UNDERSTANDING THE NATURE AND TREATMENT OF ANOMIA IN CHRONIC POST-STROKE APHASIA

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Contents

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Abstract

The typical treatment for chronic post-stroke anomia is behavioural speech and language therapy. However, such therapy is not always effective or efficient. Previous research indicates that transcranial Direct Current Stimulation (tDCS) can enhance the effects of behavioural speech and language therapy, yet these findings have been limited by the highly varied protocols used across studies. A comprehensive, longitudinal intervention programme was subsequently devised to investigate the effects of systematically varying the laterality and polarity of stimulation on a range of language measures. Outcomes following active perilesional and contralesional stimulation were directly compared with those obtained following ipsilateral sham stimulation. **Chapter 3** demonstrated that combining computer-based repetition therapy with 1mA anodal tDCS delivered to the left frontal lobe of a participant with chronic Broca's aphasia led to significantly greater improvements in treated noun naming accuracy than those achieved following therapy alone. This result is in line with neuroimaging findings linking increased activation in left frontal perilesional regions to post-stroke language recovery. **Chapter 4** extended this work by repeating the same tDCS-plus-therapy schedule with a further three participants with differing lesion profiles and aphasia diagnoses. Although significant treatment gains were noted, there were no additional benefits of any form of active stimulation for two of these individuals, and the outcomes for the remaining patient were inconclusive. As such, the results of Chapter 4 clearly highlight between-participant variability in response to tDCS.

Chapter 5 documented, for the first time, the extent and nature of response inconsistency in confrontation picture naming across multiple trials. When presented with a large corpus of object images twice, 15 participants named an average of almost 26% of items correctly on one occasion and incorrectly on the other. A wide range of demographic, behavioural and psycholinguistic factors provided an incomplete account of the observed patterns in naming response inconsistency. Finally, **Chapter 6** comprised a behavioural case series designed to determine the relative importance of visual speech articulation in computer-based repetition therapy. Five of the six participants responded positively to at least one type of therapy, and all showed the greatest therapeutic gains when therapy included articulatory cues. Links between aphasia classifications and patterns of therapeutic response were complemented by exploratory structural neuroimaging findings indicating that different neural regions may mediate the effects of each type of therapy.

The designs of the empirical studies in the current thesis facilitate in-depth analysis of therapy outcomes on a patient-by-patient basis. The findings have considerable clinical applicability, and indicate interesting potential directions for future research.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Statement

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I would also like to thank Rachel and, more recently, the Mystic Ladies for the moral support (and occasional glass of wine). Thank you to Greg, my husband, for his love and encouragement, and for generally putting up with it all. Special thanks go to my parents, Anne and John. I am eternally grateful for all that they continue to do, even though they allegedly live 3000 miles away at the moment. My final thank you is reserved for my daughter, Verity. Whilst her sleeping patterns have not always been conducive to completing a thesis, her lovely, smiling face certainly saw me through some of the tougher times.

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The Author

I graduated from the University of Sheffield in 2000 with a BSc (Hons) in Psychology. This was followed by an MSc in Occupational Psychology in 2002, again obtained at the University of Sheffield. I was then employed for a number of years in the travel industry, including roles in sales, training, human resources and management. During this period, I became interested in helping adults with acquired communication difficulties, and enjoyed volunteering as a communication support assistant for the Stroke Association in my spare time. I subsequently returned to full time education, and completed a BSc (Hons) in Speech and Language Therapy at the University of Manchester in 2012. Following my third year placement in the adult speech and language therapy department at Macclesfield District General Hospital, predominantly working with in-patients on the stroke rehabilitation ward, I volunteered in the same department throughout my final year and for several months post-qualification. In May 2013, I was offered a research assistant position by Dr Anna Woollams, which involved carrying out language assessments with stroke survivors with chronic aphasia. I began my PhD studies with the same patient population in September that year.

Chapter 1

Introduction

Thesis Overview

This thesis is presented in journal format, meaning that Chapters 2 - 6 are written in a style suitable for publication in peer reviewed journals. The current, introductory chapter will provide a broad consideration of concepts and background literature relevant to the thesis as a whole, including an overview of existing knowledge regarding the nature and treatment of anomia in chronic post-stroke aphasia. The motivation for completing the research described in Chapters 3 – 6 will be explained and the key aims of the thesis stated. Chapter 2 provides a comprehensive review of relevant literature pertaining to the use of transcranial Direct Current Stimulation (tDCS) to enhance behavioural speech and language therapy for stroke survivors with chronic anomia. This chapter also highlights outstanding methodological issues addressed by the research described in Chapters 3 and 4, which investigated the effects of systematically varying the polarity and laterality of tDCS on optimising therapeutic outcomes for individuals with chronic post-stroke anomia. The work reported in Chapter 5 explored observed patterns of picture naming response inconsistency across multiple attempts, and considered a wide range of demographic, behavioural and psycholinguistic variables that may account for such patterns. A further intervention study is presented in Chapter 6. This study was designed to determine the relative importance of providing a visual speech articulation component in computer-based repetition therapy for anomia. Chapters 3 – 6 are self-contained empirical chapters. As such, each of these chapters provides the rationale for completing the particular study, provides a thorough review of relevant background literature, describes the methods used and results found, and includes an interim discussion of findings. The final chapter, Chapter 7, comprises an integrative discussion of all of the research findings and their implications, plus potential directions for subsequent work.

The Nature of Post-Stroke Aphasia

Aphasia is an acquired neurological communication disorder characterised by impaired language production and/or comprehension (Goodglass & Kaplan, 1972). Although individuals with aphasia may have concurrent motor deficits affecting speech articulation, such as dysarthria or apraxia of speech (Fridriksson, Hubbard, et al., 2012), aphasia is a linguistic impairment caused by damage to the extensive network of brain regions involved in language processes (Hickok & Poeppel, 2004, 2007; Price, 2010). The most common cause of aphasia is a left hemisphere cerebrovascular accident (CVA), or stroke, which occurs when a blood vessel supplying language-critical regions is occluded or haemorrhages. Cerebral blood flow is restricted, resulting in neuronal death or lasting dysfunction (Deb, Sharma, & Hassan, 2010). Immediately after a stroke, approximately one third of survivors have aphasia (Bakheit et al., 2007). Of these patients, the majority will regain some degree of language function in the days and weeks that follow, however, residual deficits frequently persist into the chronic stage (typically ≥6 months post-stroke), when spontaneous recovery of language function is less likely (Lazar & Antoniello, 2008; Marsh & Hillis, 2006).

Chronic aphasia is highly disabling and language difficulties may negatively affect stroke survivors' emotional well-being, quality of life, relationships and participation in wider society, including employment opportunities in individuals of working age (Hilari, Cruice, Sorin-Peters, & Worrall, 2015; Hilari, Needle, & Harrison, 2012; Le Dorze et al., 2015; Maaijwee et al., 2014; Morris, Eccles, Ryan, & Kneebone, 2017). There may be additional, further reaching adverse consequences for the partners, families and friends of people with aphasia, who often experience 'third party disability', such as increased anxiety, financial strain, and deterioration of interpersonal relationships with the stroke survivor (Davidson, Howe, Worrall, Hickson, & Togher, 2008; Grawburg, Howe, Worrall, & Scarinci, 2013, 2014; Threats, 2010). Furthermore, the debilitating effects of chronic aphasia are frequently compounded by coexisting physical disabilities that also commonly follow a stroke (e.g. right

upper limb hemiparesis) as well as by concomitant cognitive impairments (Hatem et al., 2016; Nakling et al., 2017; Sun, Tan, & Yu, 2014).

There are currently over 367,000 individuals in the UK who have aphasia, with this number rising by approximately 20,000 each year (National Aphasia Association, 2018). These statistics, in conjunction with the considerable personal and societal costs associated with aphasia, highlight a clear need to better understand the nature of post-stroke language deficits and how best to mitigate their effects.

Symptoms of Aphasia

The linguistic difficulties experienced by stroke survivors with aphasia are heterogeneous in terms of both the severity and nature of deficits. Individuals may demonstrate impairments involving differing aspects of expressive and/or receptive language, often across multiple modalities, with detrimental effects on speaking, writing, reading and gesture use (Galletta & Barrett, 2014). However, despite wide-ranging symptoms, some commonalities exist within groups of patients, leading to the development of categorisation systems designed to assign individuals to particular aphasia subtypes. Such systems include the Boston Diagnostic Aphasia Examination (BDAE, Goodglass, Kaplan, & Barresi, 2001), Western Aphasia Battery (WAB, Kertesz, 1982) and, for German speakers, the Aachen Aphasia Test (AAT, Huber, Poeck, & Willmes, 1984). The widely used BDAE involves asking patients to complete a thorough inventory of speech, language and cognitive assessments, before mapping relative performance on all tasks to eight recognised aphasia subtypes. Each subtype is characterised by differing abilities in three key dimensions: fluency, comprehension and repetition. Figure 1.1 shows the eight aphasia subtypes identified by the BDAE and how they vary with respect to these three linguistic features.

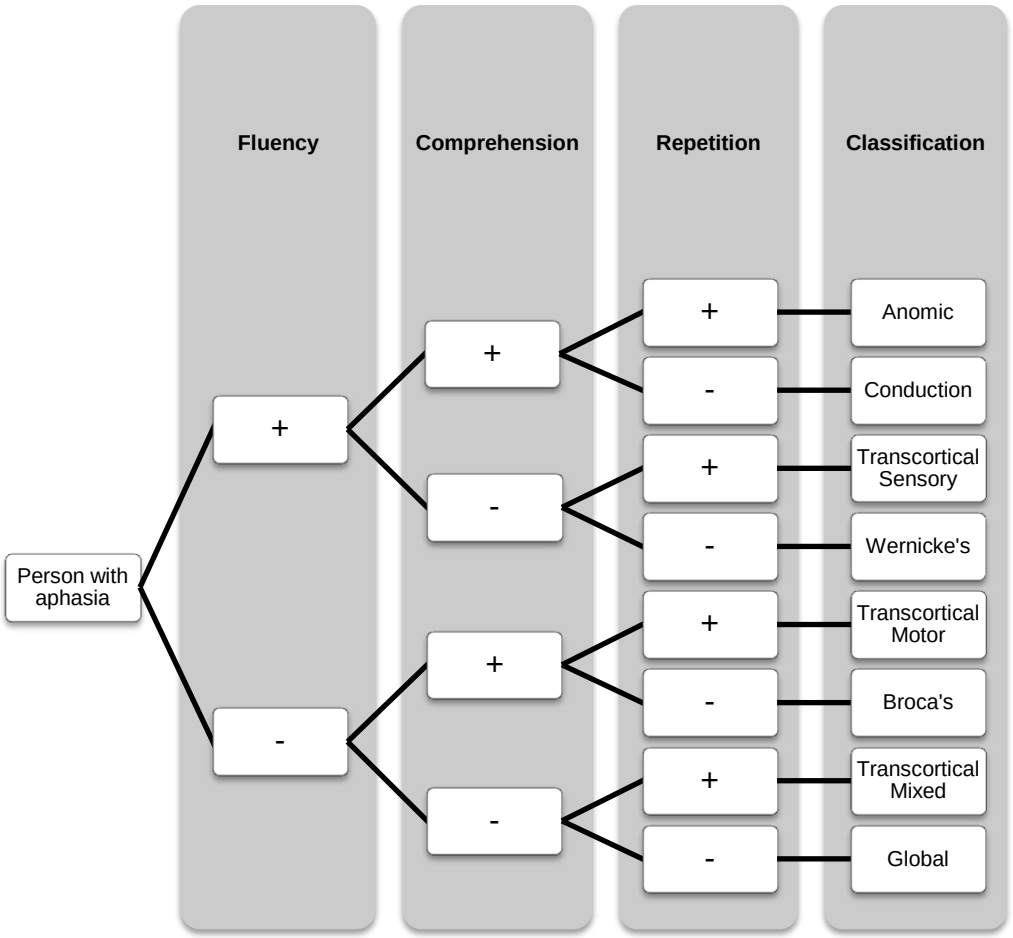


Figure 1.1: The eight aphasia subtypes identified by the BDAE. '+' indicates preserved ability, '-' indicates impaired ability (modified from Goodglass et al., 2001).

Classifications on the BDAE range from the mildest subtype, anomic aphasia, through to the most severe, global aphasia. Anomia, or problems retrieving and producing everyday words, is the primary symptom of anomic aphasia, whilst fluency, comprehension and repetition are relatively unimpaired (Dronkers & Baldo, 2009; Laine & Martin, 2006). At the opposite end of the spectrum, individuals with global aphasia have profound difficulties with all aspects of expressive and receptive language (Baker, LeBlanc, & Raetz, 2008). Verbal output, if present at all, may be limited to perseverative single words or automatic phrases, although such patients may convey and understand different meanings by way of facial expressions and intonation (Stewart & Riedel, 2016). The remaining aphasia subtypes are typified by deficits in certain aspects of language whilst others are spared. For instance,

Broca's aphasia is characterised by short, non-fluent, often agrammatic, utterances, alongside comparatively well-preserved comprehension of simple language (Fridriksson, Hubbard, et al., 2012; Stewart & Riedel, 2016). In contrast, patients with fluent Wernicke's aphasia can articulate with ease, but their output often lacks meaning and may contain many neologisms. Repetition and auditory comprehension are also impaired in individuals with Wernicke's aphasia (Goodglass et al., 2001).

It is important to note that many people with aphasia do not match all of the diagnostic criteria for any one subtype identified by the BDAE, and that there are considerable variations in performance across tasks within the same aphasia subtype (e.g. Ardila, 2010; Baker et al., 2008; Bates, Saygin, Moineau, Marangolo, & Pizzamiglio, 2005), leading to some individuals being labelled as having 'mixed' aphasia (Butler, Lambon Ralph, & Woollams, 2014). For instance, patients with mixed non-fluent aphasia present with both the sparse, effortful speech typical of individuals with severe Broca's aphasia and the substantial comprehension deficits of those with Wernicke's aphasia, but do not meet all of the criteria for a diagnosis of global aphasia. Nevertheless, the BDAE and similar classification systems can facilitate communication between clinicians and researchers, and potentially aid selection of appropriate speech and language interventions (Basso, Forbes, & Boller, 2013; Marshall, 2010). During the post-stroke recovery period, aphasia classification may evolve over time. However, across all types of aphasia, the most common symptom is anomia (Postman-Caucheteux et al., 2010), and patients who display more severe acute deficits typically continue to experience persistent word finding problems in the chronic stage, even after their other difficulties have resolved (Pedersen, Vinter, & Skyhoj Olsen, 2004). Consequently, amelioration of anomia is a frequent goal of speech and language therapy for stroke survivors (Nickels, 2002b).

Speech and Language Therapy for Anomia

The Cognitive Neuropsychological Basis of Anomia

The cognitive neuropsychological approach has been highly influential in the assessment and treatment of anomia from the 1970s to the present day (Laine & Martin, 2012; Lambon Ralph & Conroy, 2012). This paradigm maintains that word finding difficulties are the result of a breakdown in one or more of the cognitive processes involved in lexical access (Whitworth, Webster, & Howard, 2014). Most cognitive neuropsychological models of word production agree that confrontation naming comprises two key stages: lexical selection and phonological retrieval, although models propose differing levels of representation and relationships between them (Schwartz, 2014; Wilshire, 2008). For example, the interactive two-step model proposed by Dell and colleagues includes three layers of stored information (Dell & O'Seaghdha, 1992; Dell, Schwartz, Martin, Saffran, & Gagnon, 1997). The central, word (lemma) level, is linked to both the semantic and phoneme levels via bidirectional excitatory connections. Connection strengths are determined by prior learning and recent experience. When an individual views a picture of an object to be named, the item's semantic features are activated. Activation spreads to the target word unit and semantic neighbours, plus the phonemes present in the names of these words. After a fixed period of time, the word unit with the greatest current activation is chosen (lexical selection). Following lexical selection, the chosen word unit receives a boost of activation, which again spreads throughout all three levels within the network. Phonological retrieval occurs when a second fixed period of time concludes and the most highly activated phonemes are selected, ultimately leading to production of the relevant word (Dell, Chang, & Griffin, 1999; Dell et al., 1997).

An alternative theory of lexical access is provided by Levelt and associates, who maintain that activation cascades sequentially rather than interactively between layers (Indefrey & Levelt, 2004; Levelt, Roelofs, & Meyer, 1999). According to this model, visual input provided by a picture first activates the appropriate conceptual level for the item. For confrontation

naming, this is typically the 'basic level' concept for the object (e.g. horse) rather than an applicable superordinate (e.g. animal) or subordinate (e.g. thoroughbred) concept (Levelt, 1999; Rosch, Mervis, Gray, Johnson, & Boyes-Braem, 1976). Following activation of the basic level concept, at the lexical selection stage, the unique lemma node representing the syntactic properties of the item name is activated. Next, a series of consecutive, discrete processes ensure that the necessary morphemes, phonemes (phonological retrieval) and syllables to produce the target name are sufficiently active, before being converted into a motor articulatory sequence for the vocal tract to produce (Indefrey & Levelt, 2004).

Anomia is commonly assessed in both clinical and research settings using confrontation noun naming tasks, such as the Boston Naming Test (BNT, Kaplan, Goodglass, & Weintraub, 2001). Individuals with word finding difficulties are shown a series of pictures of objects and asked to generate their verbal labels (Raymer, 2011). The number of items named incorrectly provides a measure of anomia severity, and analysing the patient's pattern of naming errors may serve to highlight which faulty process/es are responsible for their picture naming deficits (e.g. Best & Nickels, 2000; Maher & Raymer, 2004). Cognitive neuropsychological models, including those proposed by Dell et al. (1997) and Levelt and colleagues (Levelt et al., 1999), propose that naming errors made by individuals with anomia when completing confrontation naming tasks (commonly referred to as paraphasias) are due to incorrect lexical selection and/or phonological retrieval (Nickels, 1995; Schwartz, 2014). Stroke-induced brain damage may lead to excess noise within the network, reduced baseline item activation, decreased connection strengths between network layers or an increased rate of activation decay (Foygel & Dell, 2000; Nickels, 1995). These factors can act to reduce the normal flow of activation between network levels, meaning that alternative words and/or phonemes have greater activation than target ones (Foygel & Dell, 2000; Schwartz, 2014; Schwartz, Dell, Martin, Gahl, & Sobel, 2006). Accordingly, semantic (e.g. pig → 'cow'), formal phonological (e.g. pig → 'pin') or mixed (e.g. pig → 'penguin') errors can occur when an item sharing semantic and/or phonological features with the target has greater activation, and is subsequently chosen by mistake during the lexical selection stage. Semantic errors may also arise in individuals who demonstrate central comprehension

deficits across language tasks when weak, underspecified semantic representations of the target fail to become more active than semantically-related items, again resulting in incorrect lexical selection (Nickels, 1995). In contrast, phonological non-word errors (e.g. pig → 'kig') are said to be the result of misselection when retrieving the target item's phonemes (Schwartz, Wilshire, Gagnon, & Polansky, 2004), whilst unrelated errors (e.g. pig → 'hotel') are believed to be due to random noise causing erroneous lexical selection and/or phonological retrieval in a highly degraded network (Dell et al., 1997; Foygel & Dell, 2000). In addition to errors of commission, patients with anomia make frequent errors of omission (Chen, Middleton, & Mirman, 2018; Dell, Lawler, Harris, & Gordon, 2004). One potential explanation why individuals do not attempt to produce a target word is the failure of any item to reach the necessary activation threshold for lexical selection and/or phonological retrieval (Laine, Tikkala, & Juhola, 1998). Alternatively, an internal lexical monitor may identify deviant planned responses and suppress them before they are produced (Levelt, 1983; Mitchum, Ritgert, Sandson, & Berndt, 1990).

Behavioural Therapy for Anomia

Following assessment, a typical treatment for anomia is restitutive behavioural speech and language therapy that aims to improve word retrieval by repairing the faulty process/es believed to underpin a particular individual's word finding difficulties (Kiran & Bassetto, 2008). Many therapies are based on the notion that different interventions are likely to be optimally effective for dysfunction at different stages of word retrieval (Nickels, 2002b). Thus, semantic impairments may be targeted by therapy tasks such as semantic feature analysis (SFA, Ylvisaker & Szekeres, 1985), word to picture matching, and semantic categorisation, whilst phonological impairments may be treated by activities including phonological components analysis (PCA, Leonard, Rochon, & Laird, 2008), phonological cueing or whole word repetition. Other treatments target both semantics and phonology, potentially making them suitable for patients with a range of apparent underlying deficits (Howard, 2000; Kiran & Bassetto, 2008). For instance, a popular therapy task, repetition in the presence of a picture (RIPP), involves presenting an individual with a picture of an item

as well as its verbal name, and asking him/her to repeat the name back. The item image provides a semantic cue, whilst repetition of the item name accesses its phonological form. Connections between semantic and phonological properties of the items are thought to be strengthened when both are active at the same time, making the item more likely to be successfully retrieved in the future (Howard, 2000).

Behavioural speech and language therapy techniques can significantly improve noun picture naming accuracy in individuals with chronic post-stroke anomia (e.g. Brady, Kelly, Godwin, Enderby, & Campbell, 2016). Nevertheless, there are some notable limitations to their effectiveness. Therapy can only directly treat a small proportion of the words that an individual has difficulty retrieving. Although generalisation to untreated items can occur (e.g. Best et al., 2013), these effects are often unreliable (Nickels, 2002b). Moreover, significant gains in naming accuracy of treated and untreated items as measured via formal assessment do not always translate to functionally meaningful improvements in word finding in everyday contexts (Best et al., 2011; Carragher, Conroy, Sage, & Wilkinson, 2012; Conroy, Sage, & Lambon Ralph, 2009b). Evidence suggests that providing intensive behavioural speech and language therapy (typically ≥9 hours per week) is more effective at remedying anomia than less frequent sessions administered over a longer time period (Barthel, Meinzer, Djundja, & Rockstroh, 2008; Bhogal, Teasell, & Speechley, 2003; Breitenstein et al., 2017). However, intensive therapy places substantial demands on patients and clinicians alike, especially if providing treatment to outpatients in the chronic stage following a stroke (Brady et al., 2016; Gunning et al., 2017; Holland & Crinion, 2012). Indeed, surveys indicate that speech and language therapy for individuals with chronic aphasia is not routinely offered by more than half of UK service providers, with insufficient resources and increasing demand for therapists to manage post-stroke dysphagia rather than communication difficulties cited as contributory factors for this lack of provision (Code & Heron, 2003; Code & Petheram, 2011; Enderby & Petheram, 2002). To reduce the burdens associated with providing therapy to patients with chronic anomia, there is a need for optimally effective treatments that generate significant language improvements within a limited number of sessions.

The search for efficacious and efficient treatments is complicated by the observation that therapeutic gains following the same interventions vary considerably between individuals with persisting anomia, even when patients have very similar language profiles. Such variability highlights the need to consider responses to therapy on a patient-by-patient basis. One possible reason for variability in therapeutic response is differing skills in related cognitive domains, such as short-term memory, attention, and executive functioning (Dignam et al., 2017; Lambon Ralph, Snell, Fillingham, Conroy, & Sage, 2010). In addition, differences in lesion profiles are also likely to affect how behaviourally-similar individuals respond to anomia therapy (e.g. Bonilha, Gleichgerrcht, Nesland, Rorden, & Fridriksson, 2016). In order to offer appropriate treatments to those anticipated to benefit most from them, it is important to understand how stroke-induced neural damage leads to anomia, and how therapy helps the post-stroke brain to recover word finding abilities (Berthier & Pulvermüller, 2011; Varley, 2011).

