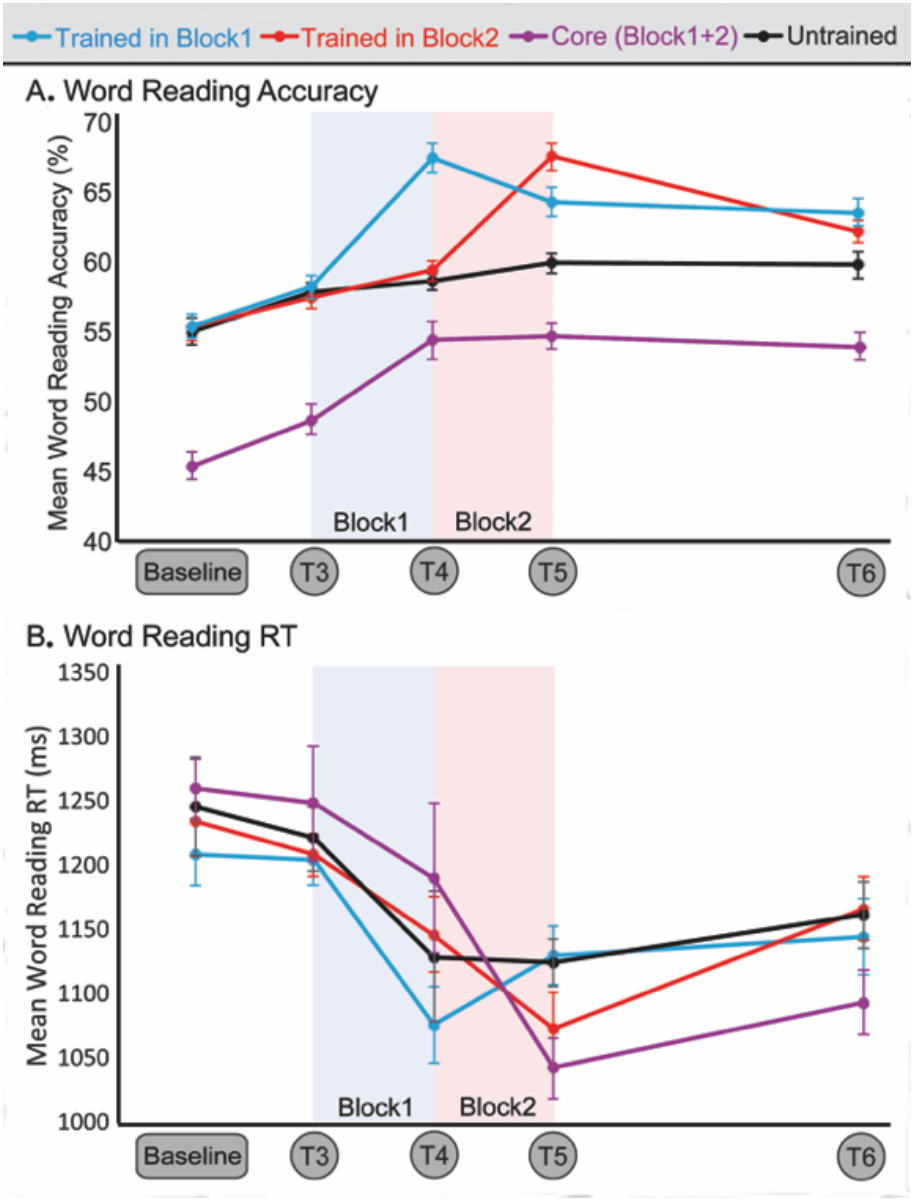

Figure 26 Therapy effects on word reading ability. *Change over time in (A) mean word reading accuracy (n = 21) and (B) reaction times (n = 20). There were four different word lists: words Trained in Block1 (blue), words Trained in Block2 (red), Untrained words (black) and the unmatched list of high-frequency, low-imageability Core words (purple). Error bars indicate within-subject standard error of the mean. Training Block1 was administered between T3 and T4; Block2 was administered between T4 and T5.*

Table 5 Unstandardised effect sizes (with 95% confidence intervals, CI) and standardised effect sizes (Cohen's d) for changes in the primary word reading outcome measures.

Measure	Time Interval	Unstandardised Effect Size (95% CI)	Cohen's d
Word Reading, Acc (%)			
Trained in Block1	T4 – T3	9.2% (6.2, 12.3)	1.29
Untrained	T4 – T3	0.7% (-1.3, 2.7)	0.16
Trained in Block2	T5 – T4	8.1% (5.3, 10.9)	1.25
Untrained	T5 – T4	1.3% (-0.6, 3.1)	0.29
Trained, both Blocks	After - Before	8.7% (6.0, 11.4)	1.38
Word Reading, RT (ms)			
Trained in Block1	T4 – T3	-128ms (-53, -202)	0.75
Untrained	T4 – T3	-92ms (44, -228)	0.30
Trained in Block2	T5 – T4	-73ms (-4, -142)	0.47
Untrained	T5 – T4	-4ms (117, -125)	0.01
Trained, both Blocks	After - Before	-100ms (-56, -145)	0.98
Core Word Reading, Acc	T4 – T3	5.7% (1.5, 9.9)	0.58
	T5 – T4	0.3% (-2.4, 3.0)	0.04
	T5 – T3	6.0 % (2.7, 9.2)	0.78
Core Word Reading, RT	T4 – T3	-66ms (-113, -245)	0.17
	T5 – T4	-144ms (-6, -281)	0.47
	T5 – T3	-210ms (-116, -304)	1.00

At the individual subject level, there was considerable heterogeneity between participants.

Figure 28 shows the change in word reading accuracy for trained and untrained words, averaged over both blocks, for each participant. This represents the average change over the 90 words trained in Block1 and the 90 words trained in Block2, compared to the change in the 90 untrained words across the same time-frame. More detailed plots showing the change over time, for each word list, and for each subject can be seen in Appendices Fig. 1s. The cause of this heterogeneity, which has considerable clinical relevance, is the subject of a parallel analyses currently being prepared for publication.

4.4.4.2 Word Reading Reaction Times

Due to participant P10's low word reading accuracy, RT could not be calculated; hence RT data was available for 20 participants only. Overall change in word reading RT, shown in *Figure 26*, largely mirrored that of word reading accuracy: there was no indication of a speed-accuracy trade-off. A small test-retest effect was apparent between Baseline and T3. Between T3, T4 and T5, improvements were observed that were strongest for trained words. Between T5 and the follow-up test at T6 reading ability diminished, but stayed above baseline levels.

There was an item-specific therapy effect of iReadMore training on word reading RT, demonstrated by a significant Block by Word-List interaction ($P<.05$). Averaging across both blocks, the average unstandardized effect size of the improvement was 100ms (CI [56, 145]; d=0.98). Post-hoc paired t-tests showed that the improvements in trained word RT were significantly greater than the test-retest effects (Baseline to T3) for Block1 but not for Block2 (Block1: $t(19)=2.4$, $P<.05$; Block2: $t(19)=1.2$, $P = 0.3$).

The effect of tDCS on word reading RT was not significant.

Exploratory paired t-tests of maintenance effects compared word reading RT at T3 versus T6, and demonstrated that improvements in RT were not maintained at the follow-up session (Trained in Block1: $t(19) = 1.8$, $P = .09$; Trained in Block2: $t(19) = 0.9$, $P = .36$). Similarly, at T6, there was no significant difference in RT

between trained and untrained words (Trained in Block1: t(19) = -.4, P = .67; Trained in Block2: Trained in Block2: t(19) = .3, P = .77).

Post-hoc paired t-tests showed no significant effects of word imageability or regularity on improvement in word reading RT after iReadMore training (imageability: t(18)=-1.18, P=0.253; regularity: t(18)=0.51, P=0.62).

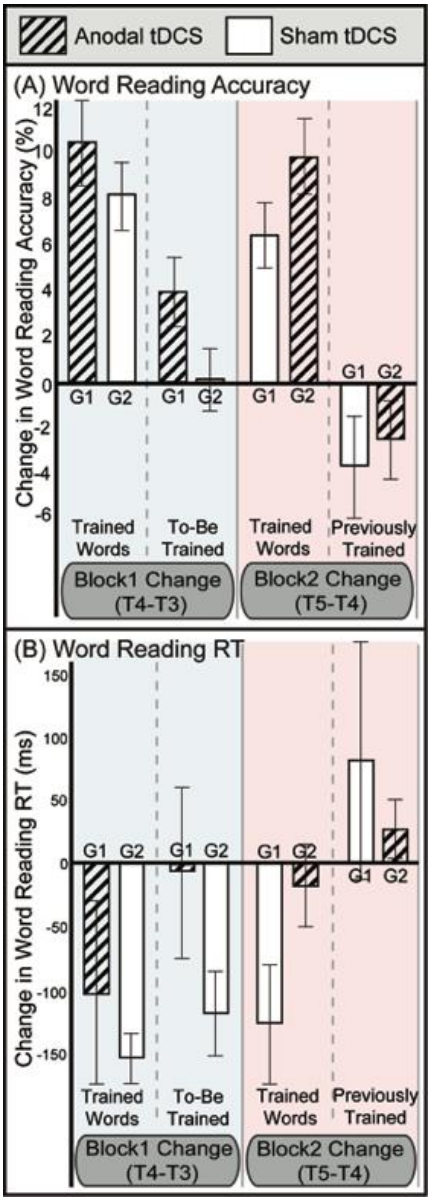

Figure 27 Change in word reading ability after therapy. Effects of iReadMore and tDCS on change in (A) word reading accuracy (n = 21) and (B) word reading reaction times (n = 20). Block1 change was calculated as accuracy or RT at T4 minus T3; Block2 change was T5 minus T4. G1 = cross-over group 1; G2 = cross-over group 2. Error bars represent the within-subject standard error of the mean.

4.4.4.3 Core Word Reading Accuracy

The Core Word-List was analysed separately because it was trained in both blocks and items were not matched in psycholinguistic properties to the other lists. Core word reading accuracy improved in Block1, but gains did not continue in Block2.

Post-hoc contrasts in the univariate Therapy ANOVA confirmed a significant improvement in accuracy between T3 and T4 ($F(1,16)=8.8$, $P<.01$). In addition, post-hoc paired subjects t-tests demonstrated that accuracy was better at T5 than T3 ($t(20)=3.6$, $P<.005$). The unstandardized effect size for Core word reading improvement between T3 and T5 was 6.0% (CI [2.7%, 9.2%]), and the standardised effect size was $d = 0.78$. However, this change was not significantly larger than the test-retest effect observed between Baseline and T3 ($t(20) = 1.0$, $P = 0.3$).

There was no significant effect of tDCS for Core word reading accuracy.

Post-hoc paired t-tests comparing Core word reading accuracy at T3 versus T6 showed that improvements were maintained at the follow-up session ($t(20)= 3.5$, $P<.005$).

4.4.4.4 Core Word Reading Reaction Times

As P10 and P16 had very low Core word reading accuracy, RT could only be calculated for 19 participants. In contrast to accuracy, Core word reading RT improved marginally in Block1 and more substantially in Block2. Post-hoc contrasts in the Therapy ANOVA confirmed that the change in RT between T4 and T5 was significant ($F(1,16) = 4.7$, $P<.05$). A paired t-test showed that the overall change between T3 and T5 (mean=210ms; CI [116, 304]; $d=1.00$) was significant ($t(18) = 3.6$, $P<.005$). This change was also significantly larger than the test-retest effect observed between Baseline and T3 ($t(17) = 2.2$, $p<.05$).

There was no significant effect of tDCS for Core word reading RT.

Finally, a paired t-test comparing Core word reading RT at T3 versus T6 showed a significant maintenance of therapy effects ($t(18) = 2.5$, $p<.05$).

4.4.5 Secondary Outcomes:

4.4.5.1 Written Semantic Matching

P8 and P10 were unable to complete the Written Semantic Matching task due to their extremely poor word reading abilities. Data is reported from the remaining 19 participants.

Accuracy at Baseline was high (93% on average), changed little over time, and was subject to ceiling effects; hence only RT data were analysed further. RT decreased linearly with repeated exposures to the test (main effect of Time-Point, P<.0001). The Therapy ANOVA showed a trend towards a Block by Word-List interaction driven by greater improvements for trained words (P=.050). There was also a Block by tDCS Group interaction (P<.05), but it was driven by greater improvements with sham than with tDCS.

To assess if reading for meaning improved to a greater extent for those with impairments in the semantic domain at baseline, changes in reaction time over Block1 (T4-T3) and Block2 were compared to baseline scores on the Pyramid and Palm Trees test. This revealed a significant positive correlation in both Block1 ($r = 0.7$, $P<0.001$) and Block 2 ($r = 0.5$, $P<0.05$).

4.4.5.2 Sentence Reading

P8, P10 and P17 were unable to complete the Sentence Reading task: data is reported from 18 participants.

Picture verification accuracy at Baseline was high (87% on average), changed little over time, and was at ceiling in some participants. Only sentence reading speed in words per minute (wpm) was analysed further.

Average reading speed did not show a test-retest effect between Baseline and T3, but improved linearly during training (T3 to T5) and at the follow-up test (T6). The Therapy ANOVA showed an interaction between Word-List and tDCS Group (P<.05), but this interaction did not reflect a tDCS advantage: G1 participants improved more on words trained in Block2 whereas G2 participants improved more on words trained in Block1. As these improvements were consistent across Block1 and Block2 they could not be ascribed to tDCS stimulation, but instead

reflected a difference between G1 and G2 participants.

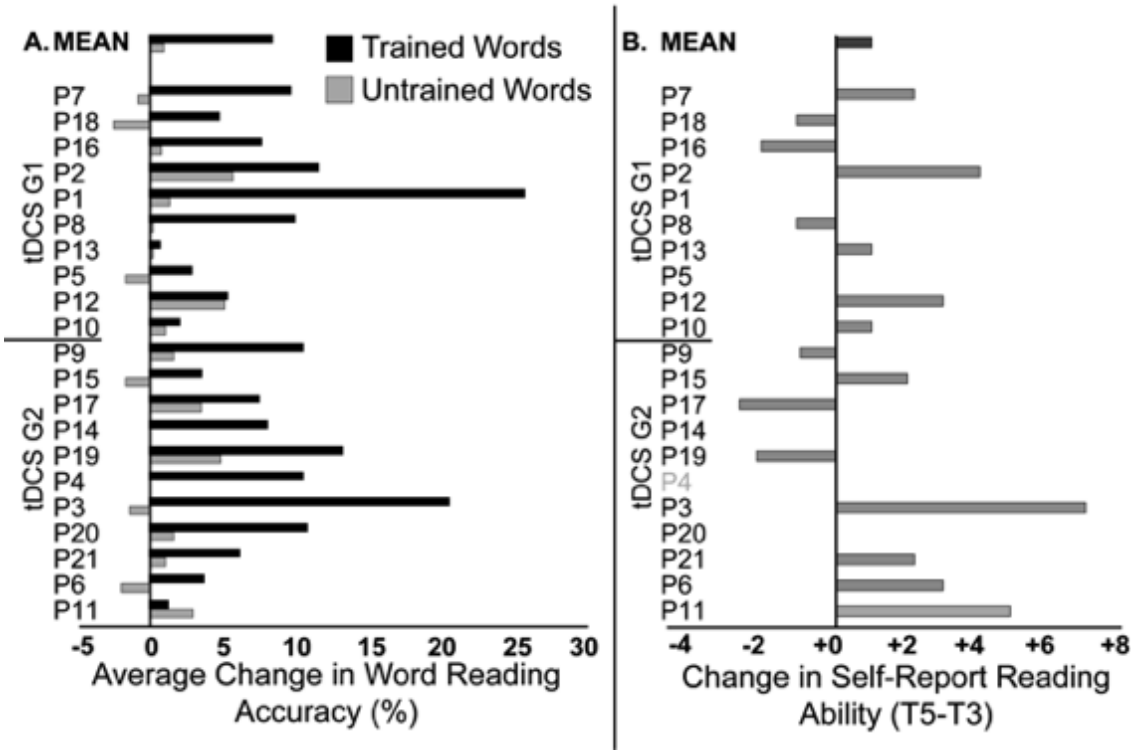

Figure 28 *Change in word reading accuracy and self-reported reading by participant. (A) Raw percentage change in word reading accuracy for trained (black) and untrained (grey) words, averaged over Block1 (T4-T3) and Block2 (T5-T4). For trained words, this represents the average of the change in the 90 words trained in Block1 between T3 and T4 and the change in the 90 (different) words trained in Block2 between T4 and T5. For untrained words, this represents the change in the 90 untrained words over the same two time periods. Participants are ordered according to tDCS group, followed by ascending CAT naming accuracy. (B) The Communication Disability Profile (CDP) measures self-report ability in silent word, sentence, text and mail reading. Score for each level is out of 4, giving a total score out of 16. Change in CDP score is the difference between T5 (after training) minus T3 (before training). Positive scores represent improvements in self-reported reading ability. CDP Data was unavailable for P4.*

4.4.5.3 Text Reading

P20 was unable to complete the Text Reading task. In the remaining 20 participants, there was little change over time in text reading accuracy, speed or

comprehension. Neither the Omnibus MANOVA nor the Therapy ANOVAs identified any significant effects or interactions.

4.4.5.4 Sustained Attention to Response Task

Due to a software malfunction, SART data was unavailable for P10 at T6. Results are reported from the remaining 20 participants.

Small changes were observed between Baseline and T6: RTs increased, false negative responses increased and false positives decreased, suggesting that participants responded more cautiously with repeated exposures to the test. However, the effect of Time-Point was not significant in the Omnibus MANOVA, nor were any significant effects observed in the Therapy ANOVAs.

4.4.5.5 Self-Report Measures

The CDP was completed at T3 and T5 in 20 out of 21 patients: P5 declined to complete the questionnaire at T5. 10 out of 20 patients reported improved reading ability (

Figure 28), but a Wilcoxon Signed Rank test showed this change was not significant (T = 98, P = .119).

Considering the four reading levels of the CDP separately, average improvements were largest for words (+0.43) and sentences (+0.35), but neither of these changes reached significance (P = .065 and P = .115 respectively).

When asked in the exit questionnaire whether participants thought their word reading had improved, 11/21 responded ‘A Lot’; 9/21 responded ‘A Little’; and only one responded ‘No’ (P7). 19/21 participants said that they would like to continue using iReadMore (P4 said ‘maybe’ and P23 said ‘no’).

4.5 Discussion

This study tested the efficacy of two concurrent therapies for CA: (1) iReadMore, a crossmodal, lexical word reading therapy; and (2) A-tDCS delivered to left IFG.

iReadMore improved word reading accuracy and RT for trained items, and, consistent with previous lexical therapies (Friedman & Robinson, 2007; Friedman et al., 2002; Kurland et al., 2008; Ska et al., 2003), did not generalise to untrained

items. The unstandardized size of iReadMore's effect on reading accuracy was 8.7% (95% CI [6.0, 11.4]) and the standardised effect size (Cohen's d) was 1.38 (large). The effect size for reading RT was 100ms (CI [56, 145]), d = 0.98 (large).

Pre-treatment reading of the high frequency, low imageability 'Core' words was initially poor, but as a result of iReadMore training accuracy improved by 6% (CI [2.7, 9.2]. d=0.78, moderate) and RT improved by 210ms (CI [116, 304], d=1.00, large). The fact that these Core words improved, coupled with the lack of evidence for an influence of word imageability or regularity on the therapy effects, suggests that the therapy can be effective for all word types.

A-tDCS paired with iReadMore had a small but significant facilitatory effect on word reading accuracy (2.6% on average, CI [-0.1, 5.3], Cohen's d=0.41), which generalised to untrained words. A-tDCS effects were not observed on word reading RT or on Core word reading (accuracy or RT). This may be due to a lack of power to detect this small to medium effect size on a set of only 50 Core words; or it may be because the same Core words were trained twice, once with A-tDCS and once with S-tDCS, meaning that the comparison between real and sham blocks was confounded by carry over effects from the preceding block.

In real-word terms, two blocks of iReadMore and A-tDCS therapy (70 hours training and 11 stimulation sessions in total) on all 350 trained words (two blocks of 150 words plus 50 Core words), patients on average could read 29 more words, with a range based on the 95% confidence intervals from 19 to 39 words. Patients were also on average 116ms faster per trained word (ranging from 65ms to 168ms). Participants were variable in the degree of improvement with therapy (see Figure 28). Participant's were varied in both their response to the therapy and A-tDCS (see figure 28). To explain this variability in response to therapy three models were tested. It was found that both behavioural and lesion location contribute to explaining response to therapy. In particular, damage to the following left hemisphere regions were all negatively associated with response to therapy; i) left Broca's area, ii) insula and iii) the white matter tract connecting the thalamus to the parietal regions.

Broca's area (the par triangularas and pars opercularus parts of the IFG) is widely associated with speech production and reading (Klein et al., 2014; Marangolo et

al., 2011; J. P. Mohr et al., 1978; Wheat et al., 2010). Activity in the IFG has been associated with tasks of phonology and semantics (Vigneau et al., 2006) and in tasks of reading outloud (Price & Mechelli, 2005). If iReadMore is effective through strengthening the relationship between these representations for trained words, it is possible that a larger degree of tissue in this region will be associated with greater therapy gains. Damage to the left insula has been reported in cases of phonological dyslexia (Lacey et al., 2010) and identified in VBM lesion-symptom mapping (Ripamonti et al., 2014). Additionally, it has a key role in speech articulation (Oh, Duerden, & Pang, 2014). The main outcome measure was single word reading aloud, which may explain the involvement of this region in some part. The ILF forms a main pathway within the ventral reading stream (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Parker et al., 2005) .. A lesion symptom mapping study of 43 chronic aphasic participants, also associated the ILF with concrete and abstract word reading (Woollams, Halai, & Lambon Ralph, 2018). As a large proportion of the participant's in this study had damage affecting the dorsal route to reading, a increased reliance on this route may be suggested and may explain why greater preservation of this tract is associated with better therapy gains.

Therapy effects on reading accuracy (but not RT) remained significantly above baseline levels at the T6 follow-up session, 3 months after cessation of training. For Core words, both accuracy and RT gains were maintained. However, the diminution of the effect size at T6 suggests that a maintenance dose of training may be required to keep up the benefits gained from the therapy.

The iReadMore therapy was designed to strengthen connections between orthographic, phonological and semantic representations. Whilst improved oral word reading indicated improved access from orthography to phonology, improvement on the semantic matching task would have demonstrated strengthening of connections with semantic representations. In fact, the effect of iReadMore on semantic matching was very close to significance (P = .050). This result may have been subject to ceiling effects, as seven patients were within the control RT range on this task; hence I speculate that iReadMore may benefit reading for meaning in patients who have deficits in the semantic domain. This impression is supported by the positive correlation between greater semantic

impairment (as measured by the Pyramids and Palm Tree test at baseline) demonstrated greater improvements in semantic matching RT.

Training effects were observed at the word level, and did not generalise to sentence or text reading. This indicates that further text training (e.g. Multiple Oral Reading, (Moyer, 1979); or Oral Reading for Language in Aphasia, (Cherney, 2004)) or multi-level training (Brown, Hux, & Fairbanks, 2015) may be required to overcome the additional syntactic, semantic or verbal working memory deficits that impede text reading in CA.

The lack of generalisation to the sentence and text level could have been driven by the text used in these assessments. As the text reading measure (Neale) is a standardised test, the text stimuli were not designed to assess therapy effects on trained versus untrained words. There is a theoretical maximum of 25% of words in the Neale having been trained, however, this is dependent on whether all of these words were included in that participant's treatment list. A pre-post therapy (comparing T3 to T5) arithmetical improvement of 1.74% was observed in the Neale, but this was not statistically significant. As therapy did not generalised beyond trained items at the individual word level, I would not expect to have observed a large change with training in this test.

The items in the sentence-reading test were controlled for trained and untrained items. Sentences consisted of between 25 and 50% of the words from the word lists. Prior to training, participants were at ceiling on the comprehension part of this test; therefore, it was only possible to analyse therapy effects on sentence reading RT. It is possible that this RT measure was not sensitive enough to detect any changes, as it was dependent on the participant indicating by button press that they had read the sentence. However, participants may have reread the sentence. It may have been more informative to use eye tracking to monitor text reading. This would have provided information about the particular words within the sentence that sustained longer fixations (indicating difficulty in reading) and which parts of the sentence were revisited. This may indicate the parts of the sentence that did not make sense or were not processed correctly on first reading. This would have allowed for statistical tests to be conducted on the number and duration of fixations on trained and untrained words. This has been

used successfully with this population elsewhere (Huck, Thompson, Cruice, & Marshall, 2017; E. Kim & Lemke, 2016).

A number of factors are known to influence text reading. Firstly, a sufficient working memory is required to hold in memory previously read words, while reading the next word. In a case study of two participants with preserved single word reading but impaired text reading, a deficit in phonological working memory was identified as a potential cause of the text reading deficit (Rhonda B. Friedman, 1996). Others have found that targeting attention in patients with mild aphasia has improved text comprehension (Coelho, 2005; J. B. Lee & Sohlberg, 2013; Sinotte & Coelho, 2007).

CA patients' ability to predict upcoming words in a sentence may also play a role in their success at text level reading (Huck et al., 2017). Indeed, using these top-down, context driven effects is one of the potential mechanisms by which MOR is effective (Moyer, 1979). However, others argue that the mechanism for MOR is bottom up (Lacey et al., 2015) and in a case study of a deep dyslexia patient who received MOR therapy, no improvement in reading comprehension was observed (Russo & Kim, 2010).

Syntax may also play a role. It is clearly important to understand not only the words, but how the order of these words affects the meaning of the sentence (Black, Chiat, & Chiat, 2014). Text-level reading can be processed at multiple levels; a shallow text based understanding (i.e. understanding a sentence) and a more complex situational model of the text, where the meaning is put in the context of existing semantic knowledge to build up a scene (Meteyard, Bruce, Edmundson, & Oakhill, 2015; Perfetti, 2000) . Put simply, improvements in word reading may not necessarily lead to improvements in text reading because of the multiple other factors involved in successful sentence and text reading. However, words are the building blocks of sentences. Providing participants with better accuracy in reading a critical mass of words may improve sentence reading. However, this study design does not afford for that to be investigated. Future investigations, could train fewer words to criterion, then test which of these multiple factors affect text reading.

Participants varied in both their response to the therapy and A-tDCS (see figure 28). To explain this variability in response to therapy three models were tested containing i) neuroimaging data, ii) behavioural and demographic data and iii) neuroimaging and behavioural data (combined model) (Aguilar, Kerry, Ong, et al., 2018). It was found that both behavioural and lesion location contribute to explaining response to therapy. In particular, damage to the following left hemisphere regions were all negatively associated with response to therapy; i) left Broca's area, ii) insula and iii) the white matter tract connecting the thalamus to the parietal regions.

Broca's area (the par triangularis and pars opercularis parts of the IFG) is widely associated with speech production and reading (Klein et al., 2014; Marangolo et al., 2011; J. P. Mohr et al., 1978; Wheat et al., 2010). Activity in the left IFG has been associated with tasks of phonology and semantics (Vigneau et al., 2006) and in tasks of reading out loud (C. J. Price & Mechelli, 2005). If iReadMore is effective through strengthening the relationship between these representations for trained words, it is possible that a larger degree of tissue in this region will be associated with greater therapy gains. However, this finding would be at odds with the results of the therapy DCM that suggested therapy effects were driven by bottom-up mechanisms.

Damage to the left insula has been reported in cases of phonological dyslexia (Lacey et al., 2010) and identified in VBM lesion-symptom mapping (Ripamonti et al., 2014). Additionally, it has a key role in speech articulation (Dronkers, 1996; Oh et al., 2014). The main outcome measure was single word reading aloud, which may explain the involvement of this region.

The ILF forms a main pathway within the ventral reading stream (Duffau et al., 2009; Parker et al., 2005). A lesion symptom mapping study of 43 chronic aphasic participants, also associated the ILF with concrete and abstract word reading (Woollams et al., 2018). As a large proportion of the participants in this study had damage affecting the dorsal route to reading (see Table 4), an increased reliance on this route may be suggested and may explain why greater preservation of this tract is associated with better therapy gains.

The hypothesis that A-tDCS delivered to left IFG would facilitate iReadMore training was also borne out. Compared to sham, A-tDCS increased gains in reading accuracy for both trained and untrained words. There are at least two possible mechanisms of this improvement. The left IFG and adjacent premotor cortex are known to play an early, automatic role in phonological processing during reading (Cornelissen et al., 2009; Wheat et al., 2010; Woodhead et al., 2014; Hoffman et al., 2015). An effective connectivity study showed feed-back connections from the left IFG to visual cortex were strengthened by reading training (Woodhead et al., 2013); hence it is plausible that left IFG stimulation may enhance feed-back and facilitate therapy effects, either by improving the veracity of the phonological representations themselves, or improving mappings between orthography and phonology via strengthened prediction error. The observation that anodal stimulation facilitated oral reading accuracy but not written semantic matching supports the inference that A-tDCS delivered to left IFG acted upon phonological rather than semantic representations.

Alternatively, A-tDCS may have enhanced the left IFG's role in speech production (Hickok & Poeppel, 2007), consistent with A-tDCS effects observed in anomic aphasia (Baker et al., 2010; Campana et al., 2015; Marangolo et al., 2011; Marangolo, Fiori, Di Paola, et al., 2013). This would explain the generalisation of my A-tDCS effects to untrained words, but would predict improved speech output in the text reading task, which was not observed. An A-tDCS induced increase in arousal or attention giving rise to these results is unlikely as I saw no effect on the patients' performance in a test of sustained attention, the cSART. This also suggests that the positive behavioural results of my study cannot simply be explained by non-specific excitation of the entire brain.

As an emerging clinical research tool, A-tDCS has a number of outstanding questions about its mechanisms of action and the anatomical specificity of the stimulation effects (Fertonani & Miniussi, 2016; Parkin, Ekhtiari, & Walsh, 2015; Schlaug, Renga, & Nair, 2008; Stagg & Nitsche, 2011). Finite modelling studies have suggested that distant bipole montages such as used here result in a wide spread of stimulation across the frontal lobe (Datta, Zhou, Su, Parra, & Bikson, 2013). Other reports stress the importance of the interaction between stimulation and the underlying neural network activity especially for cognitive/language functions (Fertonani & Miniussi, 2016). In this context the overall effect of tDCS

depends on the excitability of the stimulated brain area, meaning that even if the spread of electrical current is large, it will only serve to facilitate functionally engaged brain regions that are co-activated by the task being performed.

A previous reading training study of alexic patients showed that therapy strengthened left IFG feed-back to visual cortex (Woodhead et al., 2013). Importantly the left IFG was anatomically intact for all patients in this study; hence it is plausible that A-tDCS delivered to left IFG may have facilitated iReadMore therapy effects either by direct enhancement of left IFG activation itself or by modulation of left IFG connectivity within the patients' task engaged residual reading network.

Moreover, I demonstrated for the first time that repeated A-tDCS sessions not only resulted in enhanced improvement for specifically trained reading materials but also in enhanced transfer effects to untrained reading materials. My findings are thus in line with data from animal models (Fritsch et al., 2010) healthy individuals (Reis et al., 2009) and anomic stroke patients (Meinzer et al., 2016; Vestito, Rosellini, Mantero, & Bandini, 2014) suggesting that multisession tDCS improves memory consolidation by impacting on plasticity-related protein synthesis, which is thought to be enhanced by concurrent application of tDCS during training.

Whilst I set out to test the effects of iReadMore and A-tDCS for patients with any type of CA, all but one participant (P5) had phonological or deep dyslexia; hence, the applicability of these findings to surface alexia is limited. However, P5's results were consistent with the group average, suggesting that the therapy may benefit phonological and surface alexia alike. A post-release trial of the iReadMore app (http://www.ucl.ac.uk/aphasialab/apps/ireadmore.html) will aim to test a larger sample of patients in order to assess its efficacy for surface, deep, phonological and also pure alexia. The iReadMore app will be available to the public in January 2018.

5 Chapter 5: How does iReadMore therapy change the reading network of patients with central alexia?

5.1 Abstract

I investigated the impact of reading training (using iReadMore, a therapy app) on the reading network of patients with CA; and how neural, behavioural and demographic factors influenced the magnitude of their therapy response.

Participants with chronic post-stroke CA (n=23) completed 35 hours of iReadMore training over four weeks. Before and after therapy, MEG scans were conducted and reading accuracy for trained and untrained words. The neural response to reading trained and untrained words in the left and right occipital, ventral occipitotemporal and inferior frontal regions was examined using event-related magnetoencephalography.

Two analyses were conducted. In Analysis 1, the training-related modulation in effective connectivity between regions was modelled at the group level with Dynamic Causal Modelling (DCM). In Analysis 2, the extent to which connection strengths identified in Analysis 1 predicted individual differences in the behavioural therapy effect was explored using Automatic Linear Modelling.

iReadMore training improved participants' reading accuracy by an average of 8.4% (range: -2.77 to 31.66) while accuracy for untrained words was stable. Analysis 1 showed that training increased regional sensitivity in bilateral frontal and occipital regions, and strengthened feed-forward connections within the left hemisphere. Analysis 2 demonstrated that a linear model combining age, baseline behavioural measures and neural connection strengths gave the best predictions of the behavioural response to therapy (R^2=0.97). My data suggests that, in patients with CA, the better their residual reading network can process orthographic inputs in the right OCC and the stronger the connection form right OCC to left OCC, the bigger their therapy gains.