The Neural Basis of Anomia

Early lesion-symptom mapping approaches attempted to explain different aphasia subtypes as the consequence of localised brain lesions (Hillis, 2007). Paul Broca's seminal studies in 1861 linked severely non-fluent language production to damage to the left inferior frontal lobe (Broca's area) (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007). Similarly, in 1874, Carl Wernicke noted that deficits in language comprehension followed damage to the left posterior superior temporal lobe (Wernicke's area) (Charidimou et al., 2014). Historical work has greatly contributed to our understanding of links between brain and behaviour, and continues to influence the field of neuropsychology in the present day (Rorden & Karnath, 2004). However, more recent advances in neuroimaging have revealed inconsistent relationships between aphasia classifications and specific lesion sites (Basso, Lecours, Moraschini, & Vanier, 1985; Charidimou et al., 2014; Willmes & Poeck, 1993). For instance, studies have identified non-fluent individuals with posterior lesions and fluent patients with anterior lesions (Basso et al., 1985). Moreover, focal damage to Broca's area, comprising the pars opercularis (BA44) and pars triangularis (BA45) of the left inferior frontal gyrus

(IFG) (Keller, Crow, Foundas, Amunts, & Roberts, 2009), is now believed to be insufficient to produce the symptoms of classic Broca's aphasia. Instead, this aphasia subtype is associated with widespread damage extending from Broca's area to functionally connected regions including the left insula, basal ganglia, motor cortex, and Wernicke's area (Ardila, Bernal, & Rosselli, 2016; Dronkers et al., 2007; Fridriksson, Fillmore, Guo, & Rorden, 2015). Such findings indicate that the network of brain regions responsible for word production in healthy individuals is much broader and more complex than originally envisaged, and that chronic anomia may arise following damage to many different sites within this network.

The neural network currently believed to underlie normal speech production and comprehension has been conceptualised by Hickok and Poeppel (2004, 2007). Their dual stream model proposes that two distinct neural pathways link sensory input and phonological information with the articulatory system (the dorsal stream) and sounds with meaning and meanings with spoken output (the ventral stream). The left-dominant dorsal stream connects temporo-parietal regions to the posterior IFG (including Broca's area) via the arcuate fasciculus. In contrast, the ventral stream encompasses bilateral regions in the temporal lobes, including the middle temporal gyrus (MTG) and the inferior temporal sulcus (ITS). Both the dorsal and ventral streams are connected to additional cortical regions, such as the bilateral superior temporal gyrus (STG) and superior temporal sulcus (STS). The left STG and ventral stream structures incorporate Wernicke's area (DeWitt & Rauschecker, 2013). Successful confrontation naming relies on both the phonologically-focused dorsal and semantically-focused ventral streams. Consequently, stroke-induced lesions affecting structures within, or connected to, either or both of these pathways can lead to chronic anomia (Butler et al., 2014; Halai, Woollams, & Lambon Ralph, 2017, 2018; Schwartz, Faseyitan, Kim, & Coslett, 2012; Schwartz et al., 2009).

Neuroplasticity and Behavioural Anomia Therapy

Language recovery in the chronic stage after a left hemisphere stroke is largely possible due to neuroplasticity, or the brain's ability to undergo significant structural and functional

reorganisation following injury (Fridriksson & Smith, 2016). When language-critical neural regions are irretrievably damaged, restitutive speech and language therapy aims to facilitate neural reorganisation and ameliorate anomia by establishing new pathways and recruiting additional brain regions in order to regain lost language abilities (Fridriksson, Baker, & Moser, 2009). By the chronic period, individuals who have the most favourable language outcomes tend to be those who demonstrate reactivation in left hemisphere language areas, such as the IFG and MTG (Jarso et al., 2013; Saur et al., 2005). Specifically, spontaneous compensatory recruitment of intact, perilesional areas immediately surrounding damaged regions within the normal naming network has been consistently linked to improved picture naming in patients with chronic aphasia (Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010; Turkeltaub, Messing, Norise, & Hamilton, 2011). However, importantly, imaging studies have shown that behavioural speech and language therapy interventions may also elicit neural reorganisation and recruitment associated with improved linguistic performance. For example, treatment-induced activation increases in perilesional language regions in the left hemisphere, such as the left precentral and supramarginal gyri, have been found in individuals with chronic post-stroke anomia, which were associated with increased post-therapy oral picture naming accuracy (Cornelissen et al., 2003; Fridriksson, 2010; Fridriksson, Richardson, Fillmore, & Cai, 2012; Marcotte et al., 2012; Meinzer et al., 2008; van Hees, McMahon, Angwin, de Zubicaray, & Copland, 2014).

Evidence regarding the role of the contralesional right hemisphere in facilitating recovery from chronic stroke-induced anomia is more equivocal (e.g. Cocquyt, De Ley, Santens, Borsel, & De Letter, 2017; Fridriksson, Baker, & Moser, 2009; Geranmayeh, Brownsett, & Wise, 2014; Hope et al., 2017; Nardo, Holland, Leff, Price, & Crinion, 2017; Turkeltaub et al., 2012). Some authors propose that ongoing activity in homologous regions in the right hemisphere aids long-term language recovery, especially for individuals with large left hemisphere lesions that preclude relateralisation of word finding functions (e.g. Heiss & Thiel, 2006). In contrast, others maintain that such activity is maladaptive (e.g. Naeser et al., 2004; Price & Crinion, 2005), noting that contralesional activation has been correlated with errors in picture naming (Postman-Caucheteux et al., 2010). Additionally, the

transcallosal disinhibition hypothesis proposes that, when left hemisphere language regions are damaged, they no longer transmit inhibitory signals that normally suppress activation in their right homologues during language tasks. Contralesional regions consequently become hyperactive and, in turn, further reduce activation in the left hemisphere, preventing beneficial recruitment of perilesional areas (Martin et al., 2009; Thiel et al., 2006). Thus, activation of the right hemisphere may actually contribute to long-term anomia. A continued discussion of the contributions made by both the left and right hemispheres to recovery from anomia at different time points following a left hemisphere stroke is included in **Chapter 2**.

Neurostimulation to Augment Behavioural Therapy for Anomia

Neuroimaging findings indicate that behavioural speech and language therapy may enhance activation in perilesional brain regions, and that such activation is linked to improved word finding in stroke survivors with chronic anomia. However, as mentioned previously, behavioural therapy is not always effective or efficient for all individuals. Accordingly, a growing number of studies have explored the potential benefits of supplementing more traditional behavioural treatments with innovative, non-invasive neurostimulation techniques (ALHarbi, Armijo-Olivo, & Kim, 2017; Costa, 2012). One such technique, tDCS, has proved to be safe and well-tolerated in patients with neurological damage (e.g. Bikson et al., 2016; Poreisz, Boros, Antal, & Paulus, 2007). tDCS uses a battery pack and two saline soaked electrodes to deliver weak electrical currents to the brain. To administer unilateral stimulation, the active electrode is placed on the scalp directly above the cortical region of interest. Positive (anodal) stimulation is associated with increased neuronal activity, whereas negative (cathodal) stimulation is associated with decreased neuronal activity (Nitsche & Paulus, 2000). The second, reference electrode is usually placed on the contralateral supra-orbit or contralateral shoulder to complete the circuit (Fridriksson, 2011).

During stimulation, tDCS is believed to temporarily alter cell membrane polarity: anodal stimulation causes neuronal depolarisation, making neurones more likely to generate action potentials, whilst cathodal stimulation causes neuronal hyperpolarisation, which has the

opposite effect (Nitsche, Fricke, et al., 2003). In the longer term, tDCS is thought to regulate levels of the neurotransmitters glutamate and GABA, and the neuromodulators dopamine, acetylcholine and serotonin (Stagg & Nitsche, 2011). Modifications to neurochemical concentrations can subsequently induce long term potentiation (LTP) and long term depression (LTD), resulting in stable and persisting changes in synaptic activation (Nitsche, Fricke, et al., 2003; Stagg et al., 2009). A detailed description of how tDCS is understood to influence neural functioning is provided in **Chapter 2**. In addition, this chapter includes a comprehensive review of the available literature at the time of acceptance for publication (August 2015) pertaining to the use of unilateral and bilateral stimulation to improve confrontation picture naming ability at the single word level in individuals with chronic post-stroke anomia. The merits of tDCS as a therapeutic tool are discussed, and outstanding methodological issues and knowledge gaps to be addressed by future research in this field are also identified.

In summary, existing research indicates that tDCS can boost the effects of concurrent behavioural anomia therapy. More specifically, in accordance with imaging findings linking increased activation in left perilesional areas to language recovery in the chronic stage post-stroke, studies have demonstrated significant improvements in naming ability after applying unilateral anodal stimulation to the left hemisphere as patients carry out speech and language therapy tasks targeting their word finding difficulties (Baker, Rorden, & Fridriksson, 2010; Fiori et al., 2013; Fridriksson, Richardson, Baker, & Rorden, 2011; Marangolo et al., 2013; Vestito, Rosellini, Mantero, & Bandini, 2014). Further studies have also revealed therapeutic gains after combining behavioural anomia therapy with cathodal tDCS applied to homologous language regions in the intact right hemisphere, in line with the notion of transcallosal disinhibition (Flöel et al., 2011; Kang, Kim, Sohn, Cohen, & Paik, 2011; Rosso et al., 2014).

Whilst Chapter 2 highlights the increasing body of evidence supporting the use of tDCS as an adjunct to behavioural speech and language therapy for stroke survivors with chronic anomia, there are several key limitations of existing work. Previous studies have provided

therapy alongside no more than two active electrode montages, varying either the site or polarity of stimulation. Indeed, participants commonly received only excitatory anodal and sham stimulation (a control, no-stimulation condition) applied to left frontal regions, meaning that the effects of administering tDCS targeting the contralesional hemisphere, or more posterior language areas in the left and right temporal and parietal lobes, are relatively under-researched. In addition, considerable variation exists between studies with regards to accompanying therapy tasks, number of treatment sessions provided and participant characteristics. Overall, due to the highly varied and unsystematic protocols adopted across different studies, the optimal stimulation parameters for individuals presenting with a range of aphasia subtypes, severities, and lesion profiles remain unclear, as do the potential effects of tDCS plus behavioural therapy programmes on outcome measures other than increased picture naming accuracy of treated items (Elsner, Kugler, Pohl, & Mehrholz, 2013, 2015). All of these issues were taken into account when designing the studies detailed in **Chapter 3** and **Chapter 4**.

Additional Issues Relating to Behavioural Therapy for Anomia

During the recruitment process for the tDCS-plus-therapy studies described in Chapters 3 and 4, potential participants completed an extensive noun picture naming assessment on two separate occasions in order to determine the extent of their confrontation naming deficits and identify potential therapy items for subsequent treatment. Analysis of individuals' responses revealed that all patients named some items first incorrectly then correctly across the two naming sessions and others first correctly followed by incorrectly, and that degree of naming inconsistency varied considerably between individuals. Inconsistent picture naming across multiple trials has been previously noted in people with aphasia, but the reasons for such inconsistency are currently undetermined (e.g. Capitani et al., 2012; Freed, Marshall, & Chuhlantseff, 1996). For example, evidence suggests that attempting to name items on one occasion may facilitate naming performance on a second occasion, most likely via the strengthening of links between semantic and phonological item representations (Nickels, 2002a). However, so-called 'repetition priming' cannot explain instances in which patients

initially name items correctly but fail to do so during later trials. There are a number of potential additional explanations why oral picture naming is inconsistent in individuals with chronic aphasia, and why certain individuals are more inconsistent than others, that have yet to be investigated. Such explanations include both patient-related characteristics (e.g. aphasia classification) and item-specific properties (e.g. frequency). Increasing our understanding of the nature of, and underlying reasons for, noted patterns of naming response inconsistency has important clinical implications for the assessment and treatment of anomia, as well as evaluation of therapeutic success. For instance, different therapy tasks may be optimally effective for items named consistently incorrectly and for those named inconsistently incorrectly.

The effects of tDCS plus behavioural therapy intervention programmes for individuals with chronic stroke-induced anomia appear to be task-specific (Norise, Sacchetti, & Hamilton, 2017). It is, therefore, important to provide behavioural treatment that is believed to have the greatest potential to improve word finding in this patient population alongside stimulation. Furthermore, safety considerations mean that many people with aphasia are not able to receive neurostimulation. Contraindications for tDCS typically include the presence of metal in the head (e.g. brain stent), cardiac pacemaker, history of epilepsy, and frequent or severe headaches: all of which may affect stroke survivors either as a direct consequence of their CVA, or as a result of comorbid conditions (e.g. Bikson et al., 2016; Brunoni et al., 2012; Camilo & Goldstein, 2004; Ostwald, Wasserman, & Davis, 2006). Behavioural speech and language therapy may be the most appropriate treatment option for such individuals. As stated previously, RIPP, which involves the concurrent presentation of auditory and semantic cues for immediate repetition, is a popular and effective stand-alone therapy technique (e.g. Heath et al., 2013; Morris, Howard, & Buerk, 2014; Nardo et al., 2017). Nevertheless, neuroimaging findings indicate that speech perception and speech production tasks share a number of common neural substrates, such as the left pars opercularis and left inferior premotor cortex, at least in healthy controls (Fridriksson et al., 2008; Fridriksson, Moser et al., 2009; Skipper, Nusbaum, & Small, 2005). Moreover, Fridriksson, Baker, Whiteside et al. (2009) demonstrated that individuals with aphasia named significantly more

treated and untreated nouns when spoken word to picture matching therapy included a visual speech articulation component than when audio-only input was provided. It is plausible that repetition therapy including auditory, semantic *and* articulatory cues may lead to greater therapeutic gains than RIPP, as a result of simultaneous boosting of the links between both semantics and phonology, and phonology and articulation. However, to date, the relative importance of visual speech articulation in repetition therapy for chronic anomia has not been explored.

Aims of the Thesis

The overarching purpose of this thesis was to enhance current understanding regarding the nature and treatment of anomia in individuals with chronic post-stroke aphasia. Four empirical studies were carried out, each with their own specific aims. Due to the diverse nature of this patient population, the underlying premise of all four studies was to consider outcomes at the level of individual participants, whilst recognising the potential implications on a wider scale.

To address concerns regarding existing tDCS-plus-therapy studies, a longitudinal within-participants intervention programme was devised to investigate the effects of systematically varying the laterality (left vs. right hemisphere) and polarity (anodal vs. cathodal) of stimulation in a diverse group of stroke survivors with chronic anomia.

The primary aim of this research was to determine which tDCS parameters would result in the greatest improvements in naming ability in each individual with chronic anomia.

The secondary aim of this research was to explore the potential effects of therapy on each individual's connected speech, emotional well-being and communicative effectiveness.

Participants competed six therapy cycles, each involving a different unilateral tDCS montage (perilesional anodal, perilesional cathodal, perilesional sham, contralesional anodal, contralesional cathodal, and contralesional sham). The inclusion of sham conditions permitted comparisons between the effectiveness of tDCS combined with behavioural therapy and that of behavioural therapy alone. To minimise any potential influences of perceived differences in participants' experiences of left and right hemisphere stimulation on the results (for example, due to unilateral, stroke-induced scalp sensitivity changes, or pre-existing expectations that stimulation targeting one hemisphere would be more beneficial than stimulation targeting the opposite hemisphere), the effects of active stimulation were directly compared to outcomes following ipsilateral sham stimulation. Thus, the effects of perilesional anodal and perilesional cathodal stimulation were compared to the effects of perilesional sham stimulation, and the effects of contralesional anodal and contralesional cathodal stimulation were compared to the effects of contralesional sham stimulation. Stimulation was delivered at the same time as patients completed a computerised repetition therapy task. **Chapter 3** comprises a detailed case report from the first participant (JSc, an individual with chronic Broca's aphasia) to complete the protocol. This work was subsequently extended to include three additional individuals representing a range of language and lesion profiles. The results from all four participants are presented in **Chapter 4**.

Following the identification of substantial within- and between-patient variability in picture naming accuracy across multiple trials during the recruitment process for the tDCS-plus-therapy studies, patterns of picture naming response inconsistency were explored in greater depth, with a larger cohort of participants with chronic stroke-induced anomia. This investigation is detailed in **Chapter 5**.

The aims of this research were to describe observed patterns of response inconsistency in noun picture naming in a group of 15 stroke survivors with chronic post-stroke anomia, and to use a range of demographic, behavioural and

psycholinguistic data to investigate potential reasons why naming response inconsistency varies between individuals.

Chapter 6 reports the results of the final empirical study, which compared the relative effectiveness of three different types of repetition therapy for a group of six individuals with chronic post-stroke anomia. Each form of therapy differed with respect to the semantic, auditory and visual speech articulatory cues provided for immediate repetition, as follows: i) repetition of auditory speech in the presence of a picture and articulation (RIPPA), ii) repetition of auditory speech in the presence of a picture (RIPP), and iii) repetition of auditory speech in the presence of articulation but no picture (ARTIC).

The primary aims of this research were to determine the relative importance of visual speech articulation in computer-based repetition therapy for increasing naming ability in stroke survivors with chronic anomia, and relate patterns of therapeutic response to neuropsychological and lesion profiles.

The secondary aim of this research was to explore the potential effects of therapy on each individual's connected speech and self-perceived communicative effectiveness.

Chapter 7 brings together all of the research described in Chapters 3 – 6 within the wider context of furthering knowledge regarding the nature and treatment of anomia in individuals with chronic post-stroke aphasia. The methods chosen and results obtained are critically evaluated. Clinical implications of the findings are discussed, and appropriate directions for future work are highlighted.

Acknowledgement of Contributions of Other Authors

Dr Anna Woollams and Dr Lauren Cloutman supervised the work documented in this thesis. For all chapters of the thesis, I produced initial drafts, which were then developed further to form the final versions with guidance from both supervisors. Prior to taking part in the research studies described in Chapters 3 – 6 of the current thesis, all participants had completed a battery of speech, language and cognitive assessments and undergone structural MRI scanning during the course of their involvement in previous projects within the Neuroscience and Aphasia Research Unit (NARU) at the University of Manchester. This situation is acknowledged in the relevant sections of these four empirical chapters. I conducted all recruitment, additional behavioural testing and therapy sessions for all participants for the work included in this thesis. I also analysed all of the behavioural data presented here.

Chapter 2

Taking Sides: An Integrative Review of the Impact of Laterality and Polarity on Efficacy of Therapeutic transcranial Direct Current Stimulation for Anomia in Chronic Post-Stroke Aphasia

Adapted from a paper published in Neural Plasticity in 2016

Abstract

Anomia is a frequent and persistent symptom of post-stroke aphasia, resulting from damage to areas of the brain involved in language production. Cortical neuroplasticity plays a significant role in language recovery following stroke and can be facilitated by behavioural speech and language therapy. Recent research suggests that complementing therapy with neurostimulation techniques may enhance functional gains, even amongst those with chronic aphasia. The current review focuses upon the use of transcranial Direct Current Stimulation (tDCS) as an adjunct to naming therapy for individuals with chronic post-stroke aphasia. Our survey of the literature indicates that combining therapy with anodal (excitatory) stimulation to the left hemisphere and/or cathodal (inhibitory) stimulation to the right hemisphere can increase both naming accuracy and speed when compared to the effects of therapy alone. However, the benefits of tDCS as a complement to therapy have not yet been systematically investigated with respect to site and polarity of stimulation. Recommendations for future research to help determine optimal protocols for combined therapy and tDCS are outlined.

Introduction

Aphasia is an acquired disorder that affects the way in which an individual produces and/or understands language (Goodglass & Kaplan, 1972). Language is an essential aspect of communication, and aphasia can impact significantly on the daily functioning and quality of life of stroke survivors (Hilari et al., 2012). The neural network supporting speech production is extensive (Hickok & Poeppel, 2007) and hence easily disrupted by damage, such as a stroke. It is therefore perhaps unsurprising that anomia, or word finding difficulty, is the most common and persistent symptom across all types of aphasia (Postman-Caucheteux et al., 2010). Indeed, those with more severe acute deficits tend to recover to this level (Pedersen et al., 2004) and, consequently, amelioration of anomia is a frequent aim in post-stroke rehabilitation. The typical approach to the treatment of anomia is impairment-based behavioural speech and language therapy, which focuses on helping the patient to 're-learn' words they are unable to retrieve or produce. This type of therapy can improve both object naming (Lambon Ralph et al., 2010) and everyday communicative abilities (Best et al., 2011; Conroy et al., 2009b), yet it can be time consuming to even achieve small gains. Consequently, researchers have begun to investigate more innovative new treatments based on neuroscientific principles. Recent research has suggested that neurostimulation techniques, such as transcranial Direct Current Stimulation (tDCS), can be used to optimise therapeutic gains.

The purpose of this review is to evaluate current research on the use of tDCS in the treatment of chronic post-stroke anomia to determine what has been learnt so far regarding its application and efficacy, with particular reference to the important factors of polarity (whether stimulation is positive or negative) and site of stimulation (notably, left hemisphere versus right). Critical gaps in the literature are identified, and recommendations for future research into this combined therapeutic approach are outlined. In contrast to previous reviews on this topic (Costa, 2012; de Aguiar, Paolazzi, & Miceli, 2015; Elsner et al., 2013; Holland & Crinion, 2012; Monti et al., 2013; Torres, Drebing, & Hamilton, 2013), the present review will specifically focus on studies that have examined the effects of tDCS on

confrontation naming of noun and verb pictures in chronic aphasia via a range of research designs, with reference to current neuroscientific models of speech processing and aphasia recovery.

Naming and Recovery

The Neural Naming Network

Models of language production propose that a number of interrelated tasks are necessary in order to produce speech, involving processing at semantic, phonological and articulatory levels (Dell et al., 1997; Levelt et al., 1999). Thus, some current models of confrontation naming propose that, when presented with a picture of an object and asked to name it, individuals must first map the visual stimulus onto a stored conceptual representation of the object (visual object recognition and semantic access), then retrieve its name (lexical retrieval) and phonological form (phonological code retrieval and phonological encoding), create a phonetic representation of the name (phonetic encoding), before generating a motor articulatory sequence of the phonetic representation for the vocal tract to follow (articulation) (Dell et al., 1997; Indefrey, 2011).