5.2 Introduction

Central alexia (CA; also known as Alexia with agraphia (Dejerine, 1891) is a reading disorder that occurs within the context of a generalised language disorder (aphasia). Patients with CA find reading slow and effortful and make frequent

errors (Leff & Starrfelt, 2013). There is no agreed treatment for CA and to date there have been no group-level investigations of how neural plasticity may support reading recovery in patients with CA. The aim of the present study was to improve our understanding of the therapeutic mechanisms in CA, with a view to developing stratified therapy pathways in future.

After left hemisphere stroke, the role of spared ipsilesional regions and right hemisphere homologues in supporting aphasia recovery are unclear (Adair et al., 2000; Crinion & Leff, 2015; Hartwigsen & Saur, 2017; Tsapkini, Vindiola, & Rapp, 2011). There is evidence for functional reorganisation in spared left hemisphere regions (Abel et al., 2014, 2015; Bonilha et al., 2016; Fridriksson, 2010; Jobard et al., 2003; Pillay et al., 2017; van Hees et al., 2014); while other studies have identified right hemisphere homologues fulfilling this function (Y. S. Lee, Zreik, & Hamilton, 2017; Meinzer et al., 2006; Richter et al., 2008) both accounts may be correct and aphasia recovery may rely on a combination of mechanisms (Crinion & Leff, 2015; Kurland et al., 2008; B. Mohr et al., 2016; Saur et al., 2006; Turkeltaub et al., 2011). I modelled a bilateral reading network in patients with CA to ascertain the effects of therapy within and between the hemispheres.

While post-stroke aphasia is the result of focal damage, it is increasingly viewed as a network disorder (Hartwigsen & Saur, 2017). Neuroimaging studies of skilled readers show that word reading activates a predominantly left-lateralised network of occipitotemporal, temporal and inferior frontal areas (Carreiras et al., 2014; W. W. Graves, Desai, Humphries, Seidenberg, & Binder, 2010; Heim et al., 2005; Hoffman et al., 2015; Perrone-Bertolotti et al., 2017; Price, 2012; Xu, Baldauf, Chang, Desimone, & Tan, 2017; Zhou & Shu, 2017). Converging evidence suggests that efficient word recognition relies on interactive feed-forward (bottom-up) and feed-back (top-down) processing within this network (P. L. Cornelissen et al., 2009; Price & Devlin, 2011; Wheat et al., 2010; Woodhead et al., 2014)

Within the domain of reading rehabilitation, in participants with pure alexia (typically caused by left posterior cerebral artery (PCA) stroke), reading training was associated with stronger connectivity within the left hemisphere, and increased top-down connectivity from frontal to occipital regions (Woodhead et al., 2013). This was interpreted as evidence that predictions from phonological

and/or semantic representations in left frontal cortex facilitated visual word recognition after training. However, in CA (typically caused by left middle cerebral artery stroke), these 'central' language representations are damaged or disconnected.

In the absence of any clear predictions from the literature, this study presents an exploratory analysis of network reorganisation after reading training in chronic post-stroke CA. The training employed iReadMore, an adaptive word reading training app which improved word reading ability for trained items in pure alexia (Woodhead et al., 2013) and CA (Woodhead et al., 2018). Using Dynamic causal modelling (DCM) of magnetoencephalography (MEG) data I investigate how effective connectivity within the reading network changed as a result of therapy. My speculative hypothesis was that training would strengthen feed-back connections within the left hemisphere, and the left IFG's self-connection.

In addition, I examined what factors (demographic, behavioural and neural) predicted the magnitude of an individual's response to therapy, using Automatic Linear Modelling (ALM). Numerous factors may explain response to therapy in aphasia (Aguilar, Kerry, Ong, et al., 2018) and therefore can be included when modelling the relationship between response to therapy and neurological changes. By using a type of forward regression, I was able to place fewer pre-requisites on the non-neurological factors that influence response to therapy (Yang, 2013). It is anticipated that these exploratory analyses will yield predictions for future investigations of how neural network plasticity supports language recovery.

5.3 Method

Twenty-three CA participants were included in this study. MEG scans were conducted before and after the first four week iReadMore therapy block, in which CA participants amassed 35 hours of reading training. In each scan participants were shown Trained words and a matched list of Untrained words (as well as False Fonts and Name trials). Participants were asked to silently read the words.

After pre-processing, data from the MEG scans conducted before and after training were merged. VB-ECD was conducted to identify individualised dipole locations for each participant for Trained and Untrained word trials over both time-

points (T3 and T4). Six dipole sources were estimated; left and right OCC, vOT and IFG (see *Figure 29* for winning dipole locations).

DCM modelling was performed (see *Figure 21* for diagram of the model estimated). The A matrix was defined as the network when viewing to-be-trained words before therapy (T3_Tr). Two B matrices were defined:

1. The modulation in effective connectivity for Trained words after training (T3_Tr vs T4_Tr)
2. The modulation in effective connectivity for Untrained words after training (T3_Tr vs T4_Un)

BMA was conducted and a proportion test was used to identify connections that were significantly modulated. Connections were deemed as significantly modulated by iReadMore training if they met the following two criteria i) showed a significant effect of training and ii) did not show a simple effect of time. The second criteria aimed to avoid connections being attributed to showing a therapy effect, when actually they demonstrate a main effect of time.

Finally, an ALM was conducted to identify which of the connections that were significantly modulated by therapy were also related to the degree of change in word reading accuracy. I compared which of the following models was best able to explain participant's response to therapy i) demographic and behavioural variables (hence forth referred to as "Behavioural" model) ii) DCM neuroimaging variable (henceforth referred to as "Neuroimaging" model) iii) combined demographic (henceforth referred to as "Combined" model), behavioural and neuroimaging variables. This allowed me to explore the relationship in response to therapy when demographic and baseline behavioural factors were also in the model.

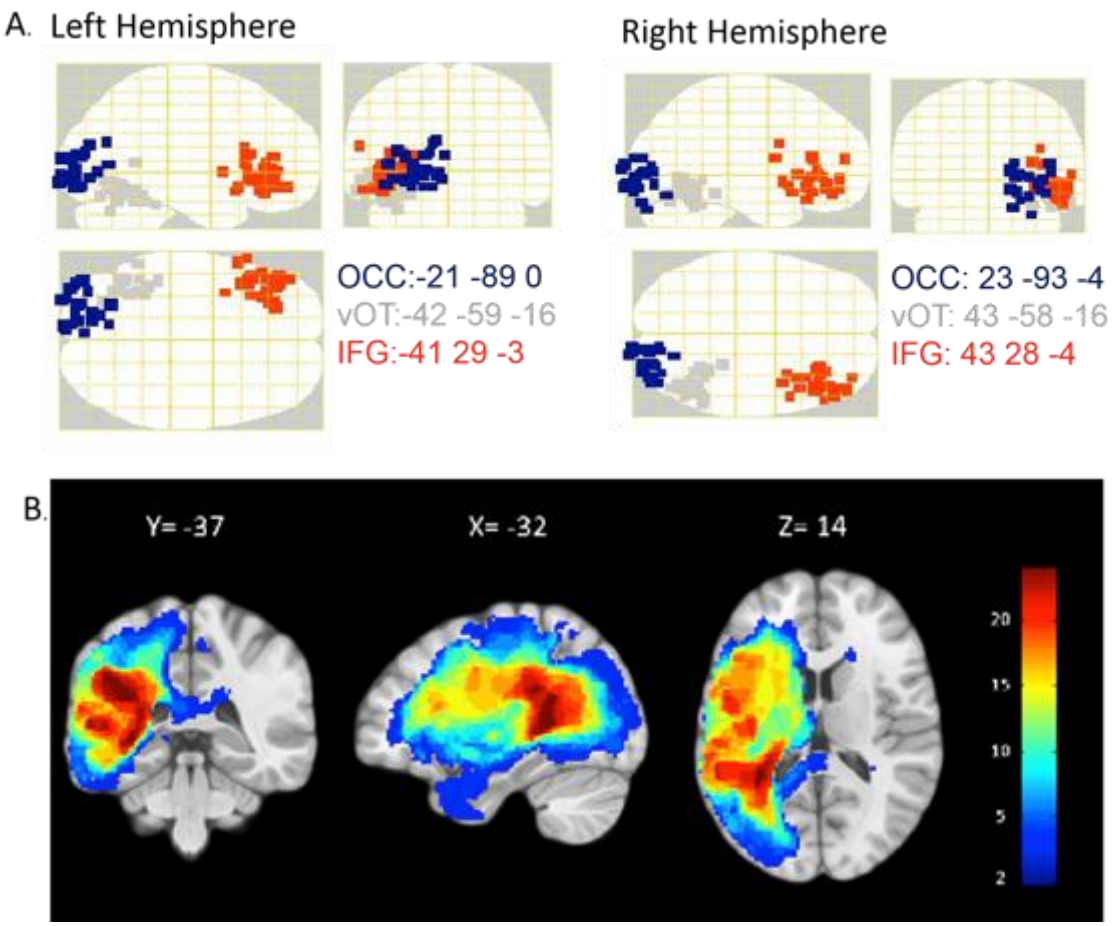

Figure 29 A) Optimal source locations identified using Variational Bayesian equivalent current dipole modelling for each subject, plotted on a glass brain in MNI space. Average dipole location across the group are given for the six sources; occipital (blue), ventral occipital temporal (grey) and inferior frontal gyrus (red). B) Lesion overlay map for the group (n=23) where hotter colours indicate greater number of patients with lesions affecting that area.

5.4 Results

5.4.1 Training effects on reading ability

Participants completed on average 33.35 hours (sd=2.65 hours; range: 25.33 to 37.21 hours) of iReadMore therapy over the training period.

Word reading accuracy was entered into an omnibus ANOVA with within-subject factors time point (Baseline, T3 and T4) and word list (Trained, Untrained) which revealed a significant time point by word list interaction (F(20)=19.31, P=0.000021) (see *Figure 30*). A paired t-test revealed a significant improvement

over the training block for trained words (t(22)=5.47, P=0.000017), which was significantly greater than the change observed over the baseline period (t(22)=7.349, P=0.0000002). No significant change over the training period was observed for untrained items (t(22)=0.10, P=0.925). This indicates that therapy significantly improved word reading accuracy for trained words only. Word reading accuracy improved by on average 8.4% for trained words compared to -0.11% for untrained words. No significant training effects (word list x time interaction) on word reading reaction times were observed in the omnibus ANOVA (F(19)=0.22, p=0.804).

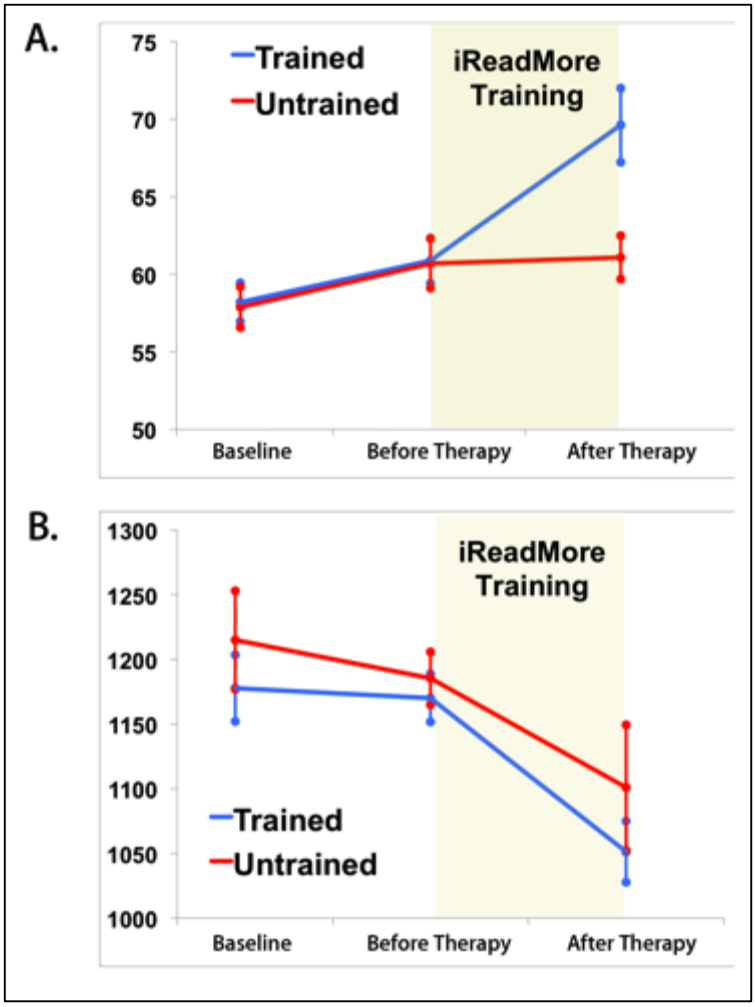

Figure 30 Change over time in (A) mean word reading accuracy (n=23) and (B) reaction times (n=22) for trained words (blue) and untrained words (red). Error bars indicate within-subject standard error of the mean.

Participants successfully completed the within-scanner name detection task. Average accuracy for name trials was 89.71% (SD=16.01) and the average percentage of false alarms (where the button was pressed for a trial other than a name) were 3.91% (SD=6.06).

5.4.2 Source Localisation

The average latency of the M170 peak was 189.71ms (range: 156.67 – 215.00) and the average peak amplitude was 37.15fT (range: 14.46-63.8fT). See *Figure 29* for each participants' dipole location plotted on a glass brain.

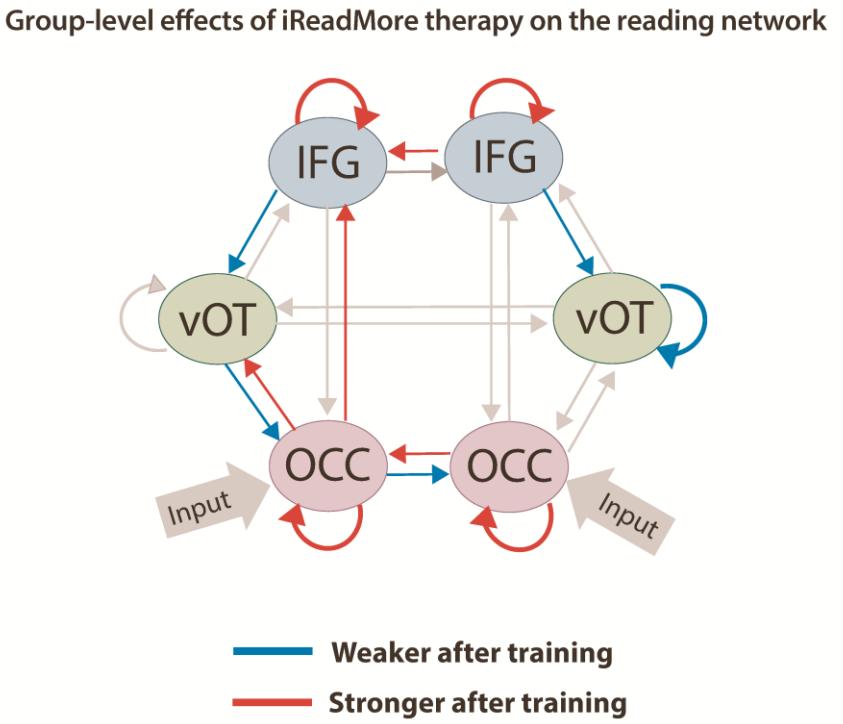

Figure 31 Results of Analysis 1: Modulated connection strengths for words trained with iReadMore after training. These are connections that met the following criteria; i) there was significant modulation in Matrix B1 (Tr_Before vs Tr_After); and ii) the therapy-specific modulation in Matrix B1 was significantly different to the non-specific change over time in Matrix B2 (Tr_Before vs Un_After). Connections in red became significantly stronger after training, whereas connections in blue because significantly weaker after training.

5.4.3 *Analysis 1: Group-level effects of iReadMore therapy on the reading network*

Table 6 displays the posterior mean and exceedance probability for connections that showed significant therapy effects; i.e. that were significantly modulated in Matrix B1 (Tr_Before vs Tr_After) and this modulation was significantly different to that in Matrix B2 (Un_Before vs Tr_After). Eight connections were significantly stronger after therapy than before, and five were significantly weaker (see *Figure 31*).