The brain areas believed to be involved in normal speech comprehension and production have been conceptualised within the dual stream framework proposed by Hickok and Poeppel (2004, 2007), a version of which has also been implemented as a neuro-computational model by Ueno, Saito, Rogers and Lambon Ralph (2011). According to the dual stream model, two distinct pathways link language-related regions: the dorsal stream and the ventral stream. The left-dominant dorsal stream is primarily responsible for mapping sensory input and phonological information onto the articulatory network. This pathway extends anteriorly from area Spt (a left-dominant area in the planum temporale, named according to its location in the Sylvian fissure at the parieto-temporal boundary) via the arcuate fasciculus to the posterior inferior frontal gyrus (IFG, including Broca's area), the anterior insula and areas of the premotor cortex. The ventral stream consists predominantly

of bilateral structures in the posterior and anterior parts of the temporal lobes surrounding the middle temporal gyrus (MTG) and inferior temporal sulcus (ITS). Both the dorsal and ventral pathways are linked to other cortical areas that play important roles in speech and language tasks, including the bilateral superior temporal gyrus (STG), superior temporal sulcus (STS) and areas of the frontal cortex. The role of the ventral stream is mapping sounds onto meanings and meanings onto spoken output. Consequently, the ventral stream is believed to be involved in a variety of semantically-mediated tasks, including auditory comprehension and picture recognition. Oral picture naming relies on elements of both the dorsal and ventral streams.

Research has shown that naming, alongside other speech production tasks, is typically lateralised to the left hemisphere in healthy individuals (Knecht, 2000). More specifically, neuroimaging studies of healthy adults have shown picture naming to be associated with left lateralised activation in the MTG, posterior STG, thalamus and posterior IFG (namely pars opercularis, BA44, pars triangularis, BA45, and BA46) (Indefrey & Levelt, 2004; Price, 2010; 2012). When the naming context is manipulated to make word finding more or less demanding, additional regions are recruited in both hemispheres, such as the bilateral fusiform gyri for less familiar items and the bilateral premotor cortex for items with longer names (Wilson, Isenberg, & Hickok, 2009). Imaging studies of stroke survivors also support the dual stream model. For example, Butler et al. (2014) localised phonological and semantic deficits to damage to the dorsal and ventral pathways, respectively. More specifically, voxel-based lesion-symptom mapping (VLSM) studies have revealed that lesions to the left orbital IFG (BA47) and posterior MTG are significantly correlated with impaired picture naming (Henseler, Regenbrecht, & Obrig, 2014) and, correspondingly, that lack of damage to the left mid-posterior MTG and underlying white matter tracts is critical for successful oral picture naming (Baldo, Arévalo, Patterson, & Dronkers, 2013). Piras and Marangolo (2007) further highlighted the complexity of the neural network underpinning naming. In their study, impaired noun naming was associated with lesions to the left STG and MTG, whilst impaired verb naming was more strongly associated with a wider range of lesion sites, extending from BA45 to the anterior temporal lobe (BA22 and BA38).

Language Recovery

Despite damage to language processing areas, most individuals who have suffered a left hemisphere stroke are able to recover at least some language skills, both spontaneously and following therapy, even many years post-onset (Marsh & Hillis, 2006). Language recovery following stroke can be considered to take place during three overlapping temporal stages: acute (hours to days), sub-acute (weeks to months), and chronic (months to years), (Marsh & Hillis, 2006). This recovery is facilitated by several different mechanisms that play key roles during different stages, such as the restoration of blood flow during the acute stage (e.g. Hillis et al., 2008; Hillis et al., 2006), the functional recovery of intact, temporarily dysfunctional brain regions during the sub-acute stage (e.g. Price, Warburton, Moore, Frackowiak, & Friston, 2001), and the brain's ability to undergo significant structural and functional reorganisation following damage, that is, neuroplasticity, well into the chronic stage.

Neural Regions Associated with Spontaneous Recovery

Researchers have attempted to explore the evolution of changes in spontaneous (re)organisation of language function within the brain, particularly in relation to the relative influence of the impaired left hemisphere versus the intact right. Saur and colleagues (2005) found that different temporal stages were associated with different patterns of cerebral activation. In their longitudinal study, participants were scanned using fMRI and completed an aphasia test battery at three points (acute: 0-4 days, sub-acute: 2 weeks, and chronic: 4-12 months after onset) during their first year post-stroke. Compared to age-matched controls, the stroke survivors showed reduced activation in the left IFG during the acute stage, with better initial language performance correlated with higher activation in this region. In contrast, two weeks later, strong bilateral activation was observed, and early relative improvement in language abilities was associated with increased activation in regions within the *right* IFG and adjacent insular cortex, and the right supplementary motor area. At the final assessment point, however, language activation had shifted back to areas

including the left IFG and MTG, and associated with further, significant improvement in language abilities.

The precise timings of changes in hemispheric dominance may vary between individuals (e.g. Jarso et al., 2013). Nevertheless, this sequence of brain reorganisation is supported by a recent review by Anglade, Thiel and Ansaldo (2014), and research confirms that, by the chronic stage, stroke survivors with the most favourable language recovery appear to be those who, like healthy individuals, demonstrate predominantly left lateralised language functions (e.g. Szaflarski, Allendorfer, Banks, Vannest, & Holland, 2013). When critical left hemisphere language areas are irretrievably damaged, compensatory recruitment of undamaged regions immediately surrounding the damaged areas ('perilesional' areas) is consistently linked to improvement in language abilities in chronic aphasia (Turkeltaub et al., 2011). For example, Fridriksson, Bonilha, Baker, Moser and Rorden (2010) found that stroke survivors with better naming ability showed greater activation than both control participants and patients with poorer naming ability in areas perilesional to Broca's area, including BA32 (anterior cingulate gyrus), and BAs 10 and 11/47 (medial and middle frontal gyrus). The role of right hemispheric activation in the chronic stage remains more controversial (Turkeltaub et al., 2012). One theory maintains that damage to the left hemisphere can lead to transcallosal disinhibition, meaning that homologous areas in the right hemisphere that are normally inhibited by the left during language tasks become overactive and, in turn, may impose greater inhibition on left hemisphere language regions (Martin et al., 2009). In support of this hypothesis, a number of fMRI studies have shown that individuals with chronic post–stroke aphasia do indeed have higher activation in areas such as the right IFG and right STG than healthy controls when carrying out a range of language tasks (e.g. Naeser et al., 2004; Perani et al., 2003). Activation in the right IFG has, however, been associated with errors of omission and semantic paraphasias in picture naming (Postman-Caucheteux et al., 2010). One potential explanation for such findings is that hyperactivation in the right hemisphere may prevent recruitment of perilesional areas in the left hemisphere, hindering long-term recovery from aphasia (Hamilton, Chrysikou, & Coslett, 2011).

Neural Regions Associated with Therapeutic Recovery

Further neuroimaging studies indicate that speech and language therapy can facilitate recruitment of perilesional language areas in the left hemisphere (such as the left precentral and supramarginal gyri) in individuals with chronic post-stroke aphasia, resulting in improved oral picture naming ability and a reduction in both semantic and phonological errors (Fridriksson, 2010, 2011; Fridriksson, Richardson, et al., 2012; Marcotte et al., 2012; Meinzer et al., 2008). In contrast, those who respond less favourably to therapy tend to activate a greater number of diverse areas in the left and right hemispheres during naming tasks (Marcotte et al., 2012). Like spontaneous re-lateralisation, left hemisphere re-recruitment following anomia therapy is likely to be a dynamic process. For instance, Menke et al. (2009) found that, immediately following a computer-based intervention programme, correct naming was related to increased bilateral and right hemisphere activity in regions including the bilateral parahippocampal gyri, right precuneus, cingulate gyrus and both occipital lobes. However, by eight months post-therapy, as naming ability was consolidated, success on trained items was associated with increased activity in left perilesional middle and superior temporal areas, along with some increased activity in the right hemisphere Wernicke's homologue. The authors suggest that the residual right hemisphere activity at eight months post therapy could have been functionally beneficial for the particular individuals in their study, all of who had large left hemisphere lesions that made full left re-lateralisation of language function unfeasible (see also Heiss & Thiel, 2006).

To conclude, stroke survivors with damage to the left hemisphere may activate homologous areas in the right hemisphere in order to recapture some degree of language ability at varying stages in the recovery process. In the longer term, this is likely to be a less effective strategy than recruitment of perilesional areas in the left hemisphere, with research strongly suggesting that left hemisphere re-lateralisation (as far as possible) is most beneficial for language recovery (Heiss & Thiel, 2006). Behavioural speech and language therapy can increase activity in the left hemisphere, and such activation is associated with superior outcomes from a variety of post-stroke treatment programmes. However, these studies have all incorporated intensive treatment protocols, which are not always available in clinical

settings and do not suit all patients (Holland & Crinion, 2012). Consequently, researchers have begun to investigate the potential of neurostimulation techniques, namely Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS), to facilitate the language recovery process.

Neurostimulation to Enhance Recovery

Transcranial Magnetic Stimulation (TMS)

TMS involves the delivery of rapidly alternating magnetic fields to underlying cortical tissue via an electromagnetic coil placed on the scalp. The effects of TMS vary according to the frequency of electromagnetic pulses. High frequency, or fast, TMS (≥ 5Hz) can induce increases in cortical excitability. In contrast, low frequency, or slow, TMS (typically 1Hz) is associated with cortical inhibition (Torres et al., 2013). The majority of studies investigating the therapeutic effects of TMS on post-stroke anomia have involved the application of low frequency TMS to the right hemisphere. This is based on the rationale discussed above that language deficits persist due to right hemispheric inhibition of perilesional left hemisphere language regions (Costa, 2012). Consequently, inhibiting this inhibition via the application of TMS should theoretically lead to improvements in naming ability.

In support of this theory, Naeser and colleagues (2002, 2005) demonstrated, across a series of studies, that applying repetitive slow (inhibitory) TMS to the right hemisphere of patients with chronic aphasia had beneficial effects on their language skills. In the first study, three non-fluent participants all with lesions involving damage to Broca's area, received single ten minute sessions of 1Hz TMS either the right Broca's homologue (pars triangularis, BA45) or to the mouth area of the motor cortex (Naeser et al., 2002). The researchers found that only stimulation to the pars triangularis portion of the right Broca's homologue significantly increased picture naming accuracy, thereby supporting the notion that dysfunctional right hemisphere overactivation had previously been adversely affecting naming skills. These effects were, however, short-lived, and disappeared within 30 minutes. In an attempt to

produce longer lasting effects, the same research group administered 1Hz TMS to the pars triangularis of the right Broca's homologue of four stroke survivors (two with Broca's aphasia, one with Broca's aphasia recovered to anomic/conduction aphasia, and one with global aphasia) for 20 minutes a day, five days a week for two weeks (Naeser et al., 2005). Language abilities were assessed at baseline and again at two weeks, two months and eight months post-TMS. As in Naeser et al.'s earlier study (2002), TMS resulted in significantly better naming ability for all four participants, this time in terms of both naming accuracy and speed. Furthermore, for three of the four participants, these effects were maintained for eight months following stimulation. This suggests that multiple stimulation sessions led to long-term brain re-organisation, although the authors did not use brain imaging tools to confirm this hypothesis.

One criticism of Naeser et al.'s studies is that all participants received only active TMS. Although unlikely, it is possible that the observed effects on naming abilities were not the direct result of suppression of right hemispheric activation, but due to an unidentified factor related to the presence of the TMS equipment. To clarify this issue, Barwood and colleagues (2011) recruited a dozen individuals with long standing aphasia of varying severities. Half of the participants received 1Hz TMS to the right pars triangularis whilst the other half acted as a control group, receiving sham stimulation instead. Only active stimulation resulted in significant increases in naming accuracy and speed both immediately and one week after the stimulation sessions, thus supporting the view that inhibition of right hemisphere activation was responsible for improvements at single word production level.

The results of the TMS studies outlined above suggest that post-stroke language production skills are optimised when activation in right frontal regions (and in particular the right pars triangularis) is reduced. However, as is the case with spontaneous recovery, individual differences play a significant role in a person's potential for language recovery following TMS. Factors shown to influence language recovery in aphasia include lesion site, lesion size, age, gender, handedness and pre-morbid intelligence levels (Lazar & Antoniello, 2008). The particular importance of lesion site was demonstrated by Martin et al. (2009), who

administered 10 sessions of slow TMS to the right pars triangularis of two individuals with chronic, non-fluent aphasia. Patient 1 (P1) responded well behaviourally to the TMS treatment. He named more object pictures and used longer phrases during an elicited speech task three, 16 and 46 months after TMS than he had done before. In line with these increases in language performance, P1 also showed increased left hemisphere activation in perilesional sensorimotor cortical regions following TMS. In contrast, TMS had no significant effects on P2's measured language abilities, nor did he demonstrate any new and lasting perilesional activation in the left hemisphere after stimulation. The authors suggest that the differences in response to TMS between P1 and P2 were likely to be related to their lesion sites. Whilst both participants had lesions to Broca's and Wernicke's areas, unlike P1, P2 had additional lesions in the left motor and prefrontal cortices and regions both inferior and posterior to Wernicke's area. The additional left hemispheric damage to P2's extended language network may have prevented him from activating perilesional areas following inhibitory TMS to the right hemisphere.

In each of the studies above, participants received only low frequency TMS in isolation. It is possible that administering TMS followed by behavioural speech and language therapy may be more efficient than either TMS or therapy alone in increasing language abilities in individuals with aphasia (Cotelli et al., 2011). To examine the potential enhancing effect of TMS on speech and language therapy, Weiduschat and colleagues (2010) applied up to 1Hz low frequency TMS to either the right pars triangularis or the vertex (as a sham condition) of small groups of sub-acute stroke survivors with different types of aphasia, five days a week for two weeks. In each session, 20 minutes of stimulation was immediately followed by 45 minutes of individually tailored speech and language therapy. Results showed that, whilst language abilities, including single word naming, increased in both groups of participants after intervention, this increase was only significant for the participants who had received TMS to the right pars triangularis. This finding indicates that therapy sessions that combine inhibitory right hemisphere TMS and more traditional speech and language therapy can result in greater therapeutic gains when compared to therapy alone, at least for sub-acute stroke survivors. Other research suggests that combining enhancing activity in the left

hemisphere via excitatory TMS with speech and language therapy can also convey therapeutic benefits. For instance, Cotelli et al. (2011) gave three patients with chronic aphasia 25 minutes of high frequency TMS to the left dorsolateral prefrontal cortex, immediately followed by 25 minutes of therapy designed to increase noun naming ability. TMS targeted a region whose excitatory stimulation has been shown to facilitate naming in both healthy controls (Cappa, Sandrini, Rossini, Sosta, & Miniussi, 2002) and individuals with Alzheimer's disease (Cotelli, Manenti, Cappa, Zanetti, & Miniussi, 2008). All patients received at least a fortnight of real TMS plus therapy. In line with expectations, two weeks of combined TMS and anomia therapy led to significant improvements in the percentage of correctly named objects. This effect generalised to untreated items, and persisted for both treated and untreated items up until the final follow-up, 48 weeks post-intervention.

In summary, applying low frequency TMS to the right hemisphere or high frequency TMS to the left hemisphere appears to have some therapeutic benefit for individuals with sub-acute or chronic post-stroke anomia, whether administered alone or in conjunction with behavioural speech and language therapy. More research is required to tease out the relative effects of TMS and behavioural therapy. However, the practical appeal of TMS as a therapeutic tool is somewhat limited. For instance, TMS can cause muscle twitching which, as well as being unpleasant for patients, may hinder verbal responses if their facial muscles are affected (Kaminski, Korb, Villringer, & Ott, 2011). Additionally, the noise of the stimulator may make it difficult for patients to complete therapy tasks. Consequently, it is not generally feasible to apply TMS concurrently with behavioural speech and language therapy, nor create effective sham conditions. To overcome these issues, research has increasingly focused on an alternative technique that shows particular promise as a therapeutic tool, transcranial Direct Current Stimulation (tDCS) (Stagg & Nitsche, 2011).

Transcranial Direct Current Stimulation (tDCS)

tDCS is a non-invasive neurostimulation technique that uses a battery pack to deliver weak electrical currents to the brain via two saline-soaked electrodes. The active electrode is

placed on the scalp over a particular region of interest, stimulating the cortex underneath, whilst the reference electrode is usually placed on the contralateral supra-orbit or contralateral shoulder (Fridriksson, 2011). Positive (anodal) stimulation is associated with increased neuronal excitability whilst negative (cathodal) stimulation is associated with inhibition of neuronal activity (Nitsche & Paulus, 2000).

Neurobiology of tDCS-Induced Excitability Changes

Research has shown that the effects of tDCS on brain activation and task performance are determined by multiple factors, including the number of stimulation sessions, the strength and duration of the current applied, as well as the task in hand (Medeiros et al., 2012). After effects have been found to be potentially long-lasting, persisting up to 12 months post-stimulation (Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009). The physiological mechanisms underlying the effects of tDCS are not yet fully understood. However, unlike TMS, the currents generated by tDCS are considered insufficient to directly induce action potentials (Torres et al., 2013), and different processes are believed to be responsible for changes in cortical activation during and after stimulation (Stagg & Nitsche, 2011). During stimulation, tDCS is thought to indirectly alter neuronal excitability by temporarily affecting membrane polarity: anodal stimulation causes neuronal depolarisation (increased sodium and calcium ion channel activity), whereas cathodal stimulation causes neuronal hyperpolarisation (decreased sodium and calcium ion channel activity) (Nitsche, Fricke, et al., 2003). This proposition is supported by the observation that blocking sodium channels (using carbamazepine, or CBZ) and calcium channels (using flunarizine, or FLU) prior to stimulation reduces the excitatory effects of anodal tDCS but does not impact on the effects of cathodal stimulation (Nitsche, Fricke, et al., 2003).

Whilst the short-term effects of tDCS appear to rely on transient changes in membrane potential, post-stimulation effects are believed to be the result of longer lasting changes in synaptic strength (Stagg & Nitsche, 2011). One likely mechanism by which tDCS may act to modulate synaptic strength is LTP. LTP is based on the Hebbian principle (Hebb, 1949) that when pre- and post-synaptic neurons repeatedly fire together, metabolic changes occur that

make the firing of one neuron more likely to result in the firing of the other in future. The result of LTP (and its reverse process, LTD), is stable changes in synaptic activation that persist over many months or even years (Bliss & Lømo, 1973). The inducement of LTP or LTD is dependent upon levels of specific neurotransmitters and neuromodulators (neurochemicals that can potentiate or attenuate the responses evoked by neurotransmitters) (Medeiros et al., 2012). In particular, tDCS appears to involve regulation of the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA, plus the neuromodulators dopamine, acetylcholine and serotonin (Stagg & Nitsche, 2011). To examine the relationship between tDCS and changes in cortical neurotransmitter concentrations, Stagg and colleagues (2009) administered 1mA of anodal, cathodal and sham tDCS to the left primary motor cortex of 11 healthy adults in three separate sessions, at least seven days apart, and examined the effects using magnetic resonance spectroscopy (MRS). These MRS results showed that anodal stimulation led to significant decreases in GABA concentration. In comparison, cathodal stimulation led to significant decreases in glutamate levels as well as correlated decreases in GABA concentration. This latter finding may initially appear at odds with expectations, however, GABA is synthesised from glutamate and, therefore, reducing the amount of available glutamate via inhibitory tDCS will result in corresponding decreases in GABA (Stagg et al., 2009). Taken together, Stagg et al.'s results indicate that the after effects of anodal tDCS are mediated, at least in part, by a reduction in GABAergic inhibition, whilst the after effects of cathodal stimulation are related to a reduction in glutamatergic neurotransmission. As well as glutamate and GABA themselves, other researchers have shown that NMDA receptors also play an important role in the development of tDCS-induced after effects. For example, Nitsche and colleagues (2003) demonstrated that administration of the glutamate antagonist dextromethorphan (DMO), which acts to block NMDA glutamate receptors, abolished the after effects of both anodal and cathodal stimulation.

With respect to neuromodulators, acetylcholine has been found to have an adverse impact on potential tDCS-induced alterations in neuronal excitability. In one study, increasing acetylcholine levels by administering the acetylcholinesterase inhibitor rivistigmine

eliminated the after effects of anodal tDCS, and reduced the after effects of cathodal tDCS (Kuo, Grosch, Fregni, Paulus, & Nitsche, 2007). In comparison, increasing serotonin levels via the use of the selective serotonin reuptake inhibitor citalopram both enhanced and prolonged the excitatory after effects of anodal tDCS, and reversed the inhibitory after effects of cathodal tDCS to produce excitation (Nitsche et al., 2009). Conversely, increasing dopamine via its precursor L-Dopa turned anodal tDCS-induced excitability to inhibition and extended cathodal tDCS-induced reductions in excitability by several days (Kuo, Paulus, & Nitsche, 2007). Thus, serotonin appears to facilitate excitatory stimulation whilst dopamine facilitates inhibitory stimulation. However, the impact of neuromodulator levels on tDCS effects is complex, and they do not appear to follow simple, linear relationships. For example, in a study examining the influence of dopamine on cathodal after effects, Monte-Silva and colleagues (2009) found that only intermediate doses (0.5 mg) of ropinirole (a D_2 dopamine receptor agonist) increased the inhibitory after effects of cathodal tDCS, with low (up to 0.25 mg) and high doses (1.0 mg) actually abolishing the effects instead. Further investigation is required to clarify the intricate interactions between neurotransmitters and neuromodulators in inducing and sustaining the behavioural effects of tDCS.

An important caveat to acknowledge regarding the use of tDCS is that applying an electrical current to the brain transcranially (as opposed to directly stimulating the cortex) may mean that the underlying cortex fails to receive the expected dose of stimulation, resulting in the recipient failing to demonstrate the desired behavioural consequences. One reason for this is the dispersion of current before it reaches the target cortex. For example, Miranda, Lomarev and Hallett (2006) modelled the spatial distribution of 2mA anodal tDCS delivered to four different cortical regions. Their results revealed that the intensity of current on the scalp directly underneath the anode varied, in that current density was observed to be higher at the perimeters than in the centre of the electrode. Although current density was more uniform once it reached the brain surface, between 41% and 61% of the current did not penetrate through the skull to the cortex underneath. Research has also revealed that, even once current reaches the cortex, the effects of tDCS on brain activity may not be restricted to areas directly under the active electrode but can extend to a wider network of functionally

related brain regions via excitatory and inhibitory neural pathways (Zheng, Alsop, & Schlaug, 2011). For instance, in one study, anodal tDCS to the dorsal lateral prefrontal cortex of ten healthy volunteers led to increased synchronous activity between distal frontal and parietal areas (Peña-Gómez et al., 2012). Finally, it is also important to note that studies that have examined the neurobiological basis of tDCS have generally only considered its effects on healthy humans, or even in animal subjects. It is possible that the neurological activation patterns and subsequent behavioural effects may not be the same in stroke-damaged human brains as they are in healthy ones (Suzuki et al., 2012). In support of this, Datta, Baker, Bikson and Fridriksson (2011) modelled the current flow as a result of anodal stimulation to the left frontal cortex (BA6) in a non-fluent patient who had responded favourably to an intervention programme combining tDCS and computerised anomia therapy. Their analysis revealed that current flow in this particular individual was indeed altered from the pattern observed in a healthy brain due to the presence of the lesion, with the current found to be most concentrated in deep, perilesional brain regions. Furthermore, they observed that current flow was also influenced by the positioning of the reference cathode, with different electric fields associated with contralateral shoulder, contralateral mastoid, contralateral supraorbital and contralateral cortical homologue cathodes. As such, all of these factors should be borne in mind when designing protocols that aim to modify individuals' behaviour with tDCS.