5.4.3.1 Stronger connections for trained words after therapy

Of the eight connections significantly strengthened by iReadMore training two were feed-forward connections in the left hemisphere, two were lateral (between hemisphere) connections from right to left and four were self-connections. More specifically they were: the feed-forward connections from left OCC to left IFG and left vOT; the lateral connections between the OCCs and IFGs in the right to left direction; the self-connections in left and right OCCs and IFGs (bottom and top of the reading hierarchy respectively). Self-connections indicate the sensitivity of a region to an input; indicating that these regions became more sensitive to trained words with therapy.

5.4.3.2 Weaker connections for trained words after therapy

Of the five connections significantly weakened by iReadMore training, three were feed-back connections, two lateral and one was a self-connection. More specifically they were: the feed-back connections from both IFGs to both vOTs and from left vOT to left OCC; the lateral connection between the OCCs in the left to right direction; the self-connection on the right vOT.

5.4.4 Analysis 2: Testing whether therapy-related modulation of connection strength predicts improvement in reading accuracy

I compared the AIC of three ALM models (‘Behavioural’, ‘Neuroimaging’ and ‘Combined’) that predicted the variability in patients’ responses to iReadMore therapy. Lower AIC indicates better performance. This analysis was explorative,

and should be interpreted with caution. The 'Neuroimaging' model performed worst (AIC=88.21, R^2=23.4); followed by 'Behavioural' (AIC=81.76, R^2=49.9); and the 'Combined' model performed the best (AIC=41.57, R^2=97.1). The 'Combined' model was able to explain 97.1% of the variance in response to therapy.

Table 6 Results of Analysis 1 (group-level effects of iReadMore therapy on the reading network). Posterior means and exceedance probabilities from Matrix B1 (Tr_Before vs Tr_After) for the 13 connections that were shown to be significantly modulated by iReadMore therapy. L/ROCC= left/right occipital; L/RvOT=left/right ventral occipitotemporal cortex; L/RIFG= Inferior Frontal Gyrus.

Connection	Posterior mean	Exceedance Probability
Stronger with training		
LOCC to LOCC	1.02	1.00
LOCC to LvOT	1.17	1.00
LOCC to LIFG	1.16	1.00
ROCC to LOCC	1.07	0.97
ROCC to ROCC	1.07	1.00
LIFG to LIFG	1.10	1.00
RIFG to LIFG	1.08	0.96
RIFG to RIFG	1.03	0.99
Weaker with training		
LOCC to ROCC	0.86	0.00
LvOT to LOCC	0.92	0.01
RvOT to RvOT	0.97	0.01
LIFG to LvOT	0.80	0.00
RIFG to RvOT	0.91	0.00

The AIC value can be converted into a Bayes Factor (BF = exp ((AIC1 - AIC2) / 2), where AIC2 is the smaller (better) of the pair). The evidence that the 'Behavioural' model was better than the 'Neuroimaging' model was 25.15 times greater than the evidence against it. However, the evidence that the 'Combined' model was better than the 'Behavioural' model was 5.3×10^8 times greater than

the evidence against. Depending on the heuristic used for interpreting this Bayes Factor, this is either ‘decisive’ (Jeffreys, 1998) or ‘very strong’ (Kass & Raftery, 1995).

Table 7 Results of the ALM analysis (Analysis 2). The winning ‘Combined’ model was better able to explain response to iReadMore training than the ‘Behavioural’ and the ‘Neuroimaging’ models. Displayed are the values for the coefficients in the ‘Combined’ model that significantly contributed to explaining the variance in response to iReadMore therapy.

Variable	Coefficient	Significance
Demographic Variables		
Age	-0.290	<0.001
Behavioural Variables		
Neale Accuracy	0.031	<0.001
Neale WPM	0.143	<0.001
CDP	0.469	<0.001
cSART RT	0.031	<0.001
Robson Task	-0.430	0.006
Neuroimaging Variables		
ROCC to ROCC	4.673	<0.001
LvOT to LOCC	-4.089	<0.001
RIFG to RvOT	-3.229	<0.001
ROCC to LOCC	4.059	<0.001

For details of the ALM coefficients and significance values see Table 7. The only significant demographic variable in the ‘Combined’ model was age (younger patients responded better to therapy than older patients). For baseline behavioural measures the following reading related variables were identified: i) accuracy in the text reading test (Neale (Neale et al., 1999); the lower the baseline reading accuracy, the better the response to therapy), ii) Neale reading test speed (similarly to accuracy, slower baseline reading speeds were associated with a better therapy response); iii) self-reported reading impairment at baseline as measured by the communication disability profile (CPD (Swinburn, Byng, Porter, & Howard, 2006) the better their self-perceived ability the better the

response to therapy). Other non-reading behavioural measures at baseline that predicted response to therapy were: i) reaction times for the non-verbal version of the Sustained Attention to Response Test (cSART; (Manly et al., 2000) slower RTs, better response); and ii) accuracy in an auditory discrimination task (Robson et al., 2011; worse auditory discrimination, better response).

In terms of connectivity parameters, the following connections had a positive correlation with magnitude of response to iReadMore therapy; i) the connection from right OCC to left OCC and ii) the self-connection with the right OCC. The following connections had a negative correlation; i) the feed-back connection from left vOT to left OCC and ii) the feed-back connection from right IFG to right vOT.

5.5 Discussion

Analysis 1 explored training-induced connectivity modulation within the reading network of stroke patients with CA at the group level. I observed changes distributed across the reading network. I identified increased regional sensitivity to trained words (changes in regions' self-connections) bilaterally at the top (frontal regions) and bottom (occipital regions) of the reading network. This included the left IFG, which I was expecting to find. The between-region connections modified by therapy were predominately in the left hemisphere or, when interhemispheric, were from right to left. Contrary to my predictions, stronger connections were observed in a feed-forward direction from left OCC to vOT and from left vOT to IFG. Together, these findings indicate that iReadMore training predominantly alters left hemisphere connectivity and increases the influence of bottom-up processes.

In Analysis 2, I aimed to explain individual differences in response to iReadMore training using ALM. The winning 'Combined' model was superior to the 'Behavioural model', indicating that therapy-induced changes in individual functional connectivity parameters explain extra variability in response to therapy that is not captured by demographic and behavioural variables alone.

The therapy induced inter-regional modulation of connectivity was predominantly in a feed-forward direction. Stronger connections were observed between the left OCC and left IFG and left OCC and left vOT. These connections were also

stronger for Words compared to False Fonts in the first 300ms of reading in a group of healthy control participants (Woodhead et al., 2014). According to the Local Combination Detector (LCD) model (Dehaene & Cohen, 2011; Dehaene et al., 2005) neurons are tuned to progressively larger fragments of the word as their location moves along the ventral pathway. It is possible that mass exposure to the orthographic stimuli enhanced the processing of word forms within the ventral reading route. These results, when viewed with the reduced strength of feed-back connections from the left IFG to left vOT and from left vOT to left OCC, suggests that iReadMore training in these patients modulates lower-order visual representations, as opposed to higher-order, more abstract ones, in order to improve word reading accuracy.

This finding is in contrast to patients with Pure Alexia (PA), where iReadMore training effects were driven by increased feed-back from the left IFG to left OCC (Woodhead et al., 2013). This was interpreted that improved predictions from the phonological and semantic representations within the IFG constrained the visual processing of trained words. This discrepancy may reflect differences in the lesion location in the two groups; with damage to the PCA territory in PA patients and the MCA territory in CA patients (see *Figure 29*). In response to therapy, each group may have maximised their available intact resources. PA patients have damage to the visual and orthographic input to the reading network. Therefore therapy effects are likely to rely on improving feed-back support from the intact phonological and semantic representation of words within their left IFG. Increased IFG involvement has been identified for task demanding subordinate levels of semantic knowledge (Nagel, Schumacher, Goebel, & D'Esposito, 2008; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011) and tasks relating to phonology (Devlin, Matthews, & Rushworth, 2003; Drakesmith, El-Deredy, & Welbourne, 2015). By contrast, CA patients have damage to the central phonological and/or semantic representations (or connections to them) (Crisp & Lambon Ralph, 2006; Hoffman et al., 2015; Robson et al., 2011). Therefore, therapy may increase reliance on orthographic processing to drive rebuilding or reconnecting of the phonological and/or semantic representations in a feed-forward manner.

Increases in self-connection strengths were observed in the left and right OCCs and IFGs. In DCM, self-connections act as a gain control; the greater the gain,

the greater the regional response will be to any given unit of neuronal input (Kiebel et al., 2007). The left IFG has been implicated the early stages of visual word recognition (P. L. Cornelissen et al., 2009; Wheat et al., 2010; Woodhead et al., 2014) and was modulated by iReadMore therapy in patients with PA (Woodhead et al., 2013); however, I did not expect the self-connection of the right IFG in my CA patients to also became stronger. Healthy readers have demonstrated right IFG hemisphere activation when reading (Rueckl et al., 2015). Support from the right IFG in language tasks has been reported in aphasia rehabilitation research (Crinion & Price, 2005; B. Mohr et al., 2016; Naeser et al., 2011; Nardo, Holland, Leff, Price, & Crinion, 2017; Turkeltaub et al., 2012). However, it has been argued by some that this strategy may be ineffective in comparison to using perilesional left hemisphere regions (Heiss & Thiel, 2006). The stronger self-connections in both IFGs may reflect the differences in patients' progress with training. In a participant with phonological dyslexia, increased right IFG activity was observed immediately following training. However, when training continued on words read correctly immediately post-therapy, increased activation was observed in left hemisphere perilesional regions (Kurland et al., 2008). It has been suggested that the right IFG has a role in assisting with error monitoring and increased attention control (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). The increased connection strength from right IFG to left IFG may suggest that the IFG has a different role in word reading, which may be related to error monitoring, which will have also been modulated by iReadMore.

iReadMore was designed to retrain word reading across all subtypes of CA through repeated activation of the semantic, phonological and orthographic representations of trained words (Woodhead et al., 2018). Retraining in this omnibus manner potentially strengthened the mappings between differing cortical representations of words (e.g. semantic, phonological or orthographic) which may explain why I saw a distributed pattern of network modulation. My study provides support for the role of both the right and left hemisphere nodes, suggesting that therapeutic effects play out among both surviving left and right hemisphere regions, albeit with a leftward bias. This pattern of distributed but left dominant modulation is consistent with results found in both healthy controls and patients (Abel et al., 2015; Rueckl et al., 2015). Studies from the motor literature demonstrate a similarly complex pattern or reorganisation post-stroke. The

contralesional M1 has been shown to inhibit the ipsilesion M1 during movements of the affected limb (Grefkes & Ward, 2014). This was particularly true of patients with stronger motor impairments (Grefkes et al., 2008). However, other findings suggest a facilitatory role of the contralesional hemisphere on movement (Fridman et al., 2004; Johansen-Berg et al., 2002). The distributed nature of the therapy effects may demonstrate a similarly complex role of the left and right hemisphere in language recovery.

This is the first such analysis of MEG DCM data of therapy effects in CA patients, indicting the infancy of the field (Meinzer & Breitenstein, 2008). Aphasic stroke patients respond differently to similar treatments (Brady, Kelly, Godwin, & Enderby, 2012). I explored the variability in individuals' responses to iReadMore training using an exploratory ALM analysis. This allowed me to also explore which connectivity adaptations best explained patients' responses to therapy, if demographic and baseline behavioural variables were also included in the model. ALM uses a process of forward regression, and it was given a large number of variables with which to makes the model. Therefore, there is a risk that the models generated by the ALM may over fit the data (Babyak, 2004). This limits the generalizability of the analysis and the variables selected by the model should be interpreted with caution. The winning model contained both demographic, behavioural and functional connectivity values to explain each person's response to therapy.

The following behavioural factors were associated with greater improvements in single word reading accuracy; older age, poorer pre-training reading performance (as measured by the Neale text reading, both accuracy and RT), slower reactions times on an attention task, poorer auditory phonological awareness and, anomalously, higher self-perceived ratings of reading ability. The finding that patients with poorer pre-treatment performance responded better to therapy could reflect that there was a larger potential for gain in these patients, as they were not subject to ceiling effect. However, it may also suggest that iReadMore is suitable for highly impaired patients, this would be congruent with the connectivity analysis which revealed iReadMore was effective through largely bottom-up rather than top-down mechanisms. This suggests that the more reading impaired the patients, the bigger the therapy gains on iReadmore.

Studies investigating the effects of age on recovery from aphasia or response to aphasia therapy are mixed. While some have demonstrated greater recovery for younger patients (Babyak, 2004; Lazar & Antoniello, 2008) others have found no evidence of such a relationship (Lazar & Antoniello, 2008; Seniów, Litwin, & Leśniak, 2009). It is unusual for older age to be associated with better recovery; however, this may reflect an ability for younger participants within the study to recover more language spontaneously, or to be more active in seeking and receiving treatment for therapy. It may also further reflect the complex involvement of age in stroke recovery.

Greater response to therapy was also associated with slower reaction times on the attention task. The attention task employed in the current study is easier if the participant slows their response. It is a go/no go task, and thus easier to inhibit a response on “no go” trials if it is completed at a slower rate. This result therefore may indicate that relationship between careful task completion and response to therapy, rather than an impairment in cognition. Other findings in the field have indicated better general cognitive abilities are associated with greater response to aphasia therapy (Dignam et al., 2017; Lambon Ralph et al., 2010). Additionally, neuroimaging data has suggested key regions involved in domain general functions (associated with cognitive function) were correlated with language performance in post-stroke aphasia (Brownsett et al., 2014).

Interestingly, poorer performance on a phonological discrimination task was associated with better therapy gains. Most of the participants in the current study demonstrated either phonological or deep dyslexia which is associated with a deficit in phonological processing (or its connection with orthography) according to the triangle model of reading. The deficit in phonological awareness may further indicate greater severity of impairment, which means they may have more to gain from the single word training. This may also suggest that iReadMore is suitable for patients with a phonological impairment, either by allowing these participants to use other intact resources (e.g. a route to reading via semantics) or it may potentially improve phonological awareness. This was not tested in the interval assessments, so is merely speculative and has not been tested in previous lexical therapies for phonological alexia (Kurland et al., 2008; Lott, Sample, Oliver, Lacey, & Friedman, 2008; Ska et al., 2003).

Higher perceived self-reported reading ability was associated with better therapy gains. This is an unusual result, as the other factors included in the model suggest that the greater the impairment, the larger the therapy gains. I am unsure how to interpret this result. The self-reported measure used to generate this result (CPD), only contained one question directly relating to single word reading. The additional 3 questions refer to sentence and text level reading. There are clear inter-personal differences involved in completing questionnaires, and it the measure is probably best used to investigate changes in perceived word reading, rather than between subject analyses.

I observed a positive modulation of two connections that were associated with greater iReadMore therapy gains across the group: a) the right OCC self-connection; and, b) the connection from right to left OCC. This probably reflects selective tuning of visual cortex to the orthographic information in trained words induced by multiple, repetitive exposure with trial-by-trial feedback. According to the split fovea theory, visual information from the front of a word is received by the right OCC as the optimal viewing position is usually just to the left of centre of any given word (Nazir, Heller, & Sussmann, 1992). Acceptable dipole locations were not restricted to V1 so extra-striate regions will almost certainly have contributed to the observed effects. As hemifield integration occurs above the level of V1, the changes in the right OCC self-connection and interhemispheric connection to left OCC suggests increased sensitivity to the front part (left of fixation) of trained words (Perea & Lupker, 2003). The combination of these two associated connections correlating with response to therapy suggests that the better the residual reading network can process orthographic inputs into the right OCC and pass these to the left OCC, the more efficient patients' reading becomes. This is consistent with reading models proposed by Cohen and Dehaene (Cohen et al., 2002; Dehaene et al., 2001; Perea & Lupker, 2003).

The ALM also revealed negative modulation of connections that were associated with greater therapy gains, namely the backwards connections from right IFG to right vOT and from left vOT to left OCC. This indicates that better therapy outcomes were predicted by weakening these feed-back connections. This effect was counter to my expectations, but further supports the bottom-up nature of my iReadMore therapy-driven changes in patients with CA.

In summary, in a group of patients with CA, improved word reading after iReadMore training was associated with distributed changes across the residual reading network. I identified a mixture of: a) within hemisphere connections (mainly left-lateralized and feed-forward), that were strengthened by therapy; b) bihemispheric connections (particularly self-connections at both the top and bottom of the reading hierarchy); c) between hemisphere connections (right to left pattern). Also, the magnitude of therapy-induced change in connections within and between the occipital lobes explained part of the patients' response to therapy. This suggests that the better the residual reading network can process orthographic inputs, the bigger the therapy gains. The iReadMore therapy app will be available to the public in 2018 (http://www.ucl.ac.uk/aphasialab/apps/ireadmore.html).