Potential Advantages of tDCS as a Therapeutic Tool

Despite the caveats noted above, a growing body of evidence indicates that tDCS can have significant positive behavioural effects on a wide variety of cognitive and motor tasks in both healthy individuals and stroke survivors (e.g. Brasil-Neto, 2012; Fregni et al., 2005; Holland et al., 2011). From a practical viewpoint, tDCS has a number of key characteristics that make it a viable therapeutic tool for use within the post-stroke population. tDCS is considered safe when administered in accordance with established conventions and, unlike TMS, is not associated with an increased seizure risk (Nitsche et al., 2008; Nitsche, Liebetanz, et al., 2003; Poreisz et al., 2007; Rossi, Hallett, Rossini, & Pascual-Leone, 2009). It is generally well-tolerated and, although individuals undergoing tDCS occasionally report

side effects such as localised tingling, itching, burning, pain and headaches, related to stimulation itself and to the bands used to hold electrodes in position. These effects are typically mild and fade within 30 seconds to 1 minute of stimulation (Flöel, Rösser, Michka, Knecht, & Breitenstein, 2008; Kessler, Turkeltaub, Benson, & Hamilton, 2012). Side effects can also be reduced by soaking the sponge electrodes in a 15-140 mM saline solution (Dundas, Thickbroom, & Mastaglia, 2007). Moreover, studies have not found any physiological differences in participants' systolic and diastolic blood pressure, heart rate or rated mood between stimulation and sham (no stimulation) conditions, further indicating the comfort and safety of tDCS (Flöel et al., 2011; Flöel et al., 2008) as well as confirming that changes in arousal do not mediate the effects of tDCS on performance. Furthermore, as tDCS does not result in action potentials, it does not induce the muscle twitches associated with TMS. Taken together, these factors make tDCS an ideal method by which to administer stimulation in conjunction with speech and language therapy, both 'online' (with therapy and stimulation administered concurrently), as well as 'offline' (with therapy following stimulation). The lack of physiological changes and the diminishing of the sensations associated with stimulation within one minute after onset also mean that recipients are often unable to distinguish sham (where active stimulation is administered for approximately 30 seconds to produce the initial sensations, before slowly being turned off) from longer periods of active stimulation (e.g., Flöel et al., 2008). The potential to include this no stimulation control condition enables studies to compare the effectiveness of behavioural speech and language therapy in conjunction with tDCS with that of behavioural speech and language therapy alone. Finally, tDCS equipment is relatively inexpensive and easily portable, making it theoretically possible for clinicians to administer tDCS to people with aphasia in a variety of contexts, including patients' own homes (Brasil-Neto, 2012).

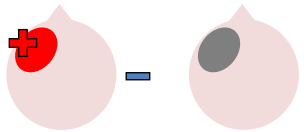
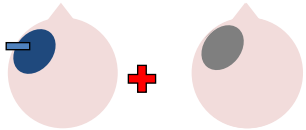
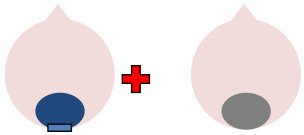
Therapeutic Effects of tDCS on Naming Ability in Aphasia

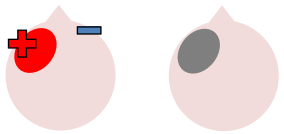
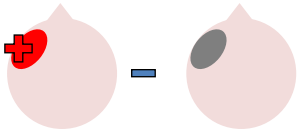
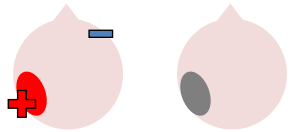
In order to thoroughly assess the therapeutic effects of tDCS on the naming performance of individuals with chronic stroke-induced aphasia, comprehensive searches of databases and other sources were carried out at several time points to obtain details of all relevant studies.

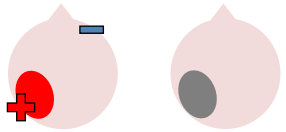
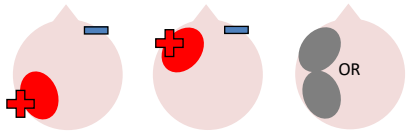
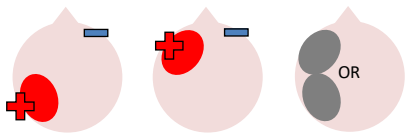
Electronic databases (CINAHL Plus, Medline, PubMed) were searched periodically between July 2013 and October 2014 to identify possible papers, published in English in peer-reviewed journals. The search terms used were 'tDCS', 'transcranial direct current stimulation', 'stimulation' or 'neurostimulation' in combination with 'language', 'aphasia' or 'anomia'. Although broad, these search terms were chosen to maximise identification of all relevant studies. No specific publication dates were imposed. In addition, the 'related citations' suggested by PubMed and the reference lists of relevant papers were also checked. All generated papers were then closely examined to confirm that they involved the use of tDCS rather than alternative brain stimulation techniques, such as TMS, and that any therapy provided and any outcome measures used focused primarily on single word confrontation naming of object and/or action pictures. Studies were only included if some or all of the participants were adult stroke survivors with chronic aphasia, meaning that studies that involved language production in healthy participants and/or stroke survivors in the acute or sub-acute stages alone were omitted (Cattaneo, Pisoni, & Papagno, 2011; Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010; Fiori, Cipollari, Caltagirone, & Marangolo, 2014; Meinzer et al., 2014; Polanowska, Leśniak, & Seniów, 2013).

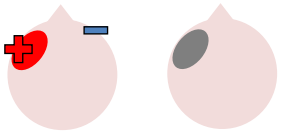
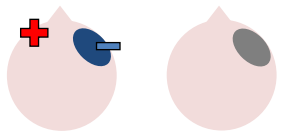
Following the literature search, 14 studies emerged that directly investigated the therapeutic effects of tDCS on single noun or verb picture naming in individuals with chronic post-stroke aphasia, both as a stand-alone technique, and in conjunction with behavioural speech and language therapy. These studies are summarised in Table 2.1. Studies are grouped by stimulation hemisphere: left, right and bilateral, and their findings are discussed with reference to previously described TMS results.

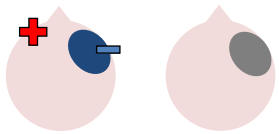
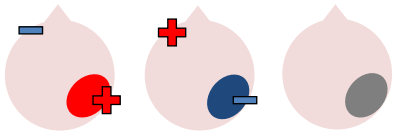
Table 2.1: tDCS studies of naming ability of individuals with chronic post-stroke aphasia. Images are supplied to illustrate key aspects of the protocol. Ovals represent stimulation site, with size reflecting electrode size. Red ovals represent anodal stimulation, blue ovals cathodal stimulation and grey ovals sham stimulation. Symbols on the ovals indicate target site, symbols alone indicate reference electrodes.

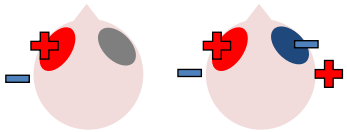
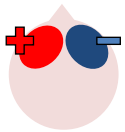
Study	tDCS protocol	No. of ppts	Months post-stroke	Aphasia profile	Concurrent therapy	Outcome measures	Initial results (mean values)	Length of follow-up
Left hemisphere								
Monti et al. 2008	2mA, 10 mins, single sessions, electrodes 35cm^2 *Experiment 1* At least a week between anodal or/and cathodal and sham 	8 in total 4 + 2 also cathodal	24-96	4 x Broca's 4 x Global	None	Noun picture naming accuracy and reaction time	Naming accuracy increased significantly (+33.6%) following cathodal stimulation but not after anodal or sham stimulation There were no significant changes in reaction time following anodal, cathodal or sham stimulation	N/A
	 4 + 2 also anodal 2 months later *Experiment 2* Time between cathodal and sham not reported  Reference electrode on contralateral shoulder				None	Noun picture naming accuracy and reaction time	There were no significant changes in either naming accuracy or reaction time following cathodal or sham stimulation	N/A

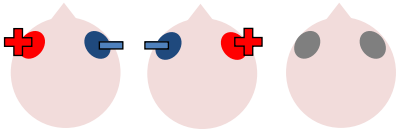
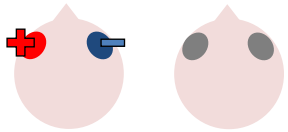
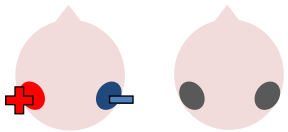
Study	tDCS protocol	No. of ppts	Months post-stroke	Aphasia profile	Concurrent therapy	Outcome measures	Initial results (mean values)	Length of follow-up
Volpato et al. 2013	2mA, 20 minutes x 5 days for 2 weeks, electrodes 35cm^2 Time between anodal and sham not reported 	8	6-126	2 x Anomic 1 x Broca's 1 x Conduction 1 x Transcortical motor 1 x Transcortical sensory 2 x Wernicke's Mild – moderate	None	Noun and verb picture naming accuracy and reaction time	Anodal tDCS significantly improved verb picture naming accuracy (+184.62%) and reduced reaction time (-32.68%) for only 1 ppt, with the most severe anomia There were no significant effects of stimulation on noun picture naming accuracy and speed	N/A
Baker et al. 2010	1mA, 20 mins x 5 days for 1 week, electrodes 25cm^2 At least one week between anodal and sham  Reference electrode on contralateral shoulder	10	10-242	6 x Anomic 4 x Broca's Wide-ranging severity of aphasia	Computerised noun naming therapy	Noun picture naming accuracy Treated and untreated items	Anodal tDCS significantly improved the naming accuracy of treated items and numerically increased (from 27.3 to 40/50 post-treatment) the number of untreated items named correctly	1 week - the significant effect of anodal stimulation was maintained and the number of untreated items named correctly increased further (42/50, still n.s.)
Fridriksson et al. 2011	1mA, 20 mins x 5 days for 1 week, electrodes 25cm^2 3 weeks between anodal and sham 	8	10-150	Fluent	Computerised noun naming therapy	Noun picture naming reaction time Treated and untreated items	Anodal tDCS significantly reduced reaction times (-455.57 ms) for 7/8 ppts on treated items vs. sham tDCS (-281.17 ms) There were no significant effects of stimulation on untreated items	3 weeks – all 8 ppts now showed reduced reaction times for treated items after anodal tDCS (-430.6 ms) and not after sham tDCS (-265.86 ms)

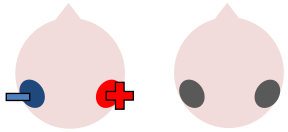
Study	tDCS protocol	No. of ppts	Months post-stroke	Aphasia profile	Concurrent therapy	Outcome measures	Initial results (mean values)	Length of follow-up
Fiori et al. 2011	1mA, 20 mins x 5 days for 1 week, electrodes 35cm^2 One week between anodal and sham 	3	21-71	Non-fluent (1 x mild, 1 x moderate, 1 x severe)	Computerised noun naming therapy	Noun picture naming accuracy and reaction time Treated items only	Naming accuracy significantly increased (+21% more than sham) and reaction time significantly reduced following anodal tDCS rather than sham tDCS (1486 ms vs. 1763 ms)	1 and 3 weeks (only 2/3 ppts) – some reduction in naming accuracy from the end of therapy to 1 week follow-up (still significant) effects on reaction times maintained
Fiori et al. 2013	1mA, 20 mins x 5 days for 1 week, electrodes 35cm^2 Six days between anodal Wernicke's, anodal Broca's and sham, one month between noun cycle and verb cycle 	7	7-84	Non-fluent with noun and verb retrieval deficits	Computerised noun and verb naming therapy	Noun and verb picture naming accuracy Treated items only	Anodal tDCS to Broca's area significantly improved verb naming accuracy (Broca's vs. Wernicke's = +24%, Broca's vs. sham = +22%). Anodal tDCS to Wernicke's area significantly improved noun naming accuracy Wernicke's vs. Broca's = +17%, Wernicke's vs. sham = +24%)	1 and 4 weeks – significant effects of Broca's stimulation on verb naming and of Wernicke's stimulation on noun naming persisted
Marangolo et al. 2013	1mA, 20 mins x 5 days for 1 week, electrodes 35cm^2 Six days between anodal Wernicke's, anodal Broca's and sham 	7	7-84	Non-fluent with verb retrieval deficits	Computerised verb naming therapy	Verb picture naming accuracy Treated items only	Anodal tDCS to Broca's area significantly improved verb naming accuracy (% correct responses: Broca's = 33% Wernicke's = 24% Sham = 23%)	1 and 4 weeks (only 6/7 ppts) – effects maintained

Study	tDCS protocol	No. of ppts	Months post-stroke	Aphasia profile	Concurrent therapy	Outcome measures	Initial results (mean values)	Length of follow-up
Vestito et al. 2014	1.5mA, 20 mins x 5 days for 2 weeks, electrodes 25cm^2 Anodal one hour after sham 	3	20-64	2 x Non-fluent (1 x high, 1 x very high severity) 1 x Anomic (moderate severity)	Noun and verb naming therapy Therapy task difficulty was increased for the second week (different item set with increased number of lower frequency words)	Noun and verb picture naming accuracy Treated items only Boston Naming Test (BNT), Aachen Aphasia Test (AAT) (naming, oral/written comprehension)	Anodal stimulation significantly increased the number of items correctly named from baseline, with initial increases following the first session and further increases over the remaining sessions each week for ppt 1 (week 1 15/24/28, week 2 8/24/30) and ppt 3 (26/30/35, week 2 27/31/36), and in week 2 for ppt 2 (16/22/26) Therapy task difficulty was unrelated to naming outcomes Anodal stimulation increased % correct responses for all ppts on the BNT (ppt 2 and ppt 3 n.s.) and AAT (ppt 3 n.s.)	4,8,12,16 and 21 weeks – effects on number of correct responses persisted significantly for all ppts to 16 weeks and persisted up to 21 weeks (n.s.) % correct responses on the AAT and BNT persisted significantly up to 12 weeks and persisted up to 21 weeks (n.s.)
Right Hemisphere								
Kang et al. 2011	2mA, 20 mins x 5 days for 1 week (starting 10 minutes into each 30 minute training session) electrodes 25cm^2 One week between cathodal and sham. 	10	6-180	2 x Anomic 3 x Global 4 x Non-fluent 1 x Transcortical motor	Individually tailored computerised noun retrieval therapy	Noun picture naming accuracy (including % cued responses) and reaction time on Korean version of BNT	Trend for increased naming accuracy following cathodal tDCS vs. sham (p = 0.058)	1 hour – trend still apparent

Study	tDCS protocol	No. of ppts	Months post-stroke	Aphasia profile	Concurrent therapy	Outcome measures	Initial results (mean values)	Length of follow-up
Rosso et al. 2014	1mA, 15 mins x single sessions, electrodes 35cm^2 Two hours between cathodal and sham. 	25	>3 (mean = 15)	Picture naming deficits Range of severity of aphasia 11 ppts with lesions involving Broca's area (B+), 14 with lesions not involving Broca's area (B-)	None	Noun picture naming accuracy (calculated as a function of the number of correct and partially correct (e.g. containing one phonemic error) responses)	Naming accuracy of B+ ppts increased significantly following cathodal tDCS, naming accuracy of 13/14 of B- ppts decreased or remained the same following cathodal stimulation Greater improvements in naming were also associated with greater integrity of the arcuate fasciculus	N/A
Flöel et al. 2011	1mA 20 mins x twice per day for 3 days (at start of each training hour), electrodes 35cm^2 3 weeks between anodal, cathodal and sham 	12	14-260	2 x Anomic 7 x Broca's 1 x Global 1 x Wernicke's 1 x Not classified	Computerised noun naming therapy involving a decreasing cueing hierarchy	Noun picture naming accuracy Treated items only	All conditions resulted in increased naming ability (= 83%) but anodal tDCS led to significantly greater improvements than cathodal or sham stimulation Ppts with more severe anomia showed the greatest therapy gains	2 weeks - effects persisted

Study	tDCS protocol	No. of ppts	Months post-stroke	Aphasia profile	Concurrent therapy	Outcome measures	Initial results (mean values)	Length of follow-up
Bilateral								
Lee et al. 2013	2mA, 30 mins, single sessions, electrodes 25cm^2, therapy given during last 15 minutes of stimulation >24 hours between anodal + sham and bilateral conditions  Reference electrodes on ipsilateral buccinator muscles	11	6+	4 x Broca's 2 x Transcortical motor 5 x Anomic	Picture naming and reading short paragraphs	Noun picture naming accuracy and reaction time on Korean version of the BNT Verbal fluency	Naming accuracy significantly increased in both conditions Reaction time decreased in both conditions, but this was only significant for the bilateral stimulation condition Stimulation had no effect on verbal fluency	N/A
Manenti et al. 2015	2mA, 25 minutes x 5 days for 4 weeks, electrodes 35cm^2 Anodal and cathodal delivered simultaneously 	1	8	Mild non-fluent	None 25 minutes of semantic-phonological therapy given directly after each stimulation session	Non-verbal reasoning, verbal fluency, Aachen Aphasia Test (AAT), Battery for the Analysis of Aphasia Deficits (BADA), Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39), noun and verb picture naming accuracy Treated and untreated items	There were a number of significant changes at 4 weeks post-stimulation: Phonemic fluency – significant increase SAQOL-39 – significant increases in psychosocial/mood and communication scales Verb naming – significant increases in % named correctly (treated and untreated items) and significant decreases in number of 'circumlocution' and 'replacement with noun' errors	12, 24 and 48 weeks Phonemic fluency - further increases at 48 weeks SAQOL-39 – effects on psychosocial/ mood scale maintained at 24 weeks and on communication scale at 48 weeks Verb naming – effects on % named correctly maintained at 48 weeks and effects on error type maintained at 24 weeks

Study	tDCS protocol	No. of ppts	Months post-stroke	Aphasia profile	Concurrent therapy	Outcome measures	Initial results (mean values)	Length of follow-up
Costa et al. 2015	1mA, 20 minutes, electrodes 16cm^2 *Pilot study* 3 single sessions, one week between conditions 	1	30	Severe non-fluent Possible crossed aphasia	None	Scores on a noun and verb naming task (calculated as a function of correct responses without cues and with one/two letter phonological cues)	Naming scores were significantly higher than baseline following anodal left/cathodal right stimulation than following either cathodal left/anodal right or sham stimulation ($p = 0.017$) There was no significant difference between noun and verb naming	N/A
	1 month later *Experiment 1* *20 minutes x 5 days for 2 weeks* 9 days between bilateral and sham 				None	Scores on the noun and verb naming task	Naming scores were significantly higher than baseline following active than following sham stimulation ($p<0.05$) There was no significant difference between noun and verb naming	Scores taken every three days post-stimulation - effect maintained for 9 days
	4 months later *Experiment 2* *20 minutes x 5 days for 2 weeks* 9 days between bilateral and sham 				None	Scores on the noun and verb naming task	There was no significant difference in naming scores following active or sham stimulation There was no significant difference between noun and verb naming	N/A

Study	tDCS protocol	No. of ppts	Months post-stroke	Aphasia profile	Concurrent therapy	Outcome measures	Initial results (mean values)	Length of follow-up
Costa et al. 2015 (continued)	4 months later *Experiment 3* *20 minutes x 5 days for 2 weeks* 9 days between bilateral and sham 				None	Scores on the noun and verb naming task	Naming scores were significantly higher than baseline following active than following sham stimulation ($p < 0.05$) There was no significant difference between noun and verb naming	Scores taken every three days post-stimulation - effect maintained for 6 days

Left Hemisphere Stimulation

Two studies investigated the effects of left hemisphere tDCS alone on naming ability in individuals with aphasia (Monti et al., 2008; Volpato et al., 2013). In a preliminary study, Monti et al. (2008) administered tDCS to eight chronic non-fluent aphasic individuals. In the first part of their study, all participants received one ten minute session of sham tDCS to Broca's area. In addition, six participants received a further session of 2mA anodal stimulation and six received a further session of 2mA cathodal stimulation to Broca's area (four participants received all three types of stimulation). Picture naming was assessed before and immediately after each stimulation session. In the second part of the study, carried out two months later, all eight participants received single sessions of both cathodal and sham stimulation to the occipital lobe (2cm above the inion). The results of both studies revealed that only cathodal tDCS to Broca's area significantly improved noun picture naming accuracy, which the authors attributed to a decreased excitability of inhibitory circuits within the left hemisphere. However, this result was obtained with a very limited sample size and, in contrast to studies showing the effectiveness of TMS alone in improving anomia (Barwood et al., 2011; Martin et al., 2009; Naeser et al., 2002; 2005), other studies involving the application of tDCS to the left hemisphere in the absence of concomitant therapy tasks have shown little benefit, even when the overall dose of stimulation is greatly increased. For instance, within a diverse group of eight stroke survivors with chronic mild to moderate aphasia, Volpato and colleagues (2013) demonstrated that, with the exception of one individual with severe anomia, 20 minutes of 2mA anodal stimulation to Broca's area once a day for two weeks had no significant effects on either object or action naming.

In contrast to the application of tDCS alone, a number of studies have found evidence for the efficacy of anodal stimulation to the left hemisphere in conjunction with speech and language therapy in improving naming abilities in individuals with post-stroke aphasia. For example, Baker, Rorden and Fridriksson (2010) gave ten patients with chronic stroke-induced aphasia (six fluent, four non-fluent) five consecutive days of anodal tDCS (1mA for 20 minutes) and five consecutive days of sham tDCS. Participants completed a

computerised matching task (following Fridriksson et al., 2009) at the same time as receiving stimulation. This involved showing a series of colour noun pictures, each immediately followed by an audio video clip of a man's mouth saying an object name. After each coupled presentation, patients were required to indicate whether the image and associated video clip referred to the same item or not. Therapy runs were separated by a seven day rest period to avoid carry over effects and the order of runs was counterbalanced across participants. During therapy, care was taken to ensure that the active electrode was placed over structurally intact perilesional cortex that had previously shown the most activation during a pre-therapy naming assessment during fMRI. Consequently, electrode positioning varied slightly for each individual, although across all participants, the active electrode was placed over either the left precentral gyrus or parts of the left frontal gyrus.

The study found that both the anodal and sham stimulation conditions resulted in increased numbers of correctly named treated items compared to baseline for the majority of participants. However, these increases were only significant in the anodal tDCS condition, with this effect maintained at follow-up, one week after therapy ceased. The number of correctly named untreated items also increased in the anodal tDCS condition, although this increase failed to reach statistical significance at either time point. More detailed inspection of Baker et al.'s results reveals that four participants (two fluent and two non-fluent) performed significantly better on the noun naming measure following anodal stimulation than following sham stimulation, indicating that they benefitted more from active tDCS than the remaining six participants. This variability in therapeutic response was unrelated to aphasia severity. However, all four good responders had damage to the left frontal cortex, meaning that the perilesional stimulation was applied especially near to their lesion sites. It is possible that targeting intact tissue situated very close to damaged regions is critical to the effectiveness of tDCS as an adjunct to behavioural anomia therapy. Utilising the same electrode positioning and therapy protocol as Baker et al. (2010), Fridriksson, Richardson, Baker and Rorden (2011) showed that anodal tDCS plus computerised anomia treatment was significantly more effective in improving treated noun picture naming speed in a group of eight patients with chronic fluent aphasia, both immediately after treatment and at the

three week follow-up. Due to the location of their participants' lesions, the active electrodes were placed more posteriorly in Fridriksson et al.'s study than Baker et al.'s in order to stimulate regions close to Wernicke's area, again demonstrating the importance of proximal perilesional stimulation for maximal therapeutic outcomes. The results of these two studies also indicate that when used in conjunction with behavioural language therapy, anodal tDCS applied to intact, perilesional cortical areas in the left hemisphere can benefit individuals with anomia associated with both fluent and non-fluent aphasia, demonstrating its wide clinical applicability.

The observation that anodal tDCS to the left hemisphere can enhance naming ability is further supported by four studies conducted by Fiori and colleagues (Fiori et al., 2013; 2011), Marangolo et al. (2013), and Vestito, Rosellini, Mantero and Bandini (2014). In the first of these studies, three individuals with chronic non-fluent aphasia completed two runs of therapy (each of five consecutive days), during which they were asked to name pictures of objects whilst receiving 20 minutes of 1mA anodal or sham stimulation to Wernicke's area (Fiori et al., 2011). During therapy, written labels were provided when participants were unable to spontaneously name any item within 15 seconds. Results revealed that unsupported confrontation naming was faster and more accurate following anodal rather than sham stimulation. These observations held true for two individuals (one with moderate and one with severe non-fluent aphasia) who completed the final follow-up, which took place three weeks post-therapy. More recently, Fiori et al. (2013) extended their earlier work by investigating the effects of tDCS-plus-therapy on both noun and verb naming. Seven non-fluent patients took part in two, three-week long therapy cycles during which they received anodal stimulation to Broca's area, anodal stimulation to Wernicke's area, and sham stimulation over either Broca's (three participants) or Wernicke's (four participants) areas. Therapy involved individuals being asked to name depicted items or enacted actions that appeared on a computer screen, initially without cues. Objects and actions were matched for imageability, length, frequency and age of acquisition. As in Fiori et al.'s previous study, in the event of failure to name the image within 15 seconds, participants were briefly presented with the written name. To minimise the potential impact of practice effects, the

order of therapy cycles was counterbalanced across participants. The main finding from this study was an interaction between anodal stimulation location and lexical class in that tDCS to Broca's area significantly improved verb naming whilst tDCS to Wernicke's area significantly improved noun naming. These effects were still clearly evident at four weeks post-therapy. Fiori et al.'s (2013) findings are supported by a similar study carried out by Marangolo et al. (2013) in which anodal tDCS to Broca's but not Wernicke's area was again associated with significant increases in verb naming accuracy for a diverse group of patients with non-fluent aphasia, both immediately after therapy and four weeks later.

Taken together, Fiori et al.'s (2013) and Marangolo et al.'s (2013) results indicate that the most effective site of stimulation depends upon the lexical class of the treatment items. This finding is in keeping with VLSM work linking noun naming to activity in the STG and MTG, and verb naming to activity in the IFG and more anterior regions of the temporal lobe (Piras & Marangolo, 2007). However, Vestito and colleagues (2014) did not find the effects of frontal anodal stimulation to be qualified by lexical class. In their study, three individuals with non-fluent aphasia received 20 minutes of sham tDCS followed by 20 minutes of 1.5mA anodal tDCS to Broca's area (with an hour's rest period between stimulation sessions) each weekday for a fortnight. Concurrently with all tDCS sessions, participants were asked to name a total of 40 nouns and verbs in the absence of any cues or feedback. Separate treatment sets were used each week, with the second week incorporating increased numbers of lower frequency words in order to increase the task difficulty. Over both intervention weeks, the number of items correctly named by all participants increased significantly from baseline only following active stimulation. These significant effects were maintained for 16 weeks post-stimulation and persisted, although no longer significant, until the final follow-up 5 weeks after this. Contrary to Fiori et al.'s and Marangolo et al.'s results, participants showed similar relative increases in both noun and verb naming following anterior stimulation.

The studies discussed above provide increasing evidence that combining anodal stimulation to the left hemisphere with concurrent speech and language therapy may significantly

improve picture naming accuracy and/or speed in individuals with chronic anomia. This is in keeping with findings obtained by Cotelli et al. (2011), who noted that high frequency TMS to the left hemisphere facilitated correct noun naming in patients with chronic anomia for up to 48 weeks post-therapy. In comparison, outcomes from unilateral left hemisphere tDCS studies have been maintained for up to 21 weeks post-intervention – the longest follow-up reported. Stimulating both left frontal and temporal regions has been shown to be effective, with precise results likely to be dependent on individual patient characteristics, including lesion site, and also the word class targeted in therapy.

Right Hemisphere Stimulation

Akin to research into the therapeutic effects of TMS, studies have also investigated whether beneficial effects on naming may be obtained by using cathodal tDCS to inhibit supposedly dysfunctional activation in the right hemisphere and encourage left activation during language tasks. One such study was carried out by Kang, Kim, Sohn, Cohen and Paik (2011), who administered five consecutive days of 2mA cathodal tDCS or sham tDCS to the undamaged right Broca's homologue of 10 participants with differing aphasia diagnoses. Participants received 30 minutes of noun retrieval therapy each day, with tDCS applied for 20 minutes during each session. In line with previous TMS studies (e.g. Naeser et al., 2002; 2005; Barwood et al., 2011), Kang et al. found that cathodal stimulation was more effective than sham in increasing scores on a Korean version of the BNT (K-BNT, Kim & Na, 1997), although this trend failed to reach statistical significance.

More recently, a larger, exploratory study carried out by Rosso and colleagues (2014) reported significant increases in naming accuracy after lower intensity (1mA) cathodal tDCS to the same right IFG site. Rosso et al. recruited 11 participants with lesions involving Broca's area (B+ participants) and 14 with lesions that left Broca's area intact (B- participants). All participants received single 15 minute sessions of both sham and cathodal tDCS to the undamaged right Broca's homologue, with the order of sessions counterbalanced across participants. Despite the facts that active and sham sessions were

separated by only a two hour wash out period, and patients did not complete a therapy task alongside stimulation, differences between conditions were significant. Results showed that changes in noun picture naming ability following cathodal tDCS were strongly related to lesion site in that naming accuracy of all B+ participants increased significantly, whilst for all but one of the B- participants, naming accuracy decreased or remained the same. This pattern of results is consistent with the notion that excessive inhibition by the undamaged right Broca's homologue on the damaged left hemisphere had been hindering naming abilities in the B+ participants until this inhibition was itself inhibited via cathodal stimulation (e.g. Costa, 2012; Martin et al., 2009). Consequently, these findings support previous TMS studies in which inhibitory stimulation to the same cortical area significantly increased stroke survivors' naming abilities (e.g. Barwood et al., 2011; Naeser et al., 2002; 2005). Rosso et al. also discovered that individuals who demonstrated the greatest improvements in naming ability were those with the greatest integrity of the arcuate fasciculus, thereby providing further support for the dual stream model and VLSM studies that posit Broca's area and the arcuate fasciculus as two neural components crucial for successful oral picture naming (e.g. Henseler et al., 2014; Hickok & Poeppel, 2007).

Although Rosso et al. (2014) did not include a concurrent therapy task, both this and Kang et al.'s (2011) study suggest that cathodal stimulation to the undamaged hemisphere may be therapeutically beneficial for certain individuals with post-stroke anomia. However, Kang et al. only collected outcome measures up to one hour post-stimulation and Rosso et al. did not incorporate any follow-up period, making it impossible to know whether their interventions had any significant lasting effects - an important aim of most therapy programmes. Furthermore, since cathodal tDCS to the right hemisphere was not compared to any other form of tDCS in either study, the relative effectiveness of each cannot be considered. In contrast, Flöel et al. (2011) compared the effects of 1mA anodal and cathodal tDCS applied to the right Wernicke's homologue of a mixed group of 12 fluent and non-fluent participants whilst they carried out a computerised anomia therapy task. During therapy, participants were asked to name object pictures presented multiple times per session. Initially the pictures were shown alongside semantic, auditory and graphemic cues, but these were

gradually reduced as participants' naming abilities improved (following Menke et al., 2009). For each condition, participants received two, one-hour therapy sessions per day for three consecutive days, with tDCS administered for the first 20 minutes of each session. At odds with Kang et al.'s and Rosso et al.'s findings, anodal rather than cathodal stimulation resulted in a significantly higher average percentage of correct, non-cued naming of trained objects, with effects still evident two weeks post-therapy. For the cathodal condition, although there was a significant improvement in naming compared to sham immediately after training, this positive effect was not maintained at the two week follow-up. One key difference between this study and those of Kang et al. and Rosso et al. that could account for the discrepant results is the location of stimulation. The expressive language functions associated with Broca's area are strongly left lateralised, however, the lexical-semantic functions associated with Wernicke's area are less so, with the right Wernicke's homologue proposed to play a role in normal language processing (see e.g. Hickok & Poeppel, 2007). As such, whilst a reduction of activation in Broca's homologue via cathodal stimulation may help restore left hemisphere functional dominance, leading to beneficial gains in naming performance, enhanced activation of the right Wernicke's homologue may help this region to better functionally compensate for the damaged left, consistent with the findings of Menke et al. (2009).

In summary, to date, a trio of studies have directly explored the effects of applying tDCS to the right hemisphere on noun naming ability, with conflicting results. Both Kang et al. (2011) and Rosso et al.'s (2014) findings that cathodal tDCS can improve naming ability are in keeping with previous TMS studies, whilst Flöel et al.'s (2011) support for anodal rather than cathodal stimulation is consistent with a positive role for posterior right hemisphere activation in naming in some patients. Alongside varying patient characteristics, there are a number of differences between studies that may account for these discrepancies in results. For instance, Kang et al. and Rosso et al. chose more anterior stimulation sites, and the intervention protocols differed between all three studies. The current used was also stronger in Kang et al.'s study than in the two other studies. Further research is needed to clarify the effects of anodal and cathodal stimulation to anterior and posterior regions of the right

hemisphere for participants with differing language and lesion profiles, and to directly compare the effects of right with left hemispheric stimulation.

Bilateral Stimulation

Lee, Cheon, Yoon, Chang and Kim (2013) investigated the added benefits of bilateral stimulation over unilateral stimulation. In their study, 11 aphasic individuals (six non-fluent and five fluent) received two 30 minute sessions of 2mA tDCS. In one session, anodal tDCS over the left IFG was applied with concurrent sham stimulation over the right IFG. In the other session, simultaneous anodal tDCS over the left IFG and cathodal tDCS over the right IFG was applied, with the order of sessions counterbalanced across participants. During both sessions, reference electrodes were placed over the ipsilateral buccinator muscles. Speech and language therapy (involving picture naming and short paragraph reading) was provided during the last 15 minutes of stimulation of each session. Participants were tested immediately before and after each type of stimulation. Results showed that correct object picture naming scores on the short version of the Korean BNT (K-BNT, Kim & Na, 1997) increased significantly following both unilateral and bilateral stimulation. Only bilateral stimulation led to significant decreases in mean reaction time, although a non-significant reduction in mean reaction time was also noted following unilateral stimulation. In addition to changes in single object naming ability, Lee et al. measured pre and post-intervention verbal fluency in terms of the number of syllables produced during a picture description task. However, neither type of stimulation had any significant effects on this measure.

Lee et al.'s findings suggest that bilateral left excitatory and right inhibitory stimulation of the IFG may be more effective than left excitatory IFG stimulation alone in improving confrontation object naming performance, yet they did not carry out any follow-up testing to check for longevity of the treatment effect, nor did they include a sham condition. Furthermore, participants received only 15 minutes of speech and language therapy in each condition. This limited amount of input may, in part at least, explain why Lee et al. failed to support previous results reported by Fridriksson et al. (2011) and Fiori et al. (2011) who both

found that unilateral anodal stimulation to the left hemisphere significantly reduced object naming reaction time following five, 20 minute therapy plus tDCS sessions.

More recently, Manenti et al. (2015) administered simultaneous bilateral stimulation to a 49 year old woman with mild non-fluent aphasia for 25 minutes every week day for four weeks. Although stimulation was delivered offline in this study, each tDCS application was immediately followed by 25 minutes of semantic phonological action naming therapy (which required the participant to repeat the name of each verb three times and answer a series of questions regarding its semantic and phonological attributes), with the rationale that the neurostimulation may prime the resting language network for subsequent learning. The electrode montage used was similar to that adopted by Lee et al. (2013), with anodal stimulation directed at the left dorsolateral prefrontal cortex and cathodal stimulation directed at the same area in the right hemisphere. The authors subsequently assessed the effects of the intervention programme on a wide range of outcome measures. Results showed post-therapy gains in naming both treated and untreated verbs, indicating some degree of generalisation, although the effects were greater for treated items. The percentage of correctly named verbs was unrelated to psycholinguistic characteristics such as frequency and number of syllables. Contrary to Lee et al.'s findings, Manenti et al.'s intervention programme resulted in improvements in the participant's phonemic fluency, as well as her self-reported quality of life. Crucially, many of these effects were still evident at the 24 and 48 week follow–up periods, demonstrating the potential long-term benefits of tDCS-enhanced speech and language therapy programmes.

There are a number of noteworthy features of Manenti et al.'s (2015) methodology that could be adopted in future research, such as their use of a diverse and extensive range of outcome measures, the length of their follow-up, and the provision of individualised therapy for their participant's verb naming deficit. However, the results generated in this study pertain to only a single individual with relatively mild language impairments, meaning that one cannot attempt to generalise the findings to the wider aphasic population. Moreover, the absence of a sham condition means that it is unclear what proportion of the observed

gains can be attributed to tDCS relative to the contribution of the large number of therapy sessions provided. In addition, the participant received only one form of bilateral stimulation, making it impossible to state whether anodal stimulation to the left hemisphere or cathodal stimulation to the right hemisphere individually would actually have been more effective than both combined. It is also unclear whether concurrent (online) stimulation with therapy would also have had even greater positive effects.

The final study identified via the literature search describes three inter-related experiments involving a single individual with suspected crossed aphasia (Costa, Giglia, Brighina, Indovino, & Fierro, 2015), a condition which occurs when a right handed individual presents with severe aphasia in the absence of structural damage to the left hemisphere (Marien, Paghera, Dedeyn, & Vignolo, 2004). Thus, the case studied by Costa and colleagues acquired her aphasia following a right middle cerebral artery (MCA) stroke, which resulted in damage to the right frontal, temporal and parietal lobes. Whilst it is also unclear from this case study whether combining bilateral stimulation with therapy would have enhanced the effects of stimulation (as again no concurrent therapy task was included), the authors investigated a wider range of bilateral electrode positions than either Lee et al. (2013) or Manenti et al. (2015). Prior to their main experiments, Costa et al. carried out a brief pilot study, during which simultaneous anodal stimulation to Broca's area and cathodal stimulation to the right Broca's homologue was found to be more effective in increasing baseline scores on a noun and verb naming task than either simultaneous cathodal stimulation to Broca's area and anodal stimulation to the right Broca's homologue, or sham stimulation. Experiment 1 extended the findings of the pilot study by showing that simultaneous anodal tDCS to Broca's area and cathodal tDCS to the right Broca's homologue led not only to a significantly higher naming scores but also that this effect was maintained for nine days. Experiments 2 and 3 followed the same procedure as Experiment 1, except that the electrodes were placed more posteriorly, in order to target Wernicke's area and the right Wernicke's homologue. In Experiment 2, anodal stimulation was delivered to the left hemisphere at the same time as cathodal stimulation to the right hemisphere, whereas Experiment 3 investigated the effects of the inverse electrode

montage. Results showed that only the electrode arrangement in Experiment 3 led to significant increases in naming ability (this time maintained for six days post-stimulation), indicating that, within this particular participant, the optimal simultaneous stimulation polarities for oral picture naming differed according to which cortical regions were targeted. Anodal stimulation to the intact (in this case, left) frontal lobe plus cathodal stimulation to the damaged (right) frontal lobe, and cathodal stimulation to the left temporal lobe plus anodal stimulation to the right temporal lobe were both linked to increased noun and verb picture naming ability. These findings are, however, difficult to interpret with respect to other studies, given that they pertain to just one individual with atypical language lateralisation.

The three studies discussed above indicate that bilateral stimulation (comprising anodal tDCS to the left hemisphere and cathodal tDCS to the right hemisphere) may enhance naming ability in individuals with chronic anomia. Nevertheless, although Costa et al. (2015) incorporated a range of bilateral stimulation montages in their case study, it is still unclear from current studies whether bilateral stimulation is more effective than sham, unilateral left anodal and/or unilateral right cathodal stimulation, and whether the effects hold true for larger groups of participants with typical left hemisphere language dominance.

Recommendations for Future Research

From the discussions above it is clear that there is a growing body of evidence in support of the use of tDCS as an adjunct to enhance behavioural therapy in individuals with post-stroke aphasia. However, it is also evident that this support is limited by its lack of systematicity, and by the highly varied protocols used across studies (Elsner et al., 2013, 2015; Monti et al., 2013). As a consequence, a number of key methodological issues regarding the application of tDCS remain unresolved, including the individualisation of electrode placement given different lesion locations, the exploration of a greater range of stimulation conditions and locations, and therapy delivery in relation to timing, tasks, targets, and outcome assessment.

Studies have varied with regards to whether electrode placement was determined on a patient by patient basis, considering lesion size and location, or on a consistent target location basis, with the same key brain regions stimulated for all individuals. For example, Baker et al. (2010) and Fridriksson et al. (2011) used fMRI to determine electrode placement to ensure that stimulation targeted structurally intact cortex which had demonstrated the greatest activation associated with correct naming on a pre-therapy naming task. However, in the majority of studies examined in the current review, a less individualised approach to electrode placement was used and, instead, electrodes were positioned over the same target brain regions in all participants regardless of lesion location and extent, even when MRI scans showing precise lesion locations were available (e.g. Costa et al., 2015; Fiori et al., 2013; Flöel et al., 2011). A possible consequence of this more general approach is that certain participants may not have benefitted as anticipated from tDCS due to electrodes being placed over areas with insufficient viable underlying brain tissue. Some authors argue that precise placement is unnecessary as the effects of tDCS are generally fairly diffuse as a result of the size of active electrodes typically used (approximately 25-35cm^2) (Datta et al., 2009; Miranda et al., 2006). Moreover, it is cheaper, simpler and less demanding of patients if they are not required to undergo scanning prior to participation. Nevertheless, research has consistently highlighted the importance of recruitment of intact perilesional areas in post-stroke recovery (e.g. Hamilton et al., 2011) and tDCS results have indicated that therapeutic benefits may be limited if stimulation does not target perilesional areas sufficiently close to patients' lesion sites (Baker et al., 2010). Consequently, it would seem prudent to use scanning data, whenever available, to place electrodes where stimulation is believed to result in the best possible therapy outcomes.

Related to the issue of stimulation site, the current review found that, in the majority of studies discussed, participants were given only one type of active stimulation to one region, whilst in others, only one further condition (altering the polarity or location of stimulation) was included. This means that it is impossible to determine whether an alternative active stimulation condition would have led to even greater gains than those reported. The effects of cathodal tDCS to right contralesional areas remain generally under-researched compared

to the effects of both anodal tDCS to the left hemisphere and TMS to the right pars triangularis. Whilst one must caution against assuming that the effects of tDCS and TMS are equivalent (Holland & Crinion, 2012), given the significant language benefits repeatedly observed after inhibiting right hemisphere activation using TMS, the role of cathodal tDCS to the right hemisphere warrants greater attention. Similarly, the effects of stimulation to posterior language regions (e.g., those surrounding Wernicke's area) are under-represented relative to the effects on more frontal regions.

With the exception of Rosso and colleagues (2014), who highlighted the differential effects of utilising the same stimulation parameters with individuals with/out Broca's area intact, none of the reviewed studies explicitly compared the effects of stimulation on individuals with non-fluent and fluent aphasia following damage to different parts of the left hemisphere. Existing knowledge suggests that anodal stimulation applied to left frontal regions and/or cathodal stimulation applied to right frontal regions will yield the best results for individuals with non-fluent aphasia associated with frontal lesions and that anodal stimulation applied to left or right posterior regions will yield the best results for individuals with fluent aphasia associated with more posterior lesions. However, additional research is required to thoroughly investigate potential interactions between aphasia type and stimulation site/polarity. Furthermore, additional research should aim to clarify the relationship between aphasia severity and therapeutic effectiveness. In two studies (Flöel et al., 2011; Volpato et al., 2013), the participants who showed the greatest gains from tDCS-plus-therapy were those with the most severe deficits. Fridriksson et al.'s (2011) results support the notion that tDCS is more likely to increase naming speed than naming accuracy of patients with less severe aphasia, whose pre-therapy accuracy may be near ceiling. It may be that tDCS has the potential to benefit individuals representing the full spectrum of symptom severities, but that the optimum stimulation parameters for these individuals differ. This possibility should be addressed via more comprehensive research designs incorporating a range of participants and stimulation montages.

Whilst several studies have suggested that tDCS can help to enhance naming for certain individuals in the absence of concurrent behavioural therapy (Monti et al., 2008; Rosso et al., 2014; Volpato et al., 2013), the majority of studies indicate that combining tDCS with a therapy task leads to more consistent gains. The therapy tasks utilised vary across studies, making direct comparison impossible, although all tasks required participants to take an active role by matching stimuli, producing item names or answering questions regarding items' properties. It may be the case that the particular therapy task is less important to the success of tDCS-plus-therapy interventions than the location and polarity of stimulation, however, this is another factor that could be explored in the future. The therapeutic protocols adopted by previous studies also differ in terms of the number of sessions, the length of any follow-up and the outcome measures adopted. With regards to the frequency of tDCS-plus-therapy sessions, the majority of studies have incorporated fairly intensive and often extensive therapy schedules, with clients receiving stimulation every day for three to 20 days. As mentioned previously, this type of schedule can be difficult to maintain in clinical practice for various reasons (Holland & Crinion, 2012). Within the domain of behavioural language therapy, studies have found that both intensive and non-intensive anomia therapy may lead to similarly significant improvements in naming ability. Indeed, there is evidence that long-term retention may actually be greater when equal hours of therapy are distributed over five rather than two weeks (Sage, Snell, & Lambon Ralph, 2011). Consequently, future research could investigate whether the observed beneficial effects of tDCS and speech and language therapy can be achieved using less frequent sessions, reducing the demands on clinicians and patients alike. On a related note, the longer that therapy effects remain evident, the less often any potentially time consuming and costly repeat or 'top up' treatment needs to be administered. Despite research with healthy adults indicating that beneficial effects of tDCS on cognitive abilities can remain significant for at least 12 months (Dockery et al., 2009), many of the studies discussed above failed to investigate any possible lasting effects of intervention. When participants were tested following a post-treatment interval, other than Manenti et al.'s (2015) notable case study and Vestito et al.'s small pilot study, the longest follow-up was four weeks post-therapy. Further, larger studies involving much longer follow-ups are clearly required to investigate how long

any significant outcomes following tDCS plus anomia therapy persist in the majority of individuals.