6 Discussion

This thesis investigated the effects of a word reading retaining app, iReadMore, on the word reading ability of 23 patients with CA and the corresponding changes within their neural reading network.

The main aims of this thesis were:

1. Chapter 3, aimed to identify how the reading network of CA participants differed from that of healthy controls. These results were explored within the context of existing neurologically inspired models of reading.
2. Chapter 4 aimed to identify if iReadMore training improved single word reading accuracy and reaction times in patients with CA. Furthermore, it aimed to identify the potential additive effects of providing A-tDCS targeted at the left IFG in conjunction with iReadMore training.
3. Modulations in the neural reading network of CA participants in response to iReadMore training were explored in Chapter 5. This aimed to identify potential mechanisms by which the iReadMore training was effective, and which connection modulations are related to response to training.

In this final chapter, I review each results chapter in turn, and provide an overview of their key contributions to the research field, the limitations of the study and potential future directions for this research. Finally, I end by discussing sentence level reading rehabilitation in CA and DCM neuroimaging and clinical practice.

6.1 Overview of key results, possible limitations, and future directions

6.1.1 Chapter 3

6.1.1.1 Key Contributions

This study aimed to explore the reading network of CA participants and how it differs from that of healthy controls. In contrast to healthy control participants whose reading network was predominately left lateralised, CA participants demonstrated a bilateral reading network. Stronger bidirectional inter-hemispheric connections between the OCCs and IFGs, and stronger feed-forward connections from OCC to IFG and vOT in the right hemisphere were

observed in CA participants compared to controls. This suggests that the right hemisphere supports reading in CA patients. Within the left hemisphere, the forward connection from OCC to vOT was weaker for words in CA patients in comparison to healthy control participants.

This was the first study to explore how the reading network of CA patients differed from that of healthy controls. It supports previous research that has identified a bilateral distribution of language processing following stroke (Abel et al., 2015; Heiss & Thiel, 2006; Kurland et al., 2008; Meinzer et al., 2006; Saur et al., 2006; Turkeltaub et al., 2011; van Hees et al., 2014).

I interpreted these results within the context the LCD (Cohen & Dehaene, 2004; Dehaene et al., 2005) and IA (Price & Devlin, 2011) models of reading. Whist neither model makes explicit claims about how the reading network would react to left hemisphere damage, I attempted to evaluate whether my results were compatible with each model. For example, my observation of differences between CA and control participants in the left ventral visual stream, distal to their stroke, seems incongruent with the feed-forward account of word recognition proposed by the LCD model of reading. The IA model of reading, and the predicting coding account upon which it is based (Friston, 2005, 2008), detail how the brain may be adaptive. The right hemisphere connection modulations may be indicative of a system in flux, with increased prediction error feeding forward in order to update long-standing representations in the right IFG, which also demonstrated an increased sensitivity for Words than False Fonts. However, the principles of the IA model are not tied down to specific brain regions and so are thus open to very broad interpretation. This study did not aim to test each model of word reading, but rather explore the reading network of CA participants with reference to the IA and LCD accounts of reading. However, these results highlight a potential need for increased specification within these models regarding MCA stroke damage.

6.1.1.2 Limitations

Unfortunately, none of the correlations relating baseline-reading skill to connection modulations in CA participants' reading network were significant. This makes it challenging to determine whether connection modulation was a beneficial adaptation in response to damage, or not.

I used catch trials as the only behavioural output for the MEG scan. In the analysis, word trials were averaged, regardless of whether they were read successfully (as there was no output data for this). Additionally, there was a large degree of variability within CA participants' baseline word reading accuracy (range: 3% to 97%). This means that the DCM modelled both successfully and unsuccessfully read words, which may have been undergone different neurological processing and added noise to the analysis making it less reliable.

The selection of participants with IFG sparing limits the generalizability of the findings. A digital atlas of MRI scans from 28 MCA stroke patients demonstrates that the IFG is commonly affected in MCA stroke (Phan et al., 2005). By selecting stroke patients without damage to the IFG, I was more likely to select those with more posterior lesions, affecting the peri-sylvian fissure, commonly associated with phonological dyslexia and phonology in word reading (Cattinelli, Borghese, Gallucci, & Paulesu, 2013; Rapcsak et al., 2009). This is represented in the resulting sample. The reading network modelled in this study did not include a dorsal reading node, such as a site in the inferior parietal lobe or posterior middle temporal gyrus, superior temporal gyrus or planum temporale. These regions have been indicated as an important nodes for semantic (Binder, Medler, Desai, Conant, & Liebenthal, 2005; W. W. Graves et al., 2010; Price & Mechelli, 2005; Seghier, 2013) and phonological processing (Juphard et al., 2011; Levy et al., 2009; Perrone-Bertolotti, Pichat, Le Bas, Baciu, & Baciu, 2011; Vigneau, Jobard, Mazoyer, & Tzourio-Mazoyer, 2005). When studies have mapped the DRC and triangle models of reading onto the brain, a dorsal region has been included (Hoffman et al., 2015; Levy et al., 2009). Preliminary analysis of the CA data revealed that a reliable parietal left hemisphere source could not be identified for all CA participants. This may be in part because participants were selected on the basis of having MCA strokes that spared at least part of the IFG. As a result, participants were more likely to have had damage to more posterior MCA areas. As a parietal source was not included, it limits the use of the DRC and triangle models in explaining the DCM data.

6.1.1.3 Future directions

In future analysis, it would be interesting to model a dorsal reading route in those participants for whom it could be found, and compare whether the eight source

model (e.g. left and right SMG, IFG, vOT and OCC) or six source model (e.g. left and right IFG, vOT and OCC) better fitted the data. This could potentially allow for the comparison of patients with and without this region, and identify more about its potential role in word reading. It is unfortunate that it is currently not possible to compare connection strength modulation in models with different number of sources. If more patients were available, it would also be useful to assess the application of the DRC and triangle model to damage relating to each subtype at a network level.

An alterative way to perform the task could have been to ask the participants to read the words aloud in the MEG scanner. This would allow for successful and unsuccessful word reading events to be differentiated and modelled separately. This may improve the accuracy of the model as it will reduce the noise that is currently being modelled as accurate and inaccurate reading attempts are currently treated equally within the model.

While speech production within the MEG scanner has successfully been performed by other groups (Laine, Salmelin, Helenius, & Marttila, 2000; Salmelin, Schnitzler, Schmitz, & Freund, 2000) this proposed study design is not without its flaws. In most study designs using reading aloud participants are required to delay their speech output. This is in part because facial muscle activity can create MEG signal artefacts. Holding the target word in working memory before producing an output maybe challenging for some of my participants as they also display cognitive and working memory deficits. Additionally, it would have meant participants inhibiting their response until cued, which may be challenging to patients who also have a speech output deficit.

An alternative way to conduct a similar analysis would be to identify words read correctly outside of the scanner. One challenge to this method is the variability in participants' performance for reading the same word. Finally, another challenge to this form of analysis is that it requires all participants to correctly read enough trials for meaningful analysis to be performed. With a word reading accuracy as low as 3% in some cases, this may not be possible.

6.1.2 Chapter 4

6.1.2.1 Key contributions

Here I demonstrated that iReadMore training of 35 hours per therapy block significantly improved word reading accuracy and reaction time for trained words in 21 participants with CA. There are over fifty aphasia apps listed on the Tavistock Trust for Aphasia website (https://www.aphasiasoftwarefinder.org/app-software-list). However, most are not clinically proven. This study provides a solid evidence base for the release of the iReadMore app, and allows us to inform patients of the average potential gains that were observed when CA participants used the app. This may help to manage their expectations of the potential benefits of the app.

Patients improved on Core words within the first therapy block. These high frequency words can be particular difficult to train (Friedman & Lott, 2002; Lott et al., 2008), potentially because of their low imageability and semantic representations. This means that the training can be applicable to all words, which may give it this app more ecological validity than therapies which only target nouns.

Finally, a within subject analysis revealed a significant effect of A-tDCS to the left IFG. This equated to an additive effect of A-tDCS of approximately 2.6% (Cohen's *d*=0.41). The effects of A-tDCS have not previously been demonstrated with a CA population.

6.1.2.2 Study Limitations

Perhaps the most striking result is that the effects of iReadMore therapy were item specific - that is, only trained words improved. While a trend towards a significant improvement was observed in reading for meaning, the iReadMore training effects also did not generalise to the sentence or text reading level. While scientifically this was helpful in quantifying the therapy effects it could be perceived as a limitation as to how functionally meaningful the app might be for participants (that is, the degree to which it has an impact on the day-to-day life).

By contrast, the A-tDCS effects of tDCS were observed for both trained and untrained items. The generalised improvement observed here may have been

induced by an improvement in speech output ability. This is particularly relevant as the primary outcome measure was word reading aloud. Stimulation of the left IFG has been associated with naming facilitation in both healthy older adults and patients with aphasia (Baker et al., 2010; Holland et al., 2011; Holland, Leff, Penny, Rothwell, & Crinion, 2016). While the text reading task also involved a spoken output and did not improve with iReadMore training, it is unfortunate that a naming measure was not included in the interval battery. Future research could consider including a naming test as an outcome measure to control for improved speech output as the mechanism improvement reading aloud.

6.1.2.3 Future directions

In moving forward with app development for aphasia, it will be important to consider how to maximise its functional meaningfulness to the user. One possible way is by allowing users to select their own words, so even if patients don't improve at the sentence level, the training stimuli are meaningful for them.

In total, over the two therapy blocks, CA participants completed over 70 hours of training. Future analysis on an item specific level would be useful to identify if the training parameters used within the app could be improved. For example, are there some words for which no amount of training will improve word reading reliably? And could these be predicted by performance after a certain number of trials? With the release of the app online it is hoped there will be many more users. In turn this will garner large amounts of data making this type of analysis possible in the future.

No CA subtype analysis was performed on this data to identify if there was a difference in the degree of response with CA subtype. This was primarily because the subtype groups were not sufficient in size to perform this analysis (1 SD, 9 DD, 11 PD). A larger data set would allow for this analysis. Again, this would enable the app to provide predictions as to whom it will be maximally effective for.

iReadMore aimed to train word reading. However, this may have been closely linked to participants' abilities to spell (Rapp & Lipka, 2011). Indeed, some therapies targeted at improving reading and spelling have reported an improvement in spelling, without an improvement in reading (Kiran et al., 2001).

Similar neurological regions have been identified as important for both reading and spelling (Purcell, Shea, & Rapp, 2014). In would be interesting to explore whether iReadMore is also effective in improving spelling as well as reading.

Training effects degraded over time, although a significant improvement was still observed at T6 (3 months after training ended) relative to T3 (prior to training). Decreases in therapy effects post treatment have been observed elsewhere in the aphasia literature (Brookshire, Conway, et al., 2014; Kiran et al., 2001). Obviously, it would be preferable if maximal therapy gains can be maintained. One possible way in which to maintain these improvements is to provide patients with "top-up" doses of treatment, for example, through low intensity exposure to trained items (Breitenstein et al., 2017). The number of hours of training and the interval between exposures would need to be tested to identify if this is effective.

The significant effect of A-tDCS is encouraging. However, in the iReadMore trial, participants attended UCL three times a week to receive stimulation. This is probably not a viable option for providing A-tDCS as a therapy adjunct given the current challenges in delivering SLT for aphasia within the NHS (Code & Petheram, 2011). However, the field of tDCS research is designing and testing tDCS kits that can be used unsupervised, at home (Charvet et al., 2015). This is a more viable option for providing CA participants with a potential additive effect for mass practice training exercises that can also be administered without supervision (e.g. iReadMore). Future research is needed to design safe home tDCS kits and test the feasibility of their use for people with aphasia.

6.1.3 Chapter 5

6.1.3.1 Key Contributions

This study aimed to investigate the training related changes in the neural reading network of CA participants. Training induced an increase in left-hemisphere feed-forward connectivity strength. Increased sensitivity in the left and right occipital and frontal regions for trained words were also observed. Using ALM I investigated the relationship between baseline behavioural variables and training related connection strength modulations. The ALM analysis showed that the self-connections within the right OCC and the connection from right OCC to left OCC were significant predictors of therapy gains. This suggests that after modelling

baseline behavioural factors, the degree of therapy response was associated with their ability to process orthographic stimuli in the right hemisphere and pass this information to the left hemisphere. Also, participants with more severe impairments in reading before treatment were more likely to exhibit larger iReadMore therapy gains.

Together with the results of Chapter 3, a tentative conclusion would be that iReadMore encourages the use of a left lateralised reading network, which was pre-therapy, highly bilateral. Changes in language lateralisation following stroke have been reported (Saur et al., 2006) and increases in activity in left-hemisphere perilesional regions have been reported by other reading therapy studies (Kurland et al., 2008).

6.1.3.2 Limitations

This study aimed to identify how the reading network of CA participant's responded to iReadMore therapy. This analysis was conducted at the group level. Within the group, some participants improved by 35% for trained items and others did not improve. Trained and untrained word stimuli were included in this analysis for all participants regardless of their improvement. This means that this analysis may have been trying to identify a change in the reading network that was not there in some patients, because they did not improve. This may have added noise to the DCM modelling.

DCM for MEG requires the specification of nodes to be included in the model. While models containing different numbers of nodes were tested (e.g. a four source model vs a six source model) this depends heavily on the pre-existing hypotheses about the potential mechanisms for therapy effects. It is possible that a region not included in the model was underlying the behavioural therapy effects observed.

The failure to reliably identify a parietal source may reflect a more general challenge to the selected analysis. A group level DCM requires all participants to have tissue in the regions included in the model. However, MCA strokes are highly variable (Phan et al., 2005), and the neuroanatomical associations between alexia subtypes are still being investigated (Aguilar, Kerry, Crinion, et al., 2018; Ripamonti et al., 2014; Woollams et al., 2018). So while the DCM is

helpful, in that it considers the reading network as a whole rather than activation in individual regions, it is hindered by the requirement for all participants to have similar lesion locations and diploes. However, when individual level DCM have been conducted to investigate the effects of aphasia therapy at the network level, there is a wide degree of variability in the resulting model, which make it hard to draw meaningful conclusions from the data (Kiran, Meier, Kapse, & Glynn, 2015).

6.1.3.3 Future directions

It would have been beneficial to perform another MEG scan after the second therapy block. This may have allowed me to explore the effects of A-tDCS. As the tDCS effects were not significant in a between subject analysis of the first therapy block, they were not investigated with the MEG data. A third MEG scan conducted after the second therapy block would have allowed for a within subjects comparison to be performed. However, modelling the tDCS effect may have been challenging as A-tDCS only resulted in a 2.6% in the behavioural effect. Modelling an effect this small, given the noise observed in the current study design, may be challenging.

To relate the changes in significant connectivity modulations highlighted by the DCM, an ALM was conducted. This allowed me to explored the relationship between the degree of improvement in word reading accuracy over the therapy block with connection modulation identified in the DCM, whilst including behavioural and demographic factors in the model. It would have also been interesting to test a model that included different regions of lesion damage. This would have allowed me to identify if connectivity modulation in the DCM explains more of the variation in response to iReadMore training than demographic, behavioural and lesion location alone. Please see the “DCM neuroimaging and clinical practice” section below for a further discussion behind the rationale of this research.

6.1.4 Sentence level reading rehabilitation in CA

Training sentence reading in CA patients continues to present a challenge for CA therapy provision. These difficulties could be caused by a number of reasons. For example, sentence reading may be affected by cognitive factors, such as maintaining words in working memory when reading a sentence (especially when

single word reading is slow and effortful); processing the grammatical structure of the sentence and appreciating and the depth of meaning within the sentence (i.e. some sentences cannot be interpreted literally) may also prove challenging. However, anecdotally, patients in CA trial reported they wanted to improve sentence and passage level reading. Given the complexity of the possible challenges to rehabilitation at the sentence level, I am not sure that simply improving single word reading ability of CA patients will translate to sentence level reading without additional training. However, it is logical that increased accuracy and faster single word reading would make sentence level reading more likely to be successful . Retraining sentence level reading is difficult problem to solve; if it was straightforward, I think we would be closer to the answer. However, I think future efforts into reading retraining should focus on including this level of training. This may start by developing tools to better identify the potential challenges in sentence reading in patients with CA (Webster et al., 2013).

6.1.5 DCM neuroimaging and clinical practice

This thesis aimed to understand more about the reading network within the brains of CA patients and how they respond to therapy. It is hoped that this will help the field develop better therapies. However, I believe directly translating the results of neuroimaging observations to therapeutic practice will require extensive further investigation.

Let us consider what we may be able to ascertain from neuroimaging that could be directly translated into therapeutic practice:

1) We know that aphasia participants are variable in their response to therapy (Aguilar, Kerry, Ong, et al., 2018; Brady et al., 2016). Patients and clinicians may benefit from being able to make personalised predictions regarding how much a CA participant can expect to gain from a given therapy. This could be achieved by estimating the degree of improvement other patients with a similar behavioural and neuroimaging (structural and/or functional) profile made on the same therapy. If this is taken one step further, and this knowledge is sought with multiple therapies, clinicians can start to “prescribe” the therapy that best suits that person.

2) Our understanding of how therapies worked could also allow clinicians to explain to patients why one task is difficult for them and others are not. This may help patients to identify which tasks might improve with training, and which are unlikely to change.
3) To use our information about the brain to develop novel therapies.

While the DCM approach has the advantage of allowing inference at the network-level, it is time consuming to perform and computationally intensive. This makes its potential contribution to clinical work sometimes difficult to ascertain. However, its use has been outlined elsewhere (Price, 2018; Price, Hope, & Seghier, 2017). Variability in stroke recovery following similar lesions has been a challenge for clinicians trying to map structure to function or predict recovery using lesion location (Lazar & Antoniello, 2008; Price et al., 2010). It has been proposed that research studies of healthy reading networks would highlight the potential networks that could be engaged to complete a task (e.g. word reading aloud) (Price et al., 2017). Possible reasons for variability in stroke patients' individual differences in stroke recovery may depend on their reliance on different processing streams to complete a task (Seghier, Bagdasaryan, Jung, & Price, 2014). For example, if a patient's dominant route to completing a task is damaged they will display a greater impairment than another patient with a similar lesion location, but for whom the same route to completing the task is their non-dominant route (Price et al., 2017). This is based on the idea that for a given process, there are many regions that may be able to perform a task. DCM can be used to identify the different routes to task completion and the variability in use in the general population (Seghier et al., 2014). This can help us divide participants based on their preserved route to reading, and suggest therapies that do not rely on this route.

Processing time and the software resources required to perform DCM analysis are being reduced by advances in the SPM software (Friston et al., 2016). I think this will make it a more accessible tool for researchers to develop our understanding of the mechanisms by which a therapy is effective. Predictions based on structural scans are probably a more viable clinical option for personalised medicine. One possible application of this would be to estimate how much a person may respond to a certain therapy app given their lesion location.

One challenge to reaching the aim of point 3 is that even when a region/network has been identified as important for word reading (perhaps on an individual patient level) translating this information into novel therapies can still prove challenging. Connectionist psychologists and speech and language therapists have identified the location of damage within the reading system (e.g. phonological dyslexia is a result of impaired GPC rule application). While this has led to the development of stepped therapies to improve phonological representations (or access to them) and GPC rule use, this still involves several hours of training with limited generalisation (Brookshire, Conway, et al., 2014; Friedman Friedman Friedman & Lott, 2002).

While using DCM is currently probably too time consuming to be conducted in a clinical setting for predicting patients' response to therapy or the suitability of an app, I think it still has applications for the clinical setting. Over my time working at UCL, in testing CA participants and working in Prof. Leff's hemianopia clinic, I have grown to appreciate how much patients appear to benefit from a better understanding of their impairment or disorder. I think in helping to understand the reading network of CA patients, DCM could be useful in ultimately helping patients' better understand their conditions. In understanding how their condition responds to therapy we may be better able to help them to identify how to compensate, and what limitations of their condition they may need to accept and what may be improved with work.

7 References

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8 Appendices

8.1 Methods Supplementary material

8.1.1 Sample size calculations

Sample size was calculated using alpha = 5% and beta = 90%. A previous study using a prototype of iReadMore in a group of stroke patients with chronic pure alexia (Woodhead et al., 2013) resulted in an improvement in word reading reaction times of 149.0ms (sd = 214.5ms). This effect size was the change in trained word reading reaction times before (T2) minus after (T3) training. The sample size required to detect a comparable improvement was calculated using an online calculator from https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/samplesizecalculators.aspx. Using alpha = 5% and beta = 10%, a required sample size of n = 18 was indicated.

The expected effect size resulting from A-tDCS to the left IFG was powered based on a study by Baker and colleagues (2010). This study compared a-tDCS and sham during anomia therapy in 10 patients with chronic aphasia. On average, they observed a 14.4% improvement in picture naming accuracy following a-TDCS, compared to only 6% following sham. The benefit of a-tDCS over sham was 8.4% (s.d. = 10.2). The sample size required to detect a comparable improvement was calculated using the same calculator, again with alpha = 5% and beta = 90%, which indicated a sample size of n=13 would be required. Taking a conservative approach to allow for possible differences between studies, I aimed to collect data from 20 subjects. Recruitment stopped at *n* = 24 (to allow for a 20% drop-out rate), of whom *n* = 21 participants completed the protocol (Fig. 1).

8.1.2 Difficulty Adaptation: Global Parameters

Task difficulty was reflected in three global adaptive parameters: 1) written word duration in exposure and challenge phases; 2) criterion score in the challenge phase; and 3) criterion reaction times for fast/slow correct responses in the challenge phase. All three parameters changed simultaneously when the difficulty level changed. The difficulty level began at 1, then increased

incrementally when the participant passed a challenge phase. If the participant failed three successive challenge phases, then the level decreased by one. The formulae for generating the task parameters at each difficulty level ('LEVEL') are shown in the table below. The word duration was initially set to the participant's average word reading RT at baseline ('baseline_RT'). Each parameter had a maximum or minimum boundary that could not be exceeded – once this was reached, the parameter remained constant, but could revert to an easier setting if the difficulty level subsequently reduced.

Parameter (y)	**Function**	**Min / max allowed**
Word duration (ms)	y = baseline_RT – 2 * LEVEL * baseline_RT / 100	Min = 100
Criterion score	y = 20 + 0.5 * LEVEL	Max = 56
Fast response criterion (ms)	y = 4000 – 30 * LEVEL	Min = 2000
Slow response criterion (ms)	y = 10000 – 90 * LEVEL	Min = 5000

8.1.3 Difficulty Adaptation: Item-Specific Parameters

The distractor word selected for each 'different' trial in the challenge phase started at the easy level. In each challenge phase, a target word could be presented up to three times, and 0-3 of those trials could be 'different' trials. Distractor difficulty level (easy / medium / hard) in subsequent challenge phases was then adapted according to the following rules:

If a DIFFERENT trial appeared once, the distractor difficulty level moved forwards (+1) if the response was correct, or moved backwards (-1) if the response was incorrect).

If a DIFFERENT trial appeared more than once, the outcome for all trials was summed, e.g. +1 for each correct trial, and -1 for each incorrect trial. If the summed value was POSITIVE then the difficulty level moved upward, if it was

NEGATIVE the difficulty level moved down; and if it was ZERO it stayed the same.

The position of the target word in the word list changed according to performance on all 'same' or 'different' trials for that word in the challenge phase. Each target word would be presented up to three times in each challenge phase. If any one of the trials was responded to incorrectly, the position of the target word in the word list would not change, so that the word would definitely appear in the next exposure phase. If all trials were responded correctly, the change in word position would be calculated by taking the average position change score using the following rules:

Same / different trial	**Easy / medium / hard level**	**Position change score**
Same	Easy	+ 20
Same	Medium	+ 20
Same	Hard	+ 20
Different	Easy	+ 20
Different	Medium	+ 50
Different	Hard	+200

The result of this position change score meant that words would be presented again soon (e.g. if the average position change score was low) or not for a long time (e.g. if the average position change score was high). The number of times that each target word in the word list was presented therefore depended on performance.

8.1.4 Cognitive Tests

8.1.4.1 Cattell Cultural Fair Test; Subtests 1 and 2

Subtest 1: In this non-verbal test, participants were presented with three drawings made of lines and dots that formed a sequence. Participant's chose the next picture in the sequence from five alternatives. The instructor demonstrated three example trials before asking the participant to complete 12 trials within 3 minutes.

Subtest 2: Five drawings of shapes and dots were presented. The participant was asked to decide which of the five drawings was different to the other drawings. Participants were given 4 minutes to complete 14 trials.

8.1.4.2 Digit span from Wechsler Adult Intelligence Scale –IV

The digit span test was administered forward and backwards. In the forward's version, participants were asked to repeat as series of digits read at a rate of one per second. The number of digits in the sequence increased by one each level, starting at two digits to a maximum of 9 digits. Two trials were administered at each level; the test was terminated when the participant failed both trials. In the backwards version, participants were asked the repeat the digit series in the reverse order to that administered by the instructor. The maximal score for the forward and backward versions of the test are 16 and 14, respectively.

8.1.4.3 Two armed bandit test

Two boxes were presented to the left and right of the screen. Participants were informed that sometimes the boxes contained a reward and the probability that a box contained a reward varied throughout the task. Their job was to choose the box that contained the reward. The box was selected by pressing the right or left arrow key. Once the box was selected, participants were informed whether it contained a reward. The test consisted of two blocks of 110 trials. Participants were given feedback on their performance between blocks. The total maximal score for this test was 220.

8.1.4.4 The Brixton Test

This non-verbal test assesses a participant ability to detect and follow a rule. On each page of the 56 page stimulus book there are two rows of five circles. A circle is shaded on each page. The location of the shaded circle changes on each page and is governed by a series of simple but changing rules. Participants are presented with one page at a time, and asked to predict the next location of the shaded circle. The total number of errors is used as the outcome measure, with 55 the maximum score and lower scores indicating better performance.

8.1.4.5 4 way Weigl

16 tokens were arranged randomly in front of the participant. Participants were instructed to sort the tokens into groups, so that within each group the tokens are similar in one particular way. The participant was then asked to sort the tokens in another way, until the tokens were sorted all four ways. There are four possible ways to sort the counters, by; colour, shape, texture or by the symbol printed on the top of the token. Participants were allowed 45 seconds to sort the tokens. If the participant is unable to sort the tokens, the experimenter provided the first assistance by sorting the tokens into one complete group and asking the participant to sort the remaining tokens. If the participant was unable to complete the sort, they were told the dimension of the sort. Points were awarded as follows: Three points for an unassisted sort, two points for a complete sort with one assist, and one point for a complete sort with two assists. The maximal score for this test was 12.

8.1.4.6 Auditory discrimination task

This task assessed phonological auditory perception (Robson et al., 2011). Participants were played three tones (A-B-C). In each trial, either A or C was the same as B. Participants were instructed to identify the tone which was the odd one out. The task had 14 levels of difficulty and all participant's started at the easiest level (14). Using a stair case design the task increased in difficulty; for every three correct responses the task increased one level of difficulty but for every incorrect response, the task decreased one level of difficulty. The test ceased when the participant reached the hardest difficulty level (1), obtained eight incorrect trials leading to a level reversal, or eight incorrect responses at the easiest level. The outcome measure was the average of the level number of the last 4 incorrect trials.

8.1.4.7 Short-term visual memory task

This test was designed to mimic the auditory digit span task in the visual domain, and hence measured visual working memory. Five grey squares were presented horizontally. For each trial, the participant was asked to observe and then replicate, using button press, the order in which the squares were illuminated. At the simplest level the sequence only included two illuminated squares. The difficulty increased by adding an additional square to the sequence until a

maximum difficulty level of eight squares was reached. Each level was tested over two trials. The test ceased after the participant successfully completed the task at the highest level (7) or after two failed attempts at the same level. The outcome variable was the total number of sequences correctly produced.

8.1.4.8 Pictorial pyramids and palm trees

A probe picture is displayed at the top of the page (Howard & Patterson, 1992). Participants are asked to select which one of the two pictures at the bottom of the page best goes with the probe picture. The two lower pictures consist of a target picture and a distractor both of which are from the same semantic category. The test consists of 52 triads and is designed to test non-verbal semantic processing. One point is awarded for each correct response. A score of <90% accuracy is considered impaired.

8.1.5 Magnetoencephalography

8.1.5.1 What does MEG measure and how?

MEG measures the magnetic flow that runs orthogonally to the electric flow generated with neuronal firing. The changes in magnetic potential caused by neuronal firing are very small (10^3 fT) in comparison to other sources of magnetic flow such as the earth's magnetic field, power cables and urban noise (10^8 fT). For this reason, the MEG scanner is housed in a magnetic shielded room, and very sensitive sensors are used to detect neural activity.

Inside the MEG scanner's dewar are 275 sensors. These sensors contain gradiometers, which consist of two oppositely wound coils. The wire coils transform the magnetic flux into electrical signal. One wire coil is closer to the head than the other. The gradiometer measures the difference in magnetic flux between these two coils. The idea being, that the upper coil will mainly capture environmental magnetic flow, whereas the lower coil will measure environmental and neuronal magnetic flow. By measuring the net magnetic flow, the magnetic flow can be measured from neuronal sources above the environmental noise. The signal from gradiometers is still too small to be measured directly, so it is passed through superconducting quantum inference device (SQUIDs). This

causes a voltage change across the superconducting loop, which can be amplified and measured.

Among cortical neurons, pyramidal cells are believed to be the main source of MEG signal. This is for a number of reasons. 1. They are found within the cerebral cortex and create a dipole current, this makes them close enough to the MEG scanner sensors to be measurable. 2. In order to create a change in the magnetic flow detectable outside the skull, many neurons are required to fire synchronously. Pyramidal neurons are arranged in an approximately parallel formation, when they are simultaneously active, the cumulative activity becomes a measureable current. 3. The current flows through the dendrites in the direction of the pyramidal cell bodies. This means that their orientation is such that it is likely to create a magnetic flow tangential to the skull surface.

8.1.6 Dynamic Causal Modelling within MEG

8.1.6.1 Estimating models

The first step in dynamic causal modelling is to estimate the models. This is achieved through the use of state equations and observer output equations (Kiebel, Garrido, Moran, Chen, & Friston, 2009). The state equations summarise the average change in spike-rate-dependent current and voltage for each subpopulation, using the following equation (Garrido et al., 2007):

$$\dot{x} = f(x, u, \theta)$$

This describes the way that the synaptic activity change over time ($\dot{x}$), is a function of the state (parameterised by θ) and the exogenous inputs (u). θ includes the parameters for forwards, backwards and lateral connections and their modulations. These parameters are the interest of DCM. The output allows for the estimation of what the pyramidal cell activity (x_0) will look like in the sensor-level MEG signal. This is achieved by applying a forward model (described in the methods section). It is summarised in the following equation:

$$y = L(\theta)x_0 + \varepsilon$$

This means the data that is observed in the sensors (y) is given by multiplying the parameterised activity (θ) in the pyramidal cells (x_0) by the lead field (L), and

some error. Using both of these equations the predicted activity from the model can be estimated, so that it can later be compared with the data gathered from the sensors.

8.1.6.2 Estimating the model parameters

In each DCM a large number of parameters are estimated. The precise number is dependent on the number of sources and the specified connections between them. Parameters are estimated using Bayesian principles. Each parameter in the model is represented by a Gaussian probability distribution with a prior mean and variance. For example, an error term may have a shrinkage prior, with a mean 0, indicating that it is expected there is little error in the model. The variance assigned to a prior reflects the level of confidence in its value.

External inputs are entered into the model equation with the priors, giving the postsynaptic potentials of the pyramid cells for each timepoint. The output model is then applied to enable comparisons to be made with the observed data. The difference of the estimated model from the observed data is obtained. This measure of model accuracy allows for new posterior probabilities of the model parameters to be approximated according to Bayes rule. The parameter probabilities are revised and updated taking into consideration the data.

This procedure is repeated over a number of iterations. At each iteration the parameters are changed slightly. When changing the parameter values fails to improve their probability, convergence is reached and the process stops. This is the point where all the parameters in the model are at their optimal mean values in light of the data.

A co-ordinated descent of model free-energy is used to optimise the model parameters. The model free-energy can be considered as an approximation of the model evidence, i.e. the probability of the observed data given the model. The free-energy approximation takes into account a) the fit of the data and b) the model complexity.

Self-connections are also modelled within the DCM. These quantify the maximal amplitude of the post-synaptic response in each cell population in that region (Kiebel et al., 2007). These maximal responses are modulated by gain

parameters. Gain parameters greater than one increase the maximal response than can be elicited from a neuronal region. As such, the gain parameters are a measure of a region's sensitivity to an input.