Predictably, given the scope of the literature search, the primary outcome measure in all of the above studies was unassisted confrontation naming of noun and/or verb pictures. In the majority of studies, only noun naming was examined, although Fiori et al. (2013) revealed an interesting potential interaction between stimulation site and word class: anodal tDCS to Broca's area resulted in significantly better verb naming and anodal tDCS to Wernicke's area resulted in significantly better noun naming. The observation that anodal tDCS to frontal regions may particularly enhance verb naming is supported by Marangolo et al. (2013) but not Vestito et al. (2014). Given the small number of studies and patients involved, more research involving within-participant designs is clearly indicated. Regardless of whether nouns, verbs, or both were considered, almost all studies looked only at improvements in naming treated items rather than the effects of therapy on naming both treated and untreated items. It is, of course, impossible to treat all words that individuals with anomia have difficulty with in therapy, therefore, it is crucial that therapies have the potential to generalise from treated to untreated items. Such generalisation has been documented in the behavioural anomia therapy literature (e.g. Best et al., 2013) and the small number of existing tDCS studies to address generalisation have suggested that stimulation plus therapy may lead to some increases in naming of untreated items (Baker et al., 2010; Manenti et al., 2015). However, future research designs could further investigate the potential for significant generalisation by incorporating testing of both treated and untreated items at baseline and all follow-up time points.

Additionally, within the field of aphasia rehabilitation, there is a general consensus that single noun and verb naming ability can be influenced by the psycholinguistic properties of the words involved, such as age of acquisition, frequency, familiarity, imageability, concreteness, length, typicality and animacy (e.g. Nickels & Howard, 1995; Rossiter & Best, 2013). As mentioned previously, there is also a growing body of evidence to suggest that different cortical regions may be involved in naming words with certain properties (Henseler

et al., 2014; Wilson et al., 2009). Given the apparent importance of psycholinguistic properties for naming, it is perhaps surprising to note that there is a current paucity of evidence regarding potential interactions between such variables and the observed effects of tDCS on confrontation naming ability. Several studies, which included treated and untreated word sets or a number of treated sets, explicitly stated that sets were matched on the basis of particular psycholinguistic variables. For example, Baker et al.'s (2010) treated and untreated noun sets were matched for frequency (low/medium/high), semantic category and word length. However, only one study (Manenti et al., 2015) provided any further discussion regarding which words benefitted most from tDCS. In this study, Manenti and colleagues (2015) found that psycholinguistic properties had no effects on verb naming in their study, although their findings pertain to a single case with mild aphasia. More detailed examination of the impact of psycholinguistic variables on the effectiveness of tDCS-based therapeutic interventions in the wider patient population is undoubtedly warranted.

Finally, it is important that statistically significant increases in picture naming performance translate into meaningful changes to patients' everyday communication (Best et al., 2011; Carragher et al., 2012; Herbert, Hickin, Howard, Osborne, & Best, 2008). Thus, whilst two existing studies assessed verbal fluency (Lee et al., 2013; Manenti et al., 2015), no studies to date have measured the potential effects of therapy on functional, real-life conversational abilities. Moreover, given the known adverse impact of aphasia on individuals' well-being and social interactions (Hilari et al., 2012), it is perhaps surprising that the majority of previous studies (again with the exception of Manenti et al., 2015) have also failed to include any outcome measures related to these factors. It is clear that ongoing research would benefit from the inclusion of a variety of outcome measures designed to assess the effects of tDCS plus anomia therapy intervention programmes on functional communication and socio-emotional factors.

Summary

Whilst there is growing evidence that tDCS can enhance the effects of behavioural speech and language therapy for chronic anomia, further research is required to segregate the effects of varying the polarity, site, timing and frequency of stimulation in order to determine optimal tDCS parameters for maximal benefits. In particular, future studies should:

1. Consider the effects of tDCS on naming ability with concurrent speech and language therapy tasks as this approach seems to provide the most consistent gains.
2. Utilise within-participants study designs, with individuals receiving sham stimulation as a control condition.
3. Consider the effects of stimulation in the context of the patient's lesion site, stage of recovery and behavioural profile/severity of anomia.
4. Optimise electrode placement by exploiting neuroimaging data, using new head models that take into account the extent to which individual lesions affect current flow.
5. Systematically consider the polarity (anodal vs. cathodal) and laterality (left and/or right hemisphere) of stimulation to determine which electrode montage leads to the greatest improvements in picture naming ability.
6. Directly examine the effects of tDCS in relation to both word class (nouns vs. verbs) and the psycholinguistic properties of targeted items.
7. Vary the number and frequency of tDCS-plus-therapy sessions to determine whether similar gains can be achieved via less intensive treatment protocols.
8. Explore the longevity of tDCS effects by incorporating post-intervention follow-ups greater than four weeks.
9. Highlight any potential generalisation by assessing the effects of tDCS on naming both treated and untreated items.
10. Incorporate a more extensive range of outcome measures to assess not only accuracy and speed of confrontation naming, but also the effects on connected

speech tasks and quality of life measures. This would facilitate fuller understanding of the range of potential gains from tDCS-plus-therapy intervention programmes.

Conclusions

Successful picture naming is a complex task that relies on multiple, interconnected brain regions, many of which are left lateralised in healthy individuals. Anomia arises when parts of the normal naming network are damaged, for example, by a stroke. Long-term recovery from post-stroke anomia is facilitated by a number of cortical mechanisms and, in particular, by spontaneous and/or therapy-induced re-lateralisation of language skills to the left hemisphere. Whilst behavioural speech and language therapy can promote re-lateralisation, research increasingly supports the use of neurostimulation techniques in lieu of, or in conjunction with, naming therapy to aid this process. Applying inhibitory TMS to the right Broca's homologue can significantly enhance naming performance in individuals with chronic aphasia, both as a standalone approach or when immediately followed by behavioural therapy. There is also limited evidence that administering excitatory TMS to left hemisphere language areas followed by such therapy produces similar benefits. However, tDCS offers increased patient comfort and safety over TMS and, consequently, may be the more useful therapeutic tool. Studies have revealed significant effects of tDCS and concurrent speech and language therapy on the naming ability of stroke survivors, in particular demonstrating that anodal (excitatory) stimulation to the left hemisphere and/or cathodal (inhibitory) stimulation to the right hemisphere can significantly increase naming accuracy and speed. To determine optimal therapeutic protocols, future research should incorporate more comprehensive designs in terms of polarity, site, frequency and timing of stimulation for patients with different lesion sites at different stages of language recovery. A greater number of well-designed studies could one day help to translate the potential of tDCS as an adjunct to behavioural speech and language therapy into clinical practice, resulting not only in increased naming ability but improved quality of life for those with chronic anomia.

Chapter 3

Manipulating Laterality and Polarity of transcranial Direct Current Stimulation to Optimise Outcomes for Anomia Therapy in an Individual with Chronic Broca's Aphasia

Adapted from a paper published in Aphasiology in 2017

Abstract

Previous research indicates that combining behavioural therapy with tDCS may be more effective than therapy alone in increasing naming ability in stroke survivors with chronic anomia. In particular, anodal (excitatory) stimulation targeting left perilesional areas and/or cathodal (inhibitory) stimulation targeting right contralesional areas may benefit non-fluent patients with localised damage to the left frontal lobe, yet studies have yet to systematically compare the effects of varying the laterality and polarity of tDCS within participants. In the current case study, an individual (JSc) with chronic Broca's aphasia (nine years post-stroke) due to a left frontal lesion completed six, four-week long therapy cycles. Each cycle involved a different stimulation condition (perilesional anodal, perilesional cathodal, perilesional sham, contralesional anodal, contralesional cathodal, and contralesional sham). The effects of active stimulation were directly compared to the results obtained following ipsilateral sham stimulation. In the first week of each cycle, JSc completed three, 20-minute therapy sessions, during which he carried out a personalised picture name repetition therapy task at the same time as receiving tDCS. JSc's naming accuracy immediately after stimulation increased significantly more following perilesional anodal stimulation than following perilesional sham stimulation, and this effect remained significant at three weeks post-therapy. Treatment effects on a range of secondary outcome measures were less consistent. These findings are congruent with previous work demonstrating the importance of activation in left frontal perilesional regions for accurate noun picture naming in stroke survivors with non-fluent aphasia. The results showed that significant gains in naming ability can be obtained following just one hour of therapy plus stimulation, and demonstrated the feasibility of a longitudinal, repeated measures design with multiple outcome measures. Greater understanding of the optimal tDCS parameters to enhance anomia therapy outcomes in individual patients with differing lesion and behavioural profiles may assist with the translation of tDCS-plus-therapy into everyday clinical practice.

Introduction

Anomia, or word finding difficulty, is the most common symptom across all types of aphasia (Postman-Caucheteux et al., 2010) and often persists into the chronic stage, when more severe acute deficits have resolved (Pedersen et al., 2004). Problems with spoken word production can adversely impact the daily functioning and quality of life of both stroke survivors and their communication partners (Hilari et al., 2012). Consequently, facilitating word finding is a frequent aim in language rehabilitation following a stroke. Impairment-based behavioural speech and language therapy aims to help a stroke survivor to "re-learn" words that they are unable to retrieve or produce (Nickels, 2002b). Therapy can lead to both improved object naming (Lambon Ralph et al., 2010) and increased word finding in everyday conversation (Best et al., 2011). However, individuals with chronic anomia may make slow progress to achieve relatively small gains, especially if treatment is not provided intensively (Barthel et al., 2008). A growing body of evidence indicates that concurrent use of neurostimulation techniques has the potential to optimise both the effectiveness and efficiency of more traditional interventions (Holland & Crinion, 2012; Torres et al., 2013). The current study investigated the effects of combining transcranial Direct Current Stimulation (tDCS), with behavioural therapy in an individual with chronic Broca's aphasia. This aphasia sub-type is typically associated with damage to language areas in the left frontal lobe and, in addition to anomia, is characterised by non-fluent, effortful spontaneous speech and short, agrammatic utterances (Fridriksson, Hubbard, et al., 2012).

tDCS is a non-invasive neurostimulation technique that uses a battery pack and two saline-soaked electrodes to deliver weak electrical currents (usually 1-2 mA) to the brain. The active electrode is positioned on the scalp over the region of interest in order to stimulate the underlying cortex. The reference electrode completes the circuit and is most frequently placed on the contralateral supra-orbit or shoulder (Fridriksson, 2011). Positive (anodal) stimulation is associated with increased neuronal activation, whilst negative (cathodal) stimulation is associated with decreased neuronal activation (Nitsche & Paulus, 2000). When administered in line with established safety protocols, tDCS is considered appropriate

for use with both healthy individuals and stroke survivors (Nitsche et al., 2008; Nitsche, Fricke, et al., 2003; Poreisz et al., 2007; Rossi et al., 2009). Unlike transcranial magnetic stimulation (TMS), tDCS is not associated with an increased seizure risk, nor does it affect the movement of the articulatory musculature. Moreover, although occasional side effects such as headaches or localised tingling have been noted, many individuals undergoing low intensity (<1.5mA) tDCS do not experience any adverse effects as a result of stimulation, and those who do typically report only mild symptoms that fade within the first minute of stimulation (Flöel et al., 2008; Gandiga, Hummel, & Cohen, 2006; Kessler et al., 2012). This latter observation means that individuals are often unable to distinguish sham conditions, in which stimulation is turned on for up to one minute before being slowly turned off, from longer periods of active stimulation, consequently allowing direct comparisons to be made between conditions in which participants receive therapy plus stimulation and those in which they receive therapy alone.

Our recent review indicates that combining tDCS with behavioural speech and language therapy can enhance picture naming ability in individuals with chronic anomia (>6 months post-stroke) (Sandars, Cloutman, & Woollams, 2016). Specifically, applying excitatory anodal stimulation to the left frontal lobe has been shown to significantly increase noun naming accuracy relative to sham treatment. For example, Baker, Rorden and Fridriksson (2010) administered 1mA anodal stimulation to left frontal areas of ten patients (four with Broca's aphasia) for 20 minutes per day for five consecutive days at the same time as carrying out a computerised therapy task. For each participant, tDCS was applied directly over the region in which activation had shown the greatest association with correct oral picture naming during pre-therapy functional scans. Active stimulation significantly increased patients' naming accuracy of treated nouns, both immediately and one week following stimulation. The naming of untreated items also increased numerically following anodal stimulation at both time points, although this trend failed to reach statistical significance. Closer inspection of Baker et al.'s (2010) results reveals that four participants (two non-fluent, two fluent) responded more favourably to left anodal stimulation than the remaining six. All four of these participants had damage to the left frontal cortex, meaning

that stimulation was applied very close to their lesion sites. Baker et al.'s results are supported by Vestito, Rosellini, Mantero and Bandini (2014), who paired noun and verb naming therapy with 20 minutes of 1.5mA anodal tDCS for five days per week for two weeks. Stimulation targeted the crossing point between points T3 and F7 on the international 10-20 electrode positioning system; a site that was again close to damaged areas in the frontal lobes of each participant. Compared to sham, active stimulation resulted in significantly greater increases in the number of items correctly named from baseline for all three participants. This effect was maintained for 16 weeks following intervention. Finally, Meinzer, Darkow, Lindenberg and Flöel (2016) combined an intensive language treatment protocol (two x 1.5 hour sessions per day x four days per week x two weeks) with 1mA anodal tDCS applied to the left motor cortex (M1) for the first 20 minutes of each therapy session. This particular frontal lobe stimulation site was selected due to identified functional links between the language production network and primary motor system (e.g. Pulvermüller & Fadiga, 2010), and because the majority of this region was structurally intact in all of their participants. In a between-participants design, 13 patients (three with Broca's aphasia) received active stimulation, whilst another 13 (six with Broca's aphasia) received sham stimulation. Results showed significant increases in treated and untreated noun naming accuracy for both groups of participants. However, gains were greater, and more likely to be maintained at the six month follow-up, for those who had received active rather than sham stimulation

Baker et al.'s (2010) and Vestito et al.'s (2014) findings are consistent with neuroimaging studies indicating that better language recovery in the chronic stage is associated with increased activation in key left hemisphere language regions, such as the inferior frontal gyrus (IFG), which encompasses what is classically known as Broca's area (Saur et al., 2005; Szaflarski et al., 2013). When language areas are irrevocably damaged, compensatory activation in undamaged regions immediately surrounding the lesioned tissue ('perilesional' areas), has been consistently linked to language improvements in stroke survivors with chronic aphasia (Turkeltaub et al., 2011). For instance, regions perilesional to Broca's area, including BA32 (anterior cingulate gyrus) and BAs 10 and 11/47 (medial and

middle frontal gyrus) have been shown to be more active in patients with better language recovery than in both those with poorer language outcomes and control participants (Fridriksson et al., 2010; Fridriksson, Richardson, et al., 2012). Similarly, facilitating activation in proximal, functionally connected frontal regions (M1) may assist linguistic recovery in individuals with left language network lesions (Meinzer et al., 2016).

fMRI studies have also revealed that activation in right hemisphere regions (including the right IFG and right superior temporal gyrus, STG) in stroke survivors with chronic aphasia is higher than in healthy controls when competing a range of language tasks (Naeser et al., 2004; Perani et al., 2003), and that such activation is associated with semantic errors and omissions during picture naming (Postman-Caucheteux et al., 2010). Although controversial, one theory proposes that transcallosal disinhibition can arise following damage to the left hemisphere (Geranmayeh et al., 2014; Karbe et al., 1998; Turkeltaub et al., 2012). According to this theory, a reduction in typical inhibition from the damaged left hemisphere during language tasks allows homologous areas in the right hemisphere to become overactive. These right hemisphere regions may, in turn, further suppress activation in existing left hemisphere regions (Martin et al., 2009). Hyperactivation in the right hemisphere may consequently prevent recruitment of perilesional areas in the left hemisphere and hinder recovery from aphasia (Hamilton et al., 2011).

In line with the notion of transcallosal disinhibition, using cathodal tDCS to inhibit dysfunctional activation in the right hemisphere of individuals with chronic anomia may indirectly facilitate left lateralisation and enhance picture naming ability. Kang and colleagues (2011) showed that administering 20 minutes of 2mA cathodal stimulation to the right Broca's homologue each weekday for a fortnight alongside individually tailored noun retrieval therapy resulted in a trend towards increased naming accuracy in a group of ten patients with chronic anomia. More recently, Rosso et al. (2014) reported significant increases in picture naming accuracy following a single 15 minute session of 1mA cathodal tDCS to the right IFG, despite the absence of a concurrent therapy task. However, this effect held true only for patients whose lesions incorporated Broca's area. One possible

explanation for this finding is that, in reducing right IFG activation, stimulation facilitated the functionally beneficial recruitment of perilesional left IFG regions in these individuals.

The majority of existing studies examining the effects of tDCS on picture naming ability in stroke survivors with chronic anomia have incorporated only one active electrode montage (Sandars et al., 2016). This means that it is impossible to compare the relative effects of, say, applying anodal stimulation to the left IFG with cathodal stimulation to the right IFG within the same individuals. A notable exception is a study carried by Shah-Basak and colleagues (2015), in which 12 chronic non-fluent patients were given single, 20-minute sessions of 2mA tDCS in four active conditions and one sham condition. Using the 10-20 EEG positioning system, electrodes were applied to site F3 in the left frontal lobe (located superior to the IFG and anticipated to be perilesional for all participants) and its right homologue, F4. In the four active conditions, participants received anodal and cathodal stimulation to F3 and anodal and cathodal stimulation to F4, whilst attempting to name 20 item pictures. Naming ability was assessed immediately before and after stimulation session to determine which electrode montage led to the greatest improvements in naming accuracy prior to participants progressing to the second stage of the project. Results showed that, at the group level, cathodal stimulation to *left* frontal areas was associated with the greatest improvements in naming accuracy.

On first glance, these findings appear at odds with those reported previously (Baker et al., 2010; Kang et al., 2011; Meinzer et al., 2016; Rosso et al., 2014; Vestito et al., 2014). However, there are several potential explanations for these discrepant results. Firstly, participants only received a single session of each type of stimulation during the first, non-therapy, stage of Shah-Basak et al.'s (2015) study, versus 10 or more sessions of active tDCS plus naming therapy in some previous studies (Kang et al., 2011; Meinzer et al., 2016; Vestito et al., 2014). Secondly, the hierarchical model proposes that patients with very extensive left hemisphere lesions that make left lateralisation impossible may necessarily rely on homologous regions within the right hemisphere in order to regain any language function, although this represents a less effective strategy than recruitment of left

perilesional areas (Heiss & Thiel, 2006). Indeed, although left cathodal stimulation was most effective overall in enhancing naming ability in Shah-Basak et al.'s (2015) study, individual level analysis indicates that the participants who benefitted the most from left cathodal stimulation were those whose lesions extended superiorly and medially into the left parietal and temporal lobes. In comparison, anodal stimulation applied to left frontal regions tended to be most effective for participants with smaller lesions confined to the left IFG and immediately surrounding tissue, in line with the work of Baker et al. (2010) and Vestito et al. (2014).

In summary, for stroke survivors with lesions localised to the left frontal lobe, combining behavioural speech and language therapy with anodal stimulation targeting perilesional tissue and/or cathodal stimulation targeting the contralesional right homologue currently appears to be most likely to result in the greatest improvements in picture naming accuracy. There exist, however, a number of limitations in the existing literature on this issue (Sandars et al., 2016). First and foremost, the relative effects of combining multiple different electrode montages with therapy have yet to be explored using a within-participants design. Secondly, although a growing body of evidence continues to highlight the importance of facilitating activation in perilesional regions, few studies have used detailed brain imaging techniques to identify such regions on a patient-by-patient basis. Thirdly, the majority of previous researchers have not investigated the potential for tDCS to improve generalisation of therapeutic effects from treated to untreated items. This is an important issue because treatment can only ever target a small proportion of the words that individuals have difficulty in retrieving, and such generalisation has been documented by others following behavioural anomia therapy (Best et al., 2013). Finally, it is important that statistically significant increases in picture naming accuracy translate into meaningful improvements in patients' everyday communicative abilities (Best et al., 2011; Herbert et al., 2008). Significant positive effects of bilateral tDCS (simultaneous left frontal anodal and right frontal cathodal stimulation) on psychosocial and mood measures have been reported (Manenti et al., 2015), and Meinzer et al. (2016) noted improvements in partner-rated perceptions of communicative effectiveness following anodal tDCS applied to the perilesional primary motor

cortex. However, studies have yet to determine the effects of unilateral tDCS-plus-therapy on a broad range of measures designed to capture changes in functional communication, connected speech, and well-being.

To address these outstanding issues, we designed a comprehensive, long-term intervention programme for stroke survivors with chronic anomia. This involved six, four week-long cycles of noun picture naming therapy, each paired with a different tDCS electrode montage (perilesional anodal, perilesional cathodal, perilesional sham, contralesional anodal, contralesional cathodal, and contralesional sham) with stimulation sites for each individual determined on the basis of high resolution structural MRI scans. Here, we report the results for a patient with chronic non-fluent aphasia associated with a relatively circumscribed left IFG lesion. The primary aim of the current study was to investigate which tDCS parameters would result in the greatest improvements in naming ability for this individual, by systematically manipulating laterality and polarity. We hypothesised that combining computerised anomia therapy with anodal stimulation applied to perilesional regions in the left IFG, and/or with cathodal stimulation applied to homologous regions in the right IFG, would be significantly more effective than combining therapy with anodal stimulation to the contralesional hemisphere, cathodal stimulation to the perilesional left hemisphere, or sham stimulation. Our design allowed us to consider the extent to which gains for each therapy cycle generalised to untreated items. A range of secondary outcome measures were also included to explore the impact of the intervention programme on JSc's emotional well-being, his connected speech elicited from a picture description task, and both self- and carer-reported perceptions of his communicative effectiveness.

Method

Participant

JSc was an 81 year old right-handed retired engineer with 12 years of formal education. He had a left middle cerebral artery (MCA) infarction in November 2005, almost nine years prior

to recruitment to the current study. He lived with his wife and enjoyed completing sudoku and jigsaw puzzles, plus watching car restoration programmes on television. Socially, he and his wife were active members of a local stroke support group and, together, they enjoyed regular day trips by coach and longer breaks to visit their children and extended family. He was able to walk independently and drive short distances. JSc had no history of epilepsy and was not taking any medications known to affect the central nervous system, although he had long-standing mild tinnitus. He presented with frequent word finding difficulties, telegrammatic speech and mild oral apraxia, with good comprehension of simple everyday conversation.

Behavioural Assessment Battery

Prior to taking part in the current study, JSc completed a comprehensive battery of background language and neuropsychological tests. These included a number of subtests from the PALPA (Kay, Lesser, & Coltheart, 1992), 64-item Cambridge Semantic Battery (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000) and Comprehensive Aphasia Test (CAT, Swinburn, Porter, & Howard, 2005), plus the short form of the Boston Diagnostic Aphasia Examination (Goodglass et al., 2001), the latter of which resulted in a diagnostic classification of Broca's aphasia. The results of these assessments are shown in Table 3.1. Formal testing indicated that JSc had significant difficulties with phonological input and output processing and performed poorly on tests of non-word auditory discrimination (PALPA 1) immediate non-word repetition (PALPA 8) and oral confrontation naming. His anomia was moderate-severe and he made frequent phonological and omission errors, and occasional semantic substitution errors, on both the 64-item naming test and Boston Naming Test (BNT, Kaplan et al., 2001). Although JSc also had some receptive syntactic difficulties at sentence level, his single word comprehension was within normal limits, as evidenced by his performance on the spoken and written word-to-picture matching tasks. Other strengths included forward and backward digit span and performance on the Raven's Coloured Progressive Matrices test of non-verbal reasoning (Raven, 1962).