8.1.6.3 Automatic linear modelling

Variables entered into the model

Table 8 Table of variables entered into the ALM modelling

Variable	Timepoints	Outcome
Demographic variables		
Age	T1	Age in years
Sex	T1	
Time post stroke	T1	Time in months
Lesion volume	T1	Lesion size in cm^3
Language variables		
Single word reading	Interval (Bx – T6)	Baseline accuracy (%) Baseline reaction time (ms)
Written semantic matching	Interval (Bx-T6)	Baseline accuracy (%) Baseline reaction time (ms)
Sentence Reading	Interval (Bx–T6)	Baseline accuracy (%) Baseline reaction time (ms)
NEALE	Interval (Bx–T6)	Baseline word reading accuracy (%) Baseline words per minute (ms) Baseline comprehension accuracy (%)
Communication Disability Profile (CPD)	Interval (T1 & T6)	Baseline perceived reading ability (max. 16)
Auditory discrimination task	Baseline	Score (max .14, min. 1)
Pyramid and palm tree	Baseline	Accuracy (%)
Non-word reading test	Baseline	Accuracy (%)
CAT: naming objects and actions	Baseline	Naming objects score (max. 48) Naming actions score (max. 10) Combined naming total
Cognitive Variables		

cSART	Interval (Bx–T6)	Baseline hits (%) Baseline RT for hits (ms) Baseline false negative hits (%) Baseline false positive hits (%) Baseline correct rejections (%) Baseline post-error slowing (ms)
Cattell: subtests 1 & 2	Baseline	Total correct trials for subtest 1 (max. 12) Total correct trials for subtest 2 (max. 14) Combined Total for subsets 1& 2
WAIS IV Digit span: forwards and backwards	Baseline	Total correct trials forwards (max. 16) Total correct trials backwards (max. 14) Combined total correct trials all trials
Two armed bandit	Baseline	Correctly selected reward boxes (%)
Brixton	Baseline	Total number of errors (max. 55)
4 way Weigl	Baseline	Total score (max. 12) Failure to complete sort (less than 2 tokens are left unsorted; N) Number of perseveration (repetition of a previous sort; N) Total sorts (N)
Short term visual memory test	Baseline	Score (max. 7)
DCM variables		
LOCC Self-connection	T3 & T4	Connection strength (normalised log values)
LOCC to ROCC	T3 & T4	Connection strength (normalised log values)
LOCC LvOT	T3 & T4	Connection strength (normalised log values)
LOCC to LIFG	T3 & T4	Connection strength (normalised log values)
ROCC to LOCC	T3 & T4	Connection strength (normalised log values)

ROCC Self-connection	T3 & T4	Connection strength (normalised log values)
LvOT to LOCC	T3 & T4	Connection strength (normalised log values)
RvOT Self-connection	T3 & T4	Connection strength (normalised log values)
LIFG to LvOT	T3 & T4	Connection strength (normalised log values)
LIFG Self-connection	T3 & T4	Connection strength (normalised log values)
RIFG to RvOT	T3 & T4	Connection strength (normalised log values)
RIFG to LIFG	T3 & T4	Connection strength (normalised log values)
RIFG Self-connection	T3 & T4	Connection strength (normalised log values)

8.2 Results Supplementary material

8.2.1 Participant Performance

Accuracy in the challenge phase was generally high, with participants answering 90.6% of trials correctly on average (s.d. = 8.4). Performance ranged from 65.0% to 97.4%. Data from all subjects can be seen in Supplementary Table 3s.

Due to the design of the item-specific difficulty adaptation, the number of times each word was presented during training correlated closely with accuracy for that word. On average over all participants and both blocks there were 76.6 presentations of each word per block, but this could vary widely depending on performance.

8.2.2 CA damage to white matter tracts

Table 9 Number of CA participants with grouped degrees of damage (as a percentage of whole white matter tract volume) to four major white matter tracts. White matter tracts identified using the John Hopkins University White Matter tracts Atlas. IFOF=Inferior fronto-occipital fasciculus; ILF= Inferior longditudinal fasciculus; SLF=Superior longditudinal fasciculus; Unc= uncinate fasciculus.

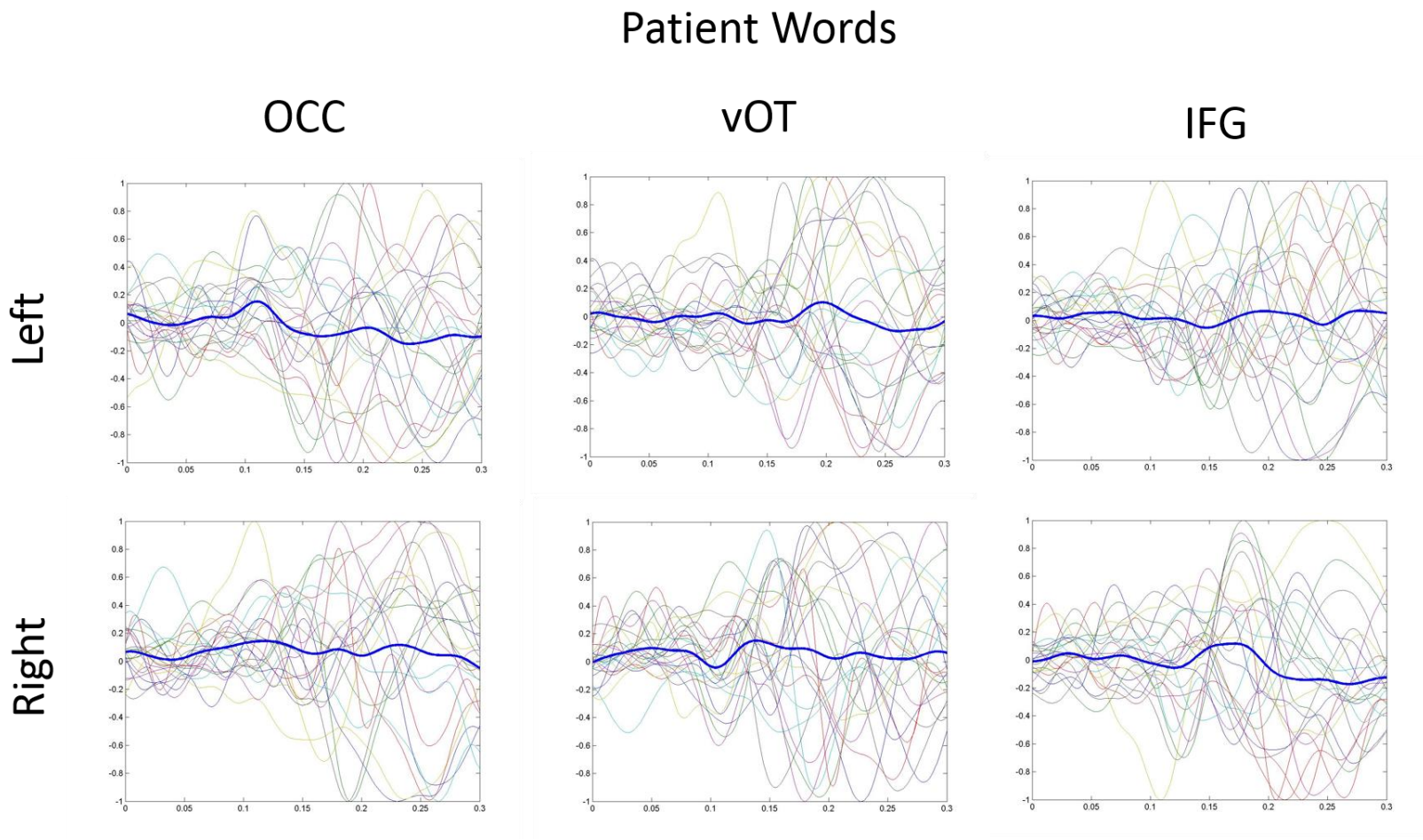
	Number of CA participants elidgable			
Degree of Damage	**IFOF**	**ILF**	**SLF**	**Unc**
>10%	20	20	22	11
>20%	16	16	21	9
>30%	13	15	19	8
>40%	11	11	17	6
>50%	6	7	14	5
>60%	4	5	12	5
>70%	2	3	11	1
>80%	0	2	8	0
>90%	0	2	6	0

Appendices Table 10. Mean scores on all outcome measures at all time-points for tDCS Groups 1 and 2. G1=Group1, G2=Group2, Acc=accuracy, RT=reaction time, wpm=words per minute, CDP=Communication Disability Profile, B=Baseline.

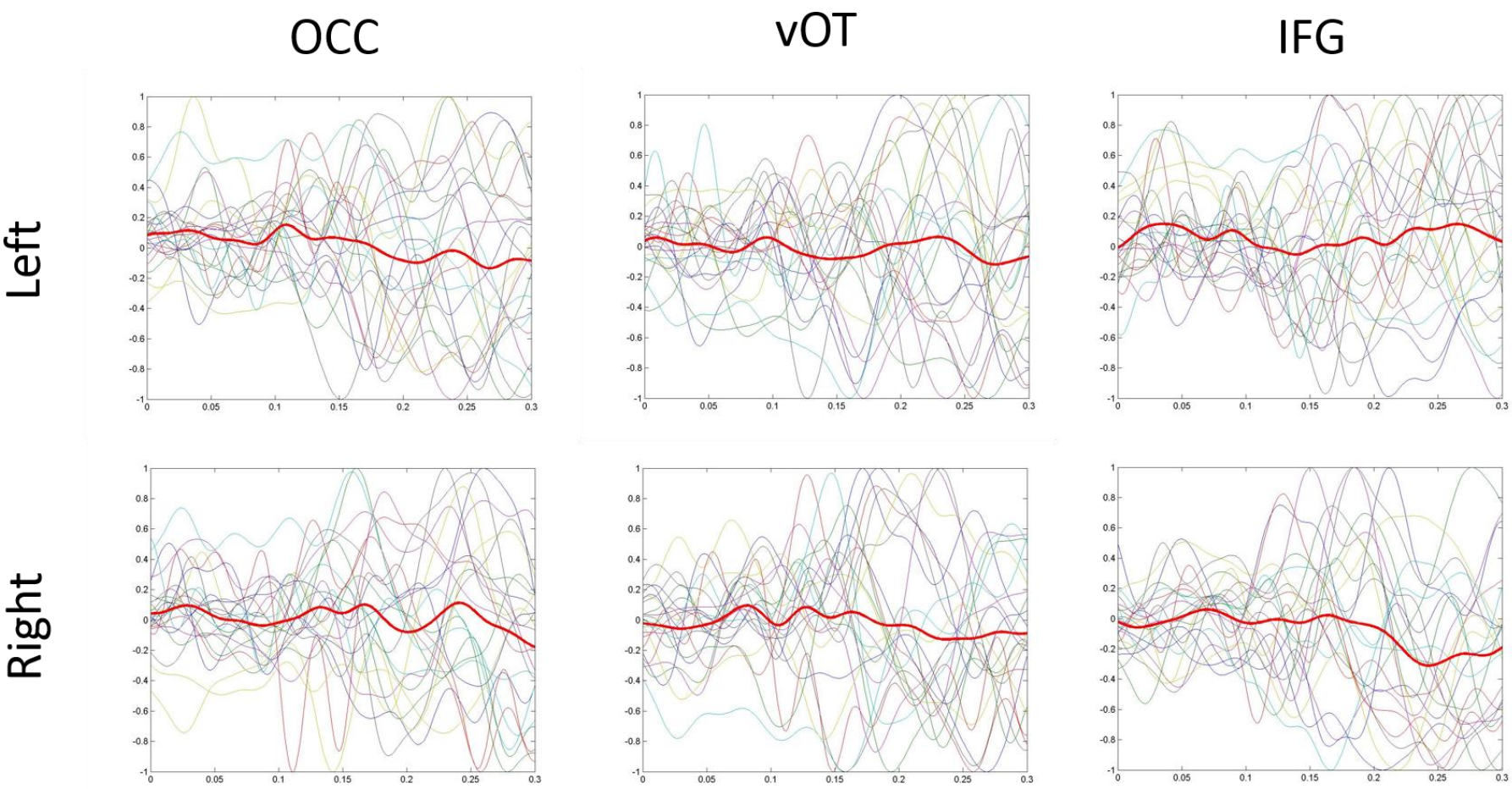
Measure	**N G1:G2**	**tDCS Crossover Group 1**					**tDCS Crossover Group 2**					**Omnibus (M)ANOVA (Baseline to T6)**	**Therapy ANOVA (Block1 and Block2)**
		B	**T3**	**T4**	**T5**	**T6**	**B**	**T3**	**T4**	**T5**	**T6**		
Word Reading, Acc (%)	10 : 11											Time-Point: F=16.6, *p*<.0001	Block: F=7.3, *p*<.05
Trained in Block1		54.2	56.6	67.1	63.3	61.6	56.5	59.7	67.8	65.3	65.4		Word-List: F=10.1, *p*<.005
Trained in Block2		54.4	56.6	60.6	66.8	61.0	56.1	58.1	58.3	68.2	63.2		**Block x Word-List: F=23.3, *p*<.0005**
Untrained		54.0	57.9	58.4	59.9	59.1	56.0	57.9	58.8	59.9	60.4	Word-List: F=5.7, *p*<.01	**Block x tDCS: F=5.3, *p*<.05**
Word Reading, RT (ms)	10 : 10											**Time-Point x Word-List: F=9.3, *p*<.05**	**Block x Word-List: F=7.1, *p*<.05**
Trained in Block1		1291	1228	1126	1208	1199	1122	1175	1021	1047	1085		
Trained in Block2		1339	1220	1214	1087	1261	1124	1192	1073	1054	1067		
Untrained		1380	1282	1206	1202	1220	1107	1155	1047	1043	1097		
Core Word Reading, Acc (%)	10 : 11	48.2	54.0	58.1	58.0	56.5	42.9	43.9	51.1	51.7	51.7	Time-Point: F=20.1, *p*<.0001	Time-Point: F=7.0, *p*<.005
Core Word Reading, RT (ms)	9 : 9	1419	1329	1372	1090	1168	1096	1162	1004	990	1014		Time-Point: F=4.4, *p*<.05
Semantic Matching, Acc (%)	9 : 10											Not analysed due to ceiling effects	Not analysed due to ceiling effects
Trained in Block1		94.4	90.7	93.1	91.7	93.5	92.5	95.4	93.8	93.3	92.9		
Trained in Block2		94.4	90.3	92.6	94.0	89.8	91.3	93.3	93.8	93.3	93.3		
Untrained		94.0	89.4	89.4	90.7	90.3	92.1	95.0	90.4	91.7	92.5		
Semantic Matching, RT (ms)	9 : 10											Time-Point: F=7.0, *p*<.05	Block: F=5.1, *p*<.05
Trained in Block1		5065	3419	3075	2905	3299	4945	4023	3197	3424	3333		**Block x Word-List: F=4.4, *p*=.05**
Trained in Block2		5350	3457	3332	2897	3170	4813	4244	3533	3538	3757		Block x tDCS: F=6.9, *p*<.05
Untrained		5094	3366	3327	2880	3201	4972	4625	4031	3880	4000		
Sentence Reading, Acc (%)	8 : 10											Not analysed due to ceiling effects	Not analysed due to ceiling effects
Trained in Block1		87.5	90.0	91.3	91.3	93.8	84.0	86.0	87.0	85.0	87.0		
Trained in Block2		87.5	86.3	88.8	85.0	87.5	91.0	87.0	88.0	91.0	94.0		
Untrained		83.8	83.8	86.3	82.5	82.5	88.0	88.0	91.0	86.0	95.0		
Sentence Reading, Speed (wpm)	8 : 10	79.9	85.4	92.1	91.1	104.9	80.0	72.0	96.0	104.9	96.8	Time-Point: F=3.7, *p*<.05	Word-List x tDCS: F=6.6, *p*<.05
Trained in Block1		78.7	77.5	92.7	94.2	110.4	76.0	74.6	93.1	96.3	87.3		
Trained in Block2		76.7	80.9	90.8	92.0	117.8	77.3	78.1	93.0	96.6	96.9		
Untrained													
Text Reading	9 : 11											Not significant	Not significant
Accuracy (%)		70.7	69.2	72.8	71.4	69.3	66.7	64.8	37.2	66.2	68.9		
Speed (wpm)		32.5	32.0	35.0	34.3	36.0	25.5	26.5	28.0	27.7	26.0		
Comprehension (/12)		5.8	7.0	7.4	6.3	6.2	6.3	5.6	7.5	7.6	7.2		
SART	10 : 11											Not significant	Not significant
False Positives (/24)		9.8	8.3	8.5	8	8.2	6.7	7.0	6.6	3.6	4.7		
False Negatives (/192)		6.6	3.9	5.6	6.6	7.8	4.3	8.5	6.7	6.5	8.4		

Go Trial RT (ms)		495	488	472	459	506	367	398	400	405	405		
CDP	10 : 10											Not applicable	Not applicable
Single Words (/4)		-	2.50	-	2.85	-	-	2.30	-	2.80	-		
Sentences (/4)		-	2.20	-	2.65	-	-	2.00	-	2.25	-		
Text (/4)		-	1.30	-	1.50	-	-	1.00	-	1.30	-		
Letters (/4)		-	1.40	-	1.10	-	-	1.00	-	1.25	-		

Figure 32. Plots displaying the power (fT) in each of the six dipole locations across trials for first 300 ms post stimulus onset when participants were viewing Words and False Fonts. Each participant is displayed as a fine line, with the mean power across participantsin bold. Colours used in these plots correspond to those in Fig. 22.