Table 3.1: JSc's percentage scores on the behavioural assessment battery. Scores in bold indicate performance outside the normal range.

Subtest	Score
Minimal pairs (non-words) PALPA 1	**75.00**
Minimal pairs (words) PALPA 2	86.11
Non-word repetition (immediate) PALPA 8	**36.67**
Non-word repetition (delayed) PALPA 8	63.33
Word repetition (immediate) PALPA 9	**90.00**
Word repetition (delayed) PALPA 9	91.25
64-item Naming	**71.88**
Boston Naming Test	**53.33**
Spoken word to picture matching (CAT)	98.44
Written word to picture matching (CAT)	98.44
Spoken sentence comprehension	75.00
96 Synonym judgement	**76.04**
Semantic association (written) Camel and Cactus Test	**82.81**
Forward digit span	62.50
Backward digit span	42.86
Brixton Spatial Anticipation Test	**43.64**
Raven's Coloured Progressive Matrices*	77.78

*Norms were unavailable for this assessment

Neuroimaging

A high resolution structural T1-weighted MRI scan (Figure 3.1) was acquired on a 3.0 Tesla Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an 8-element SENSE head coil. TR (repetition time) = 9.0ms, TE (echo time) = 3.93ms, flip angle = 8°, 150 contiguous slices, slice thickness = 1mm, acquired voxel size 1.0 x 1.0 x 1.0 x1.0 x

1.0mm^3, matrix size 256 x 256, FOV = 256mm, T1 (inversion time) = 1150ms, SENSE acceleration factor 2.5, total scan acquisition time = 575 seconds

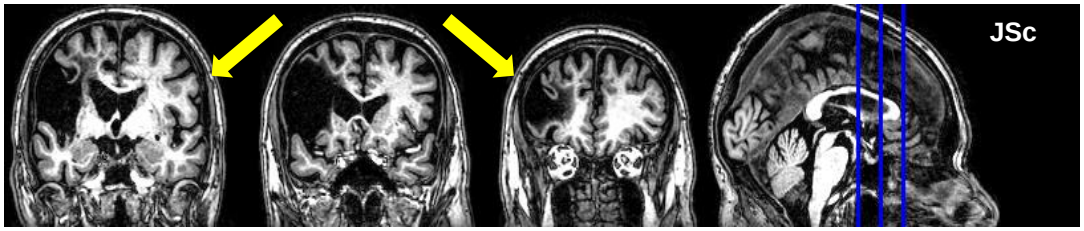


Figure 3.1: MRI images of JSc's lesion, with arrows showing the location of tDCS stimulation sites.

As shown in Figure 3.1, JSc's lesion (volume = 18163 voxels) involved both inferior and medial areas of the left frontal cortex (including Broca's area), and the left insula.

Procedure

The design of the current study is illustrated in Figure 3.2. The study was approved by the Health Research Authority NRES Committee North West (13/NW/0844).

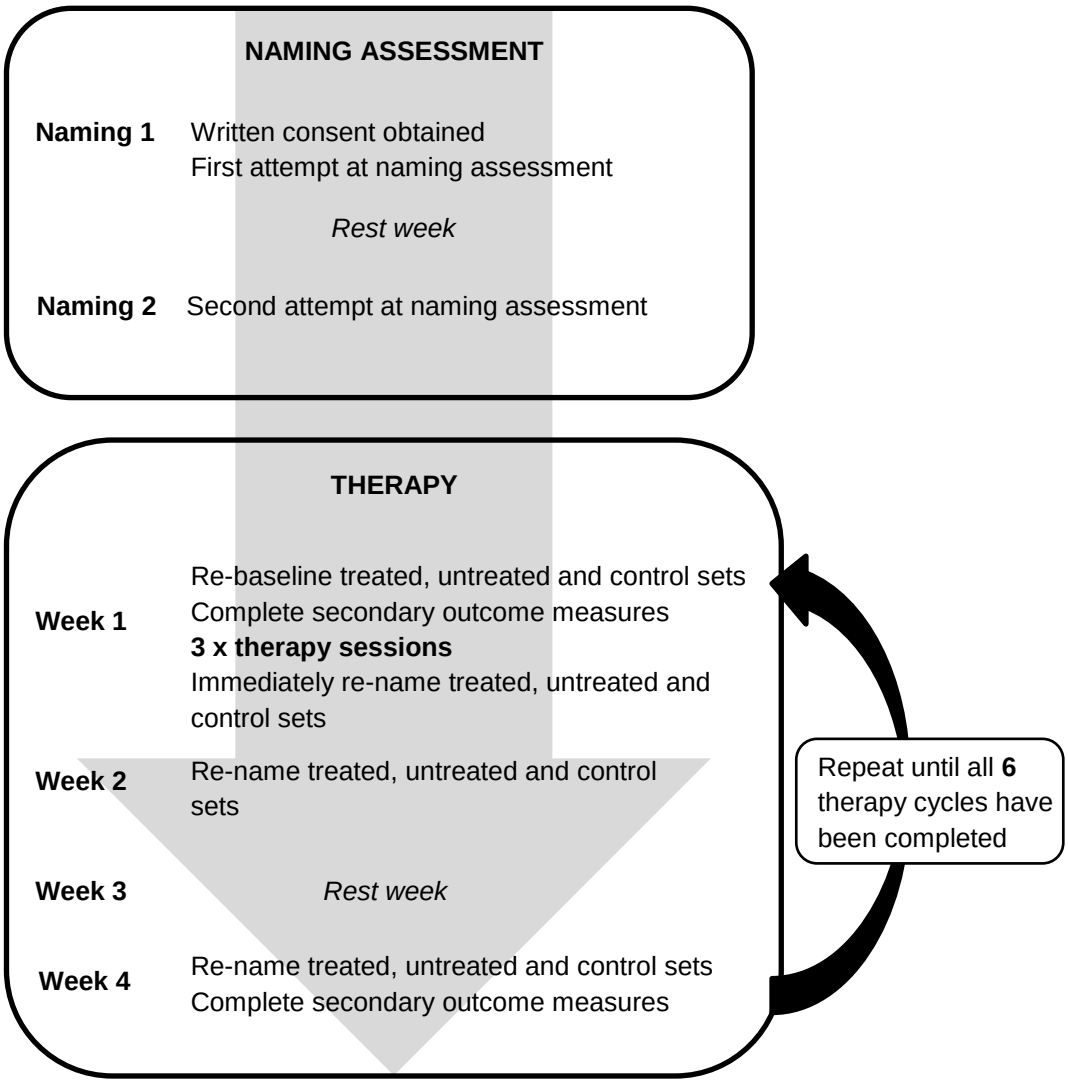


Figure 3.2: Flowchart to show the design of the current study.

Naming Assessment

JSc gave written consent to participate in the study. Prior to commencing therapy, JSc completed a detailed naming assessment in his home. The stimuli were 408 black and white images taken from the International Picture Naming Project (IPNP, 2000, available at https://crl.ucsd.edu/experiments/ipnp/1stimuli.html), randomly divided into eight blocks of 51

items matched on length in phonemes, number of syllables, frequency, and age of acquisition (Appendix A). The items were presented on a laptop computer using E-Prime (Psychology Software Tools Inc., Sharpsberg, Philadephia), with the initial presentation of each image accompanied by a discreet beep sound to facilitate later measurement of naming speed. JSc was asked to try to produce the name of each item. No cues were provided, although general encouragement was given. Each image was shown for up to 10 seconds, after which time images automatically timed out if they had not yet been named correctly. JSc completed blocks 1-8 in order in the first assessment session and in the reverse order (i.e. from 8-1) in the second session. Both sessions were recorded using an Olympus VN-713PC digital voice recorder, placed to the side of the laptop computer. JSc's first naming attempts were graded as correct or incorrect. Other verbalisations, including filler words/phrases (e.g. 'er', 'come on, think'), were ignored. From a total of 405 items that were presented twice (three items were inadvertently skipped), JSc named 116 incorrectly on both occasions, 162 correctly on both occasions, and 127 items incorrectly on one occasion.

A total of 18, personalised 20-item sets were created using JSc's responses across both naming assessment sessions. All 116 items named incorrectly twice and 124 randomly selected items named incorrectly once were randomised and used to create 12, 20-item therapy sets (six treated, six untreated). Six sets contained ten double incorrect and ten single incorrect items, one set contained 11 double incorrect and 9 single incorrect items, and the remaining five sets contained 9 double incorrect and 11 single incorrect items. From the 162 items named correctly twice, 120 were randomly selected to create six, 20-item correct control sets.

All 12 treated and untreated therapy sets were matched, as far as possible, on a number of psycholinguistic variables (Appendix B). The values for each of these variables were taken from the IPNP. There were no significant differences between the 12 sets with regards to length in phonemes ($F(11,228)=0.173$, $p=0.999$), number of syllables ($F(11,228)=0.227$, $p=0.996$), frequency ($F(11,228)=0.718$, $p=0.721$), or name agreement ($F(11,228)=1.470$,

p=0.144), nor were there any significant differences between the items named incorrectly once and those named incorrectly twice within the 12 sets in terms of length in phonemes ($F(1,238)=2.524$, $p=0.113$), number of syllables, ($F(1.238)=3.573$, $p=0.060$), and frequency ($F(1.238)=2.281$, $p=0.132$), although the difference between the single and double incorrect items in terms of name agreement was significant ($F(1,238)=10.189$, $p=0.002$). The single incorrect items had higher name agreement compared to the double incorrect items.

All six correct control sets were matched to each other on the same psycholinguistic variables (Appendix C). There were no significant differences between the control sets in terms of length in phonemes ($F(5,114)=0.090$, $p=0.994$), number of syllables ($F(5,114)=0.231$, $p=0.948$), frequency ($F(5,114)=0.452$, $p=0.811$), or name agreement ($F(5,114)=0.083$, $p=0.995$). There were significant differences between the six correct control sets and the 12 incorrect therapy sets with respect to length in phonemes ($F(1,358)=6.760$, $p<0.05$), number of syllables ($F(1,358)=5.245$, $p<0.05$), and frequency ($F(1,358)=4.492$, $p<0.05$). The items that JSc named correctly across both naming assessment sessions had fewer phonemes and syllables and were more frequent than the items that he named incorrectly during at least one naming assessment session.

The 12 incorrect sets were randomly allocated to be treated or untreated, and all sets were randomly allocated to the six therapy cycles. Each therapy cycle included one treated, one untreated and one correct control set.

Computerised Naming Therapy

All therapy sessions were carried out in a designated treatment room in a large, general hospital in the North West of England. Microsoft PowerPoint slides were created for the 20 treated items to be included in each therapy cycle. JSc was shown these on a laptop computer. The slides included a colour Google image of each item (i.e. not the line drawings used in the assessments) and an audio video clip of a woman's mouth saying the name of the item, which were presented side by side in the centre of the slide. All images depicted typical examples of single items, with no visible brand names or other text. There

was an automatic two second delay after the slide appeared to allow JSc time to process the item image before the audio video clip began to play. After the audio video clip had finished playing, JSc was asked to try to repeat back the item name. Once he had attempted to name the item, the next slide was revealed. Repetition targets the phonological processes of word production and has been shown to be an effective method of improving single word naming in individuals with aphasia (Conroy et al., 2009b). Furthermore, previous studies have shown that the same language regions in the left frontal lobe are important for both speech production and perception (Fridriksson et al., 2008), and consequently, greater therapeutic gains may be achieved in individuals with word finding difficulties, as well as apraxia of speech, when pictures are accompanied by AV rather than audio-only speech (Fridriksson, Baker, Whiteside, et al., 2009; Whiteside et al., 2012).

JSc received computerised therapy three times per week for 20 minutes during the first week of each therapy cycle. Each item was repeated 10 times per therapy session. Although previous studies have more commonly included at least five treatment sessions (e.g. Baker et al., 2010; Kang et al., 2011; Meinzer et al., 2016; Vestito et al., 2014), three sessions per cycle were provided in the present study in order to reduce JSc's participant burden across the six therapy cycles, both in terms of overall time commitment, and demands of travelling between home and the hospital setting. A second motivation for reducing the number of sessions relative to existing studies was to investigate the potential for similar gains to be achieved following less intensive therapy input.

tDCS

tDCS was applied whilst JSc received computerised naming therapy. JSc completed two, four-week therapy runs, spread over approximately eight months. Each run comprised three therapy cycles involving anodal, cathodal or sham stimulation. The first run targeted perilesional site F5 (as per the international 10-20 electrode positioning system) in the left hemisphere and the second run targeted its right homologue, FC6 (as per Nicolo, Fargier, Laganaro, & Guggisberg, 2016). JSc completed the six therapy cycles in the following order: perilesional anodal, perilesional cathodal, perilesional sham, contralesional anodal,

contralesional cathodal, and contralesional sham stimulation. Ideally, each cycle began the week immediately following week 4 of the preceding cycle (as per Figure 3.2). In practice, some adjustments were required in order to accommodate Christmas, New Year, and JSc's other commitments. The exact intervals were: perilesional anodal / 25 days / perilesional cathodal / 28 days / perilesional sham / 39 days / contralesional anodal / 26 days / contralesional cathodal / 26 days / contralesional sham. Hence there was a minimum 25 day wash out period between the offset of one type of stimulation and the onset of another.

In each therapy session, 1mA tDCS was delivered for 20 minutes by a NeuroConn DC Stimulator Plus device via two saline-soaked electrodes (5 x 7 cm). The active electrode was placed on the chosen location on the scalp and the second (reference) electrode was placed on the contralateral shoulder, in order to minimise the likelihood of inadvertently inducing simultaneous electrical currents in the contralateral hemisphere (Datta et al., 2011). During sham sessions, the stimulation was turned on for one minute to invoke the initial tingling sensation of tDCS before being gradually ramped down to nil over a further 30 seconds. All tDCS-plus-therapy sessions were carried out by the lead author. Although she was not blinded to the type of stimulation administered, the same protocol was strictly followed during every session. This included placing the tDCS display screen out of JSc's sight in order to further minimise the risk of him distinguishing between active and sham stimulation conditions.

Outcome Measures

Naming

The primary outcome measure was naming accuracy. This was measured before the start of the first therapy session in each cycle in order to re-establish baseline accuracy for all of the treated, untreated and correct control items within that cycle. Naming ability was assessed again immediately after the third therapy session, at one week post-therapy and at three weeks post-therapy. On each occasion, JSc was presented with black and white line drawings (the same images used in the initial naming assessment) of all 60 items used in

the current therapy cycle on a laptop screen. As in the initial naming assessment sessions, JSc was asked to try to produce the name of each item without any cues. Items were shown for up to 10 seconds, after which time images automatically timed out if they had not yet been named correctly. Previous studies have indicated that anodal tDCS plus naming therapy may increase noun naming speed of individuals with fluent aphasia (Fridriksson et al., 2011), although similar effects have not been reported following frontal stimulation in individuals with non-fluent aphasia (Fiori et al., 2011; Kang et al., 2011; Monti et al., 2008; Volpato et al., 2013). To investigate any effects of treatment on JSc's naming speed, the time he took to correctly name the correct control items was measured at the same four time points. The time from initial item presentation (signified on the recording by the accompanying beep) to the onset of the first naming attempt was calculated manually for each item, in milliseconds, using Audacity 2.0.0 (available at http://audacity.sourceforge.net/).

Secondary Outcome Measures

A range of secondary outcome measures were collected prior to the first therapy session in each cycle, at one week post-therapy and at three weeks post-therapy. In order to assess the extent of generalisation of therapy to connected speech, JSc completed a picture description task ('Cookie Theft', Goodglass et al., 2001) . His verbal responses on each occasion were transcribed and timed, and the number of silent pauses (of at least one second duration) per response recorded. The following measures were also calculated: 1) total number of words or 'tokens' per sample, which indicated quantity of speech output, 2) mean length of utterance (MLU) in morphemes, which indicated grammatical complexity, and 3) type/token ratio (TTR, calculated by dividing the number of unique words per sample by the total number of tokens), which indicated lexical diversity (as per Borovsky, Saygin, Bates, & Dronkers, 2007). A bespoke 10-item mood questionnaire was adapted from a subscale of the Communication Disability Profile (Swinburn & Byng, 2006) (Appendix D). Each item asked JSc to consider how he had felt over the last week, and was scored from 0-4, with 4 representing the most positive emotional states (e.g. not at all angry, frequently able to do things). His response selection was supported using a visual analogue scale of

face drawings depicting different emotions, taken directly from the Communication Disability Profile. Total scores at each administration were converted to percentages, with higher percentages indicating better outcomes.

To examine any effects of therapy on JSc's perceptions of his functional communication and quality of life, he completed the validated 20-item Communication Outcome After Stroke (COAST) scale (Long, Hesketh, Paszek, Booth, & Bowen, 2008). JSc's wife completed the 20-item validated Carer version of the COAST (Long, Hesketh, & Bowen, 2009) to gain an additional perspective regarding his communication skills. Fifteen items on the Carer COAST ask carers to rate their partner's functional communicative abilities, whilst the remaining five ask the carer to indicate the extent to which their own quality of life is affected by their partner's communication difficulties. The total scores on both the COAST and Carer COAST were converted to percentages, with higher percentages indicating better outcomes.

Results

JSc completed all six therapy cycles and reported no adverse effects (such as scalp reddening, tingling or headaches) during or after any of the therapy plus tDCS sessions. When debriefed following his participation in the study, JSc confirmed that he had not perceived any differences between any of the six stimulation conditions, and could not tell the difference between active and sham conditions, although he felt that all of the cycles involving stimulation to the right hemisphere had been more beneficial and more comfortable.

Naming Accuracy

Raw naming accuracy data is provided in Appendix E. To assess changes in naming accuracy, the percentage changes in the numbers of items named correctly from baseline (at the start of each cycle) to immediately post-therapy, one week post-therapy, and three weeks post-therapy, were calculated for each stimulation condition.

Treated Items

Figure 3.3 shows the percentage changes in naming accuracy from baseline for all treated items in each stimulation condition, at each time point.

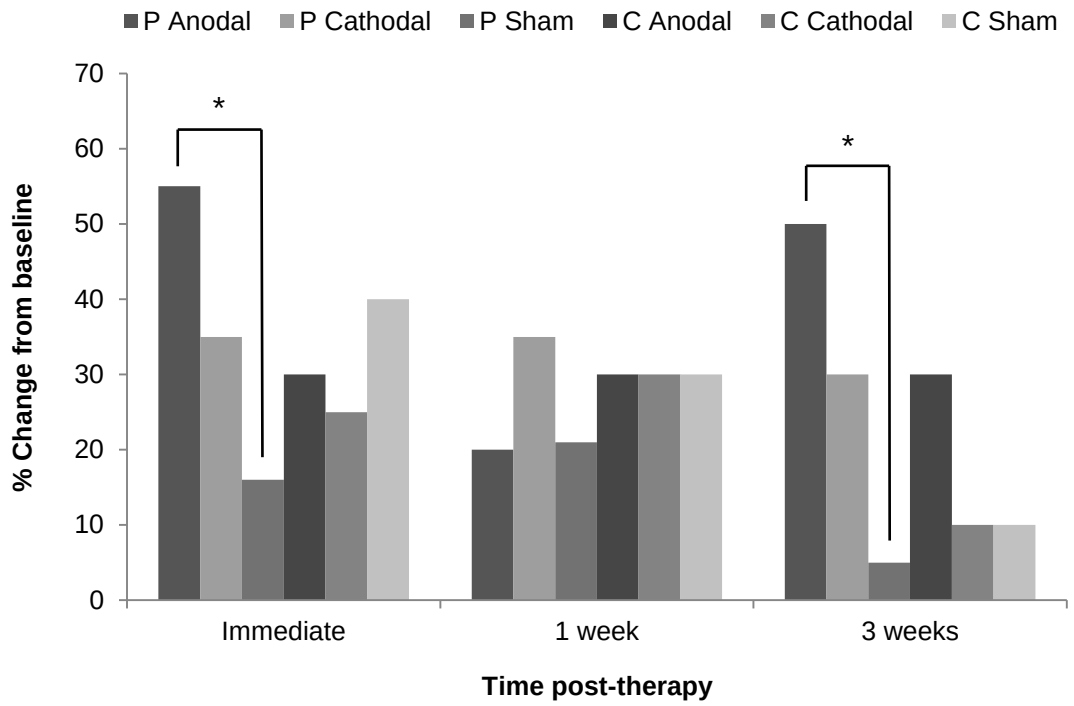


Figure 3.3: Percentage changes in naming accuracy from baseline for all treated items. Asterisks indicate significantly greater gains for active than sham stimulation.

McNemar tests were used to determine the statistical significance of any changes in raw naming accuracy scores within the six stimulation conditions. Naming accuracy for the treated items increased numerically from baseline in all stimulation conditions, at all three time points, indicating a strong overall beneficial effect of this brief, targeted therapeutic intervention. Perilesional anodal stimulation resulted in the greatest increases immediately post-therapy (55%) and three weeks post-therapy (50%). These increases were significant at both time points (immediate χ^2=6.67, p=0.007; 3 weeks χ^2=6.75, p=0.006). Increases in naming accuracy were also significant in the perilesional cathodal condition at all three time points (immediate χ^2=5.14, p=0.016; 1 week χ^2=7.11, p=0.004; 3 weeks χ^2=6.13, p=0.008), and in the contralesional sham condition immediately post-therapy (χ^2=4.90, p=0.021). Chi square tests (again based on raw naming accuracy scores) indicated that the effect of

perilesional anodal stimulation was significantly greater than that for perilesional sham, both immediately post-therapy (χ^2=4.57, p=0.032), and three weeks later (χ^2=6.99, p=0.008). The effect of perilesional cathodal stimulation was not significantly greater than that for perilesional sham, at any time point (immediate χ^2=1.31, p=0.253: 1 week χ^2=0.43, p=0.510; 3 weeks χ^2=3.01, p=0.083).

Untreated Items

Figure 3.4 shows the percentage changes in naming accuracy from baseline for all untreated items.

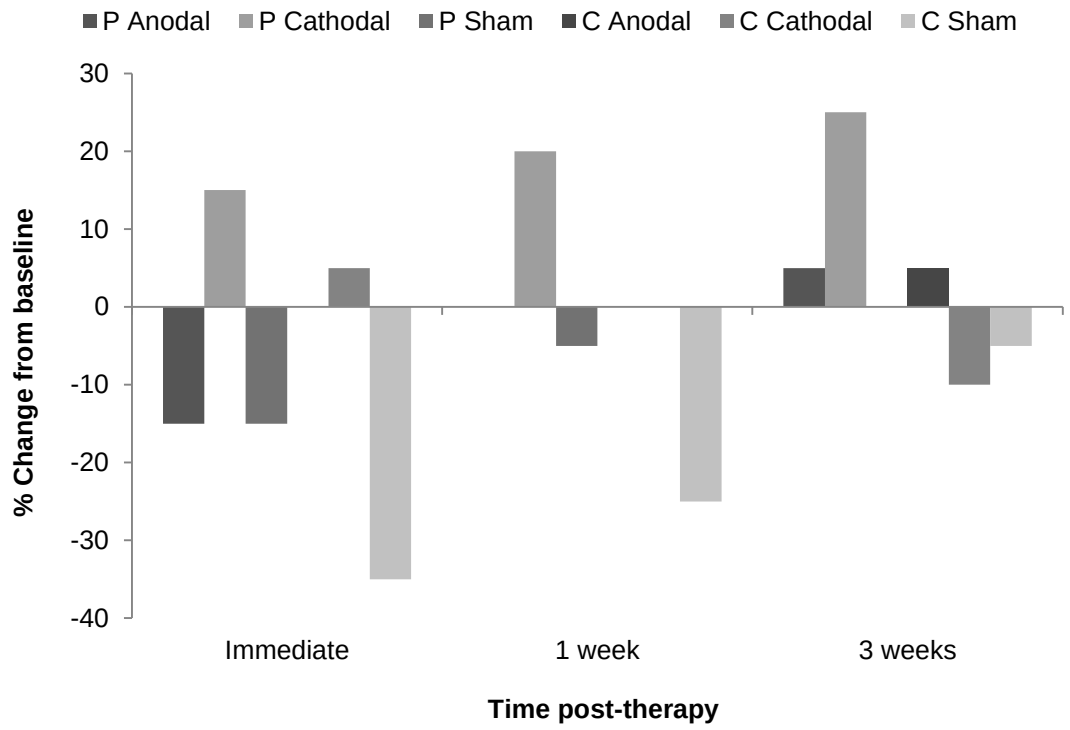


Figure 3 4: Percentage changes in naming accuracy from baseline for all untreated items.

McNemar tests were used to determine the significance of any changes in raw naming accuracy scores within the six stimulation conditions. Naming accuracy increased numerically at all three time points following perilesional cathodal stimulation, immediately post-therapy following contralesional cathodal stimulation and at three weeks post-therapy following perilesional anodal and contralesional anodal stimulation. In the remaining

conditions/at the remaining time points, naming accuracy remained the same or decreased following therapy. None of the post-therapy increases or decreases in naming accuracy for the untreated items were significant.

Speed of Naming

For the 20 double correct control items in each therapy cycle, the mean time JSc took to name items correctly at baseline, immediately post-therapy, one week post-therapy and three weeks post-therapy are shown in Figure 3.5. Wilcoxon Signed Ranks tests showed that there were no significant changes from baseline in the length of time taken to correctly name the control items following therapy in any of the six conditions, at any of the follow-up points.

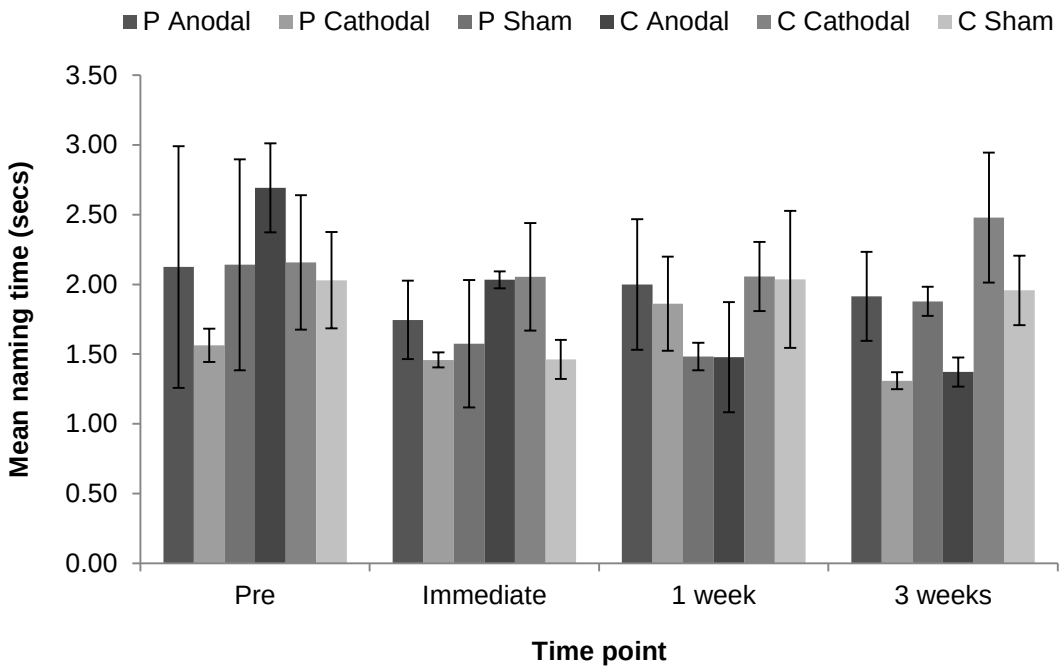


Figure 3.5: Mean time (secs) taken by JSc to correctly name control items. Error bars show +/-1 standard error.

Secondary Outcome Measures

Picture Description Task

The total response length (in seconds), number of pauses, total number of tokens, total number of morphemes, mean length of utterance (MLU) in morphemes, and type to token ratio (TTR, expressed as a percentage) were calculated for all the responses JSc gave when asked to describe the Cookie Theft image before therapy, one week post-therapy and three weeks post-therapy in each of the six stimulation conditions. These values are shown in Table 3.2.

Table 3.2 indicates that JSc's scores on all six measures were highly variable across the eighteen assessment sessions. Within each of the stimulation conditions, there were no consistent patterns of improvement or reduction in performance on any of the measures from baseline to one week or three weeks post-therapy. However, between the conditions, three trends emerged over time from the first cycle (perilesional anodal) to the last (contralesional sham), namely, the total length of JSc's responses and the number of pauses he made tended to decrease over time, whilst his MLU increased, consistent with a cumulative improvement over the course of repeated cycles of behavioural therapy. There were no obvious trends between stimulation conditions with regards to JSc's total number of tokens, total number of morphemes, and TTR.

Table 3.2: Total response length (secs), number of pauses, number of tokens, number of morphemes, MLU, and TTR for the picture description task.

Condition	Time point	Connected speech measure					
		Length	Pauses	Tokens	Morphemes	MLU	TTR
P Anodal	Pre	107.8	15	78	88	6.3	43.6
	1 Week	73.9	10	41	51	4.6	63.4
	3 Weeks	89.6	10	60	71	7.1	56.7
P Cathodal	Pre	68.9	10	47	52	6.5	67.0
	1 Week	110.2	17	57	66	3.7	52.6
	3 Weeks	68.7	10	55	65	5.9	60.0
P Sham	Pre	63.8	10	43	49	4.9	48.8
	1 Week	94.8	18	74	88	6.3	55.4
	3 Weeks	46.0	9	48	52	5.8	62.5
C Anodal	Pre	68.5	17	63	69	4.3	52.4
	1 Week	38.2	5	51	61	10.2	72.6
	3 Weeks	59.7	8	64	73	10.4	59.4
C Cathodal	Pre	47.5	10	64	73	6.6	59.4
	1 Week	47.5	10	63	70	6.4	54.0
	3 Weeks	64.7	9	62	70	8.8	59.7
C Sham	Pre	29.2	3	46	51	12.8	67.4
	1 Week	50.1	7	52	60	8.6	55.8
	3 Weeks	50.9	6	50	61	8.7	72.0

Mood Questionnaire, COAST and Carer COAST

Table 3.3 shows the total percentage scores on the 10-item bespoke mood questionnaire, COAST and Carer COAST before therapy, one week post-therapy and three weeks post-therapy, in each of the six stimulation conditions.

Table 3.3: Total percentage scores on the mood questionnaire, COAST and Carer COAST.

Condition	Time point	Mood questionnaire	COAST	Carer COAST
P Anodal	Pre	80.0	52.5	63.8
	1 Week	60.0	37.5	55.0
	3 Weeks	67.5	41.3	73.8
P Cathodal	Pre	67.5	47.5	73.8
	1 Week	70.0	42.5	61.3
	3 Weeks	67.5	42.5	67.5
P Sham	Pre	55.0	36.5	63.8
	1 Week	47.5	45.0	60.0
	3 Weeks	50.0	42.5	66.3
C Anodal	Pre	42.5	43.8	60.0
	1 Week	60.0	46.3	66.3
	3 Weeks	65.0	46.3	63.8
C Cathodal	Pre	87.5	46.3	67.5
	1 Week	72.5	55.0	67.5
	3 Weeks	62.5	43.8	66.3
C Sham	Pre	70.0	52.5	70.0
	1 Week	77.5	65.0	68.8
	3 Weeks	70.0	51.3	70.0

JSc's scores on the mood questionnaire varied both within and between stimulation conditions (total range = 42.5% - 87.5%). Wilcoxon Signed Ranks tests showed that the decreases in percentage score from the start of the perilesional anodal therapy cycle to one week post-therapy ($z=-2.13$, $p=0.033$) and three weeks post-therapy ($z=-2.24$, $p=0.025$) were both significant, as were the decreases in percentage score from the start of the contralesional cathodal therapy cycle to one week post-therapy ($z=-2.45$, $p=0.014$) and three weeks post-therapy ($z=-2.43$, $p=0.015$). The pre-therapy percentage scores on the mood questionnaire were, however, higher in the perilesional anodal and contralesional cathodal stimulation conditions than in the other four cycles. For the contralesional anodal condition, scores on the mood questionnaire were significantly greater at one week post-therapy ($z=2.07$, $p=0.038$), and three weeks post-therapy ($z=2.46$, $p=0.014$).

As with the mood questionnaire, JSc's total percentage scores on the COAST varied both within and between stimulation conditions (total range = 36.5% - 65.0%). Wilcoxon Signed Ranks tests showed that the decrease in percentage score from the start of the perilesional anodal therapy cycle to one week post-therapy was significant (z=-2.97, p=0.003), and persisted at the three week post-therapy mark (z=-2.07, p=0.038), although the pre-therapy percentage score in this cycle was numerically higher than in all the other conditions other than the contralesional sham condition. In contrast, the increased scores from baseline to one week post-therapy in the perilesional sham condition (z=2.33, p=0.020), the contralesional cathodal condition (z=2.65, p=0.008) and the contralesional sham condition were also significant (z=2.89, p=0.004). Overall, there was a trend for JSc to score more highly on the COAST as he continued to participate in the study: his average percentage score across the three measurement points within the final stimulation condition (contralesional sham, 56.3%) was significantly greater than his average percentage score across the three measurement points within the first stimulation condition (perilesional anodal: 43.8%, z=3.76, p=0.000).

JSc's wife's scores on the Carer COAST showed less variability within and between cycles (range = 55.0% - 73.8%) than his scores on the COAST. Wilcoxon Signed Ranks tests confirmed that there were no significant differences in baseline scores across the six stimulation conditions nor from baseline to either one week or three weeks post-therapy within any of the stimulation conditions, although in the perilesional anodal condition, the increase in scores from one week post-therapy to three weeks post-therapy was significant (z=2.51, p=0.012).

Discussion

The purpose of the current study was to systematically investigate the effects of varying the laterality and polarity of tDCS on the noun naming ability of an individual stroke survivor with chronic anomia in the context of Broca's aphasia due to a left frontal lesion. On the basis of previous research, we anticipated that combining behavioural therapy with left anodal

perilesional stimulation, and/or with right cathodal contralesional stimulation, would lead to the greatest therapeutic gains. This hypothesis was partly confirmed by our results. Pairing a computer-based repetition therapy task with anodal stimulation applied to perilesional areas in JSc's left frontal lobe led to a significant increase in his immediate confrontation naming accuracy of treated items over and above the behavioural therapy gains following left sham stimulation. The significant benefit of perilesional anodal over perilesional sham stimulation was also evident at the final follow-up, three weeks post-therapy. The finding that anodal stimulation to left frontal perilesional areas significantly increased noun naming accuracy relative to sham stimulation in this participant with Broca's aphasia agrees with previous findings that have used a group study approach to explore left hemisphere anodal stimulation (Baker et al., 2010; Meinzer et al., 2016; Vestito et al., 2014). This result is also in keeping with neuroimaging research highlighting the important role of left frontal perilesional areas in language recovery for patients in the chronic stage post-stroke, both spontaneously and following therapy (Fridriksson, Richardson, et al., 2012; Marcotte et al., 2012; Meinzer et al., 2008). In contrast, cathodal stimulation applied to the right Broca's homologue did not significantly enhance JSc's naming accuracy, and therefore our results are not consistent with those reported by Kang et al. (2011) and Rosso et al. (2014), or more generally with the transcallosal disinhibition hypothesis (Geranmayeh et al., 2014; Karbe et al., 1998).

It is unclear why significant post-therapy improvements in naming accuracy were present immediately and three weeks following perilesional anodal stimulation but not evident at the interim one week follow-up. Anecdotally, JSc reported during the one week post-therapy follow-up session that he had been "getting more words all week", but this perception was not reflected in his naming assessment scores. A potential explanation is that different neural mechanisms are responsible for immediate learning versus longer-term retention following tDCS-plus-therapy (Stagg & Nitsche, 2011). During stimulation, tDCS is thought to temporarily alter neuronal excitability via temporary changes in membrane polarity, whilst persisting effects are believed to be the result of lasting changes in synaptic strength via the process of LTP (Nitsche, Fricke, et al., 2003). It is possible that a period of consolidation

may be required to solidify immediate transient learning, during which time naming is unstable (Meinzer et al., 2016). Although this hypothesis would be difficult to confirm, repeating the same intervention protocol with additional individuals may help to clarify whether this unexpected finding is unique to JSc or common to the wider population of patients under similar stimulation conditions.

A limitation of the current study is that one cannot be certain that the significant effects of perilesional anodal stimulation on naming ability are unrelated to the fact that JSc completed this condition first. There was no obvious trend for JSc to respond more or less favourably to therapy plus stimulation as he continued his involvement in the study: although the perilesional cathodal condition, completed second, also resulted in significant gains in naming accuracy from baseline, so did the contralesional sham condition, completed last. Baseline naming accuracy was also measured at the start of each therapy cycle for the words to be treated in subsequent sessions. Nevertheless, it is still possible that JSc, who had not received any speech and language therapy for a number of years prior to his involvement in the current study, was particularly receptive to the first therapy cycle, with his response to subsequent cycles somewhat diminished due to factors such as motivation, or having already approached ceiling with regards to his potential to respond to the therapy provided. The risk of confounding order effects is unavoidable within single case research. However, counterbalancing the order in which future participants receive the six stimulation conditions should separate any influence of treatment order from true therapeutic gains.

With respect to the untreated items, our results show that naming accuracy increased numerically immediately following therapy in the perilesional cathodal and contralesional cathodal conditions, one week post-therapy in the perilesional cathodal condition and three weeks post-therapy in the perilesional anodal, perilesional cathodal and contralesional anodal conditions, although these increases were not significant. It is possible that increases in the number of untreated items named correctly after therapy reflect some generalisation of treatment effects, in accordance with Best et al. (2013). However, another possibility is that simply asking JSc to attempt to name the same items repeatedly provided

retrieval practice and primed his subsequent naming attempts (Nickels, 2002a). If this kind of 'repetition priming' had occurred, one would expect any gains in JSc's naming accuracy to grow over time within each therapy cycle. This was indeed the case in the perilesional cathodal condition, but not in the other conditions. Future studies need to consider the impact of repetition priming when assessing therapeutic generalisation.

We also investigated the potential effects of tDCS-plus-therapy on JSc's speed of correct naming for the double correct control items, but found no significant decreases in response time. The most likely reason for this is that these items were untreated; indeed, therapy plus anodal tDCS only resulted in significant increases in naming speed of treated items for the fluent patients in Fridriksson et al.'s (2011) study. Alternatively, speed of correct noun naming may be better facilitated for both fluent and non-fluent patients via stimulation to different cortical regions, such as Wernicke's area in the temporal lobe (Fiori et al., 2011; Fridriksson et al., 2011). Adapting the design of the current study in the future to include treatment for double correct items could help to clarify whether or not tDCS plus naming therapy can increase naming speed as well as accuracy in individuals with chronic non-fluent aphasia.

An additional aim of the current study was to explore the effects of tDCS plus behavioural therapy for anomia on a range of secondary outcome measures designed to capture any changes in JSc's connected speech output, mood, and perceptions of his communicative effectiveness. To date, only one study has examined the effects of unilateral tDCS on one such measure: partner-reported everyday communication skills (Meinzer et al., 2016). Consequently, the majority of our results cannot be directly compared with previous findings, but provide some interesting foundations for future investigation. With regards to the picture description task, there were no consistent patterns of improvement on any of the included measures within each of the stimulation conditions, indicating that the quantity, grammatical complexity and lexical diversity of JSc's elicited connected speech did not change as a result of any particular form of stimulation. This finding was disappointing but not entirely unexpected, given that generalisation from single words to connected speech is notoriously

difficult to achieve, especially if the required vocabulary for detailed picture description is not directly targeted in therapy (e.g. Conroy et al., 2009). Over the course of JSc's involvement in the study, however, the length of his utterances and the number of pauses he made tended to decrease, whilst his MLU increased. MLU is calculated by dividing the total number of morphemes by the total number of utterances, providing a measure of grammatical complexity (Borovsky et al., 2007). The total number of morphemes JSc produced each time he described the Cookie Theft picture was relatively stable. Consequently, in JSc's case, increasing MLU over time reflects a reduction in the number of utterances (as a function of fewer pauses) rather than increasing grammatical complexity per se. Overall, his picture description became faster and less hesitant (i.e. more fluent) with repeated attempts. This finding is likely the result of accumulated retrieval practice for the same lexical items over the course of JSc's involvement in the study, and is consistent with script training studies for people with non-fluent aphasia that have directly aimed to improve the production of particular narratives by providing multiple production opportunities (Lee, Kaye, & Cherney, 2009).

One may have predicted that JSc's mood would increase following therapy as naming ability improved, or alternatively, that it would decrease due to frustration and heightened awareness of his confrontation naming impairment. In fact, JSc's scores on the mood questionnaire varied significantly both within and between stimulation conditions, indicating that his emotional state fluctuated throughout the duration of his participation in the study, and there were no consistent pre- to post-therapy patterns. The stimulation conditions in which JSc's emotion scores significantly decreased following therapy (perilesional anodal and contralesional cathodal) had the highest baseline scores. Consequently, as naming ability for treated items increased in the perilesional anodal condition, JSc's emotional state actually worsened. Conversely, his mood scores significantly increased only in the contralesional anodal condition, which had the lowest baseline, thereby allowing greater room for improvement. The most plausible explanation for these findings as a whole is that JSc's mood simply differed from week to week as is the case for many individuals, for reasons likely completely unrelated to the present study.

JSc's perceptions of his own communicative competence (as measured by the COAST) also fluctuated within and between stimulation conditions, with similar patterns of increases following the lowest baselines and vice versa to those seen for the mood questionnaire. However, there was a general tendency for his perceptions to become more positive over time throughout his participation in the study. It is possible that this trend reflects a cumulative effect of therapy. Alternatively, it may be related to JSc's belief that the three later cycles involving right hemisphere stimulation had, as a whole, been more effective than the earlier ones targeting the left hemisphere, despite this perception not being borne out in the naming data. For the Carer COAST, there was some variability in JSc's wife's ratings over the first month of completing the questionnaire, which yielded a significant increase between the one and three week follow-up that did map on to a naming benefit for treated items. This finding is in line with Meinzer et al. (2016), who found that partner-reported improvements in everyday communication were significantly greater following left anodal than sham stimulation, however, beyond the first therapy cycle, JSc's wife's responses became highly stable over time. Overall, these results indicate that her perceptions of her husband's functional communicative abilities and her own self-rated quality of life did not alter dramatically over the duration of his involvement in the study.

Conclusions

Our results indicate that, for this particular individual with chronic non-fluent aphasia, combining anodal tDCS delivered to perilesional regions in the left frontal lobe with speech and language therapy was significantly more effective in increasing his naming accuracy than therapy alone. These observations not only confirm previous findings but also demonstrate that correct naming can be significantly increased and maintained for three weeks via a very limited amount of input, in a patient almost a decade post-stroke. Our motivation for supplementing computerised anomia therapy with tDCS was to increase the efficiency as well as the effectiveness of behavioural treatment alone. In the current study, JSc received a total of just one hour of stimulation, whereas in previous studies involving left anodal frontal stimulation, similarly significant results were obtained following five, 20-minute

sessions over the course of a week (Baker et al., 2010), or either 10 (Vestito et al., 2014) or 16 (Meinzer et al., 2016) sessions over a fortnight. The gain in naming treated items achieved in the current study compared to previous ones suggests that may be possible to decrease the therapeutic dosage without compromising effectiveness. Fewer sessions would not only reduce patient burden but also be more practically viable in clinical settings. We have also shown that it is feasible to complete a relatively long-term, multiple outcome measure tDCS plus behavioural therapy programme that systematically varies the laterality and polarity of stimulation with stroke survivors in the chronic stage, something which the majority of previous studies have not attempted. Whilst it is not possible to make any generalisations about the wider population of stroke survivors from the results obtained from one individual, our own future work will continue to try to determine the optimal tDCS parameters to enhance the language recovery, well-being and quality of life of greater numbers of individuals with differing lesion and behavioural profiles. Establishing these parameters may facilitate the adoption of tDCS into mainstream clinical practice.

Chapter 4

Manipulating Laterality and Polarity of transcranial Direct Current Stimulation to Optimise Outcomes for Anomia Therapy: A Case Series Highlighting Between-Participant Variability in Response to Treatment

Abstract

A growing body of research indicates that combining behavioural therapy with tDCS may be more effective than therapy alone in increasing naming ability in stroke survivors with chronic anomia. However, studies have yet to compare the effects of systematically manipulating the laterality and polarity of tDCS within participants with differing behavioural and lesion profiles. Four patients with chronic anomia (two non-fluent and two fluent) completed six therapy cycles, each involving a different stimulation montage (perilesional anodal, perilesional cathodal, perilesional sham, contralesional anodal, contralesional cathodal, contralesional sham). Participants received three, 20-minute therapy sessions in the first week of each therapy cycle, during which they carried out a personalised picture name repetition therapy task at the same time as receiving tDCS. tDCS was applied to intact, perilesional regions in the left hemisphere or their contralesional homologues in the right hemisphere. The effects of active stimulation were directly compared to the results obtained following ipsilateral sham stimulation. Treated item naming accuracy for one participant with non-fluent aphasia was significantly greater immediately and three weeks after perilesional anodal stimulation than after perilesional sham stimulation, and significantly greater three weeks following both contralesional anodal and contralesional cathodal stimulation than following contralesional sham stimulation for one participant with fluent aphasia. For the two remaining participants, active tDCS did not result in greater increases in naming accuracy than sham stimulation, irrespective of laterality or polarity. Treatment effects on a range of secondary outcome measures were inconsistent for all participants. The findings highlight considerable between-participant variability in response to tDCS-plus-therapy. Further work is required to better understand why certain patients experience greater language improvements than others following tDCS, and to establish which stimulation parameters are most likely to maximise therapeutic gains for these individuals.

Introduction

Post-stroke aphasia typically arises following damage to parts of the extensive network of left hemisphere brain regions and neural pathways involved in speech production (Fridriksson, 2010; Hickok & Poeppel, 2004). The most common and enduring symptom of post-stroke aphasia is anomia, or word finding difficulty (Pedersen et al., 2004; Postman-Caucheteux et al., 2010). Chronic anomia (typically persisting