Patient Falsefonts



Controls Words

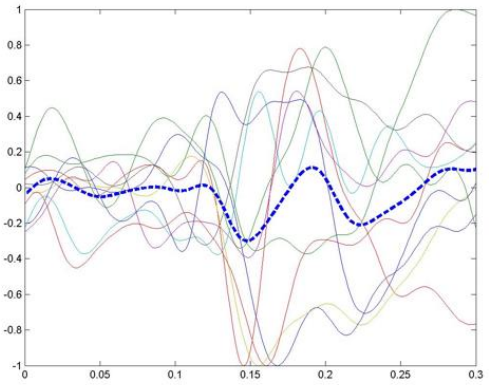
OCC

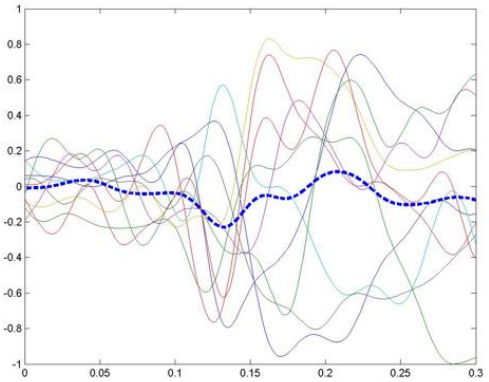
vOT

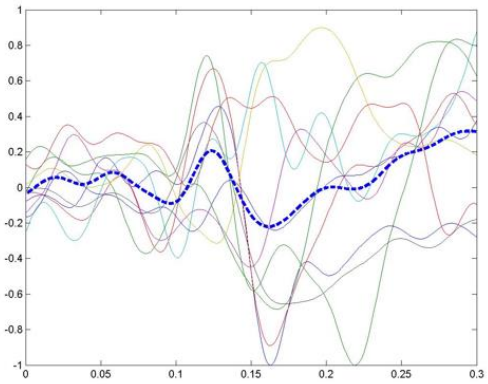
IFG

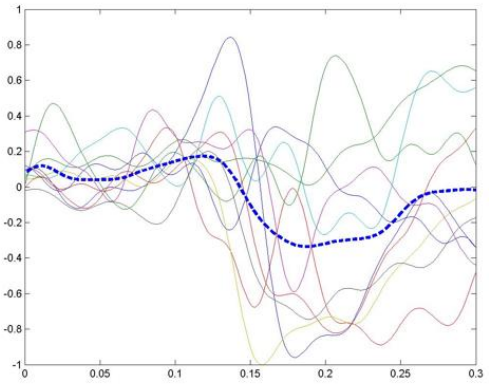
Left

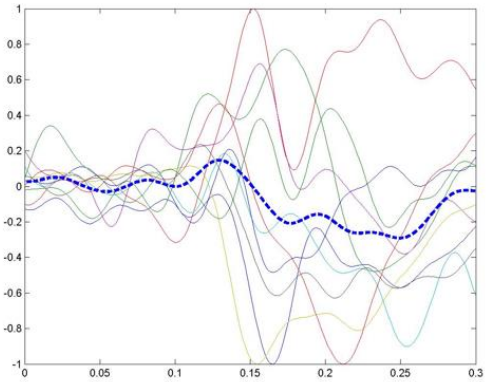
Right

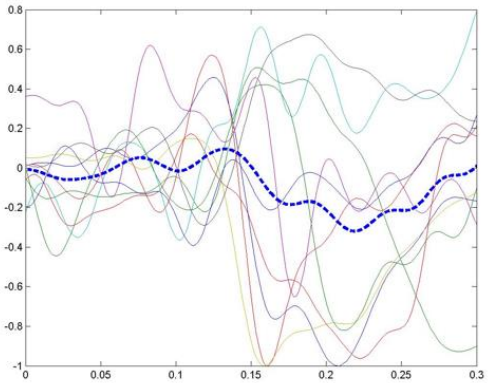




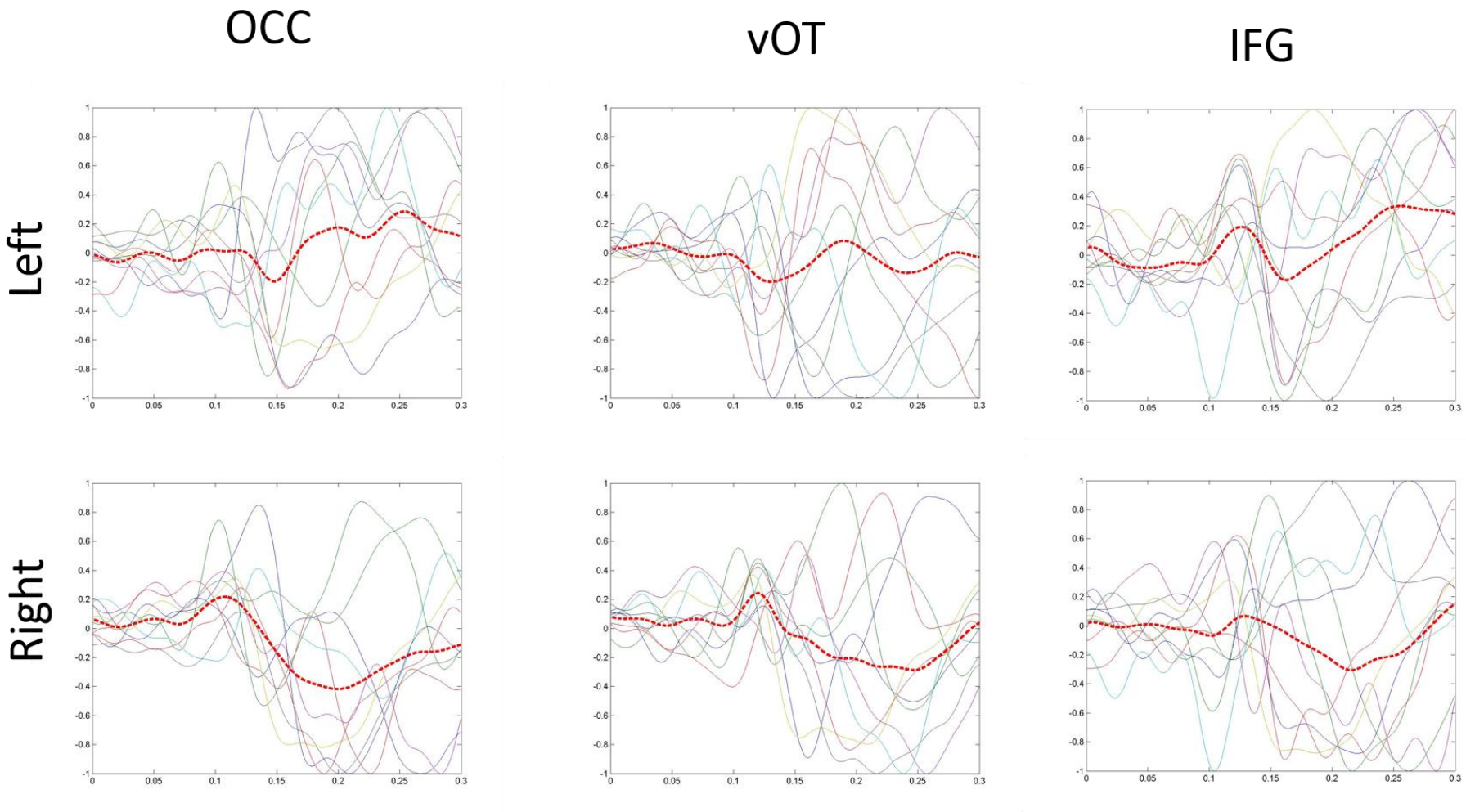


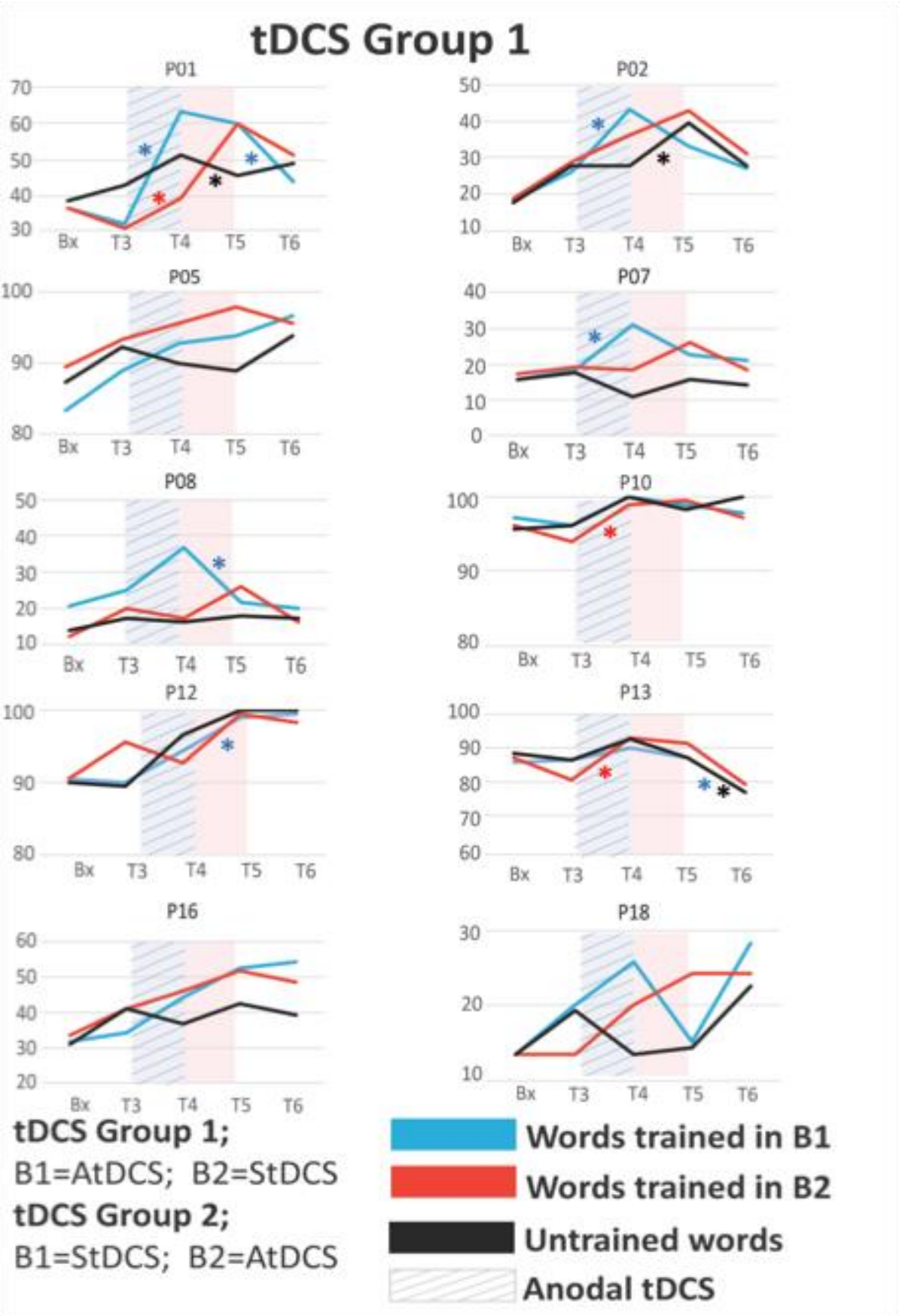






Controls Falsefonts




tDCS Group 1
P01
P02
P05
P07
P08
P10
P12
P13
P16
P18
Bx
T3
T4
T5
T6
tDCS Group 1;
B1=AtDCS; B2=StDCS
tDCS Group 2;
B1=StDCS; B2=AtDCS
Words trained in B1
Words trained in B2
Untrained words
Anodal tDCS

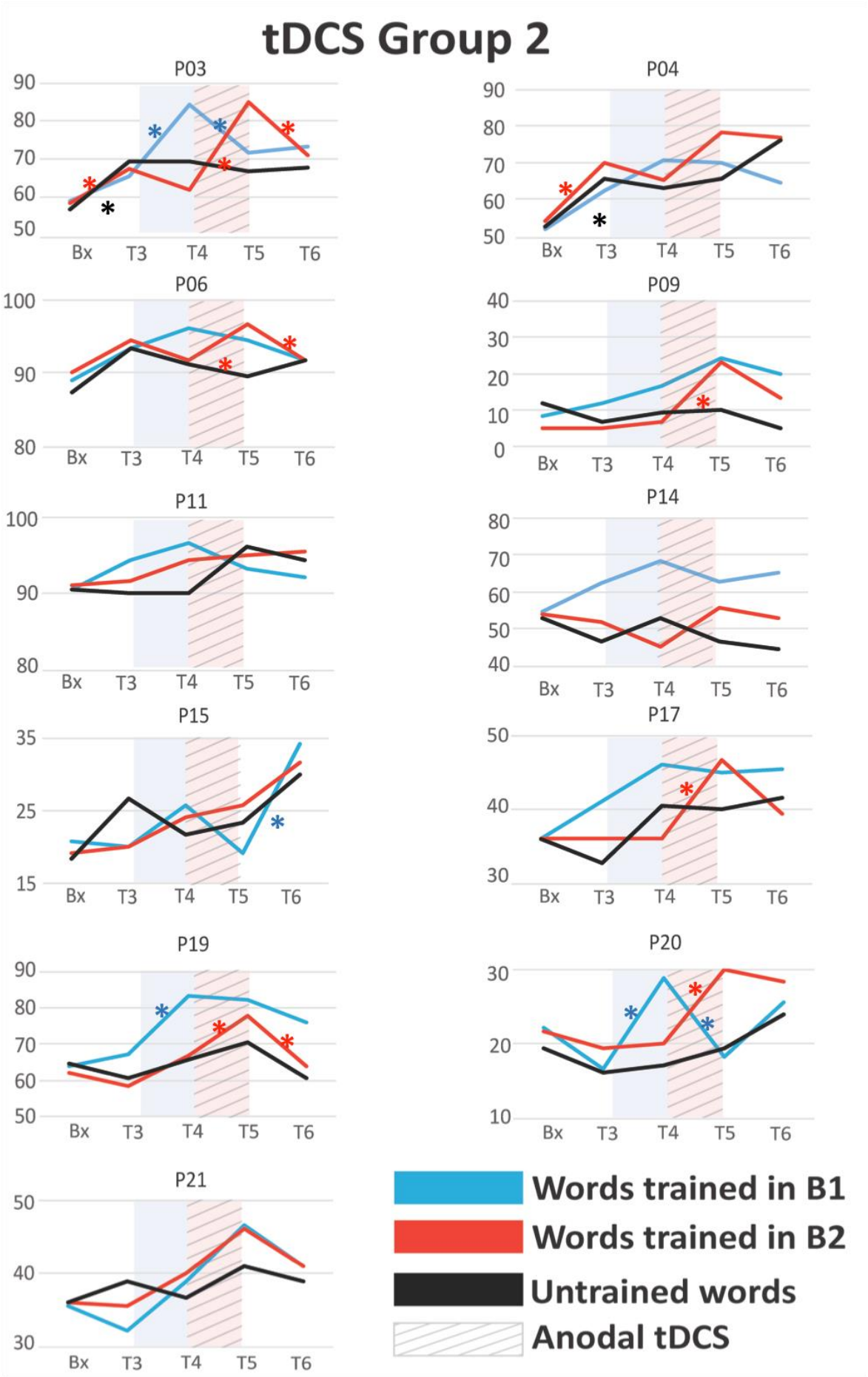

tDCS Group 2
P03
P04
P06
P09
P11
P14
P15
P17
P19
P20
P21
Bx
T3
T4
T5
T6
Words trained in B1
Words trained in B2
Untrained words
Anodal tDCS

*Figure 33. Subject specific therapy effect on single word reading accuracy for i) words Trained in Block1 (blue), ii) words Trained in Block2 (red), iii) Untrained words (black). Training Block1 was administered between T3 and T4 (shaded blue); Block2 was administered between T4 and T5 (shaded pink). tDCS Group1 received Anodal tDCS A(tDCS) over Block1 and sham tDCS (StDCS) over Block2, whereas tDCS Group2 received the stimulation types in the reverse order. Cross-hatching indicates the AtDCS block on each plot. * indicate significant changes in correct responses between incremental timepoints as determined by McNemar test, the colour of the mark denotes associated word list. Graphs use either a 40-percentage point or 20-percentage point scale, depending on the individual's performance.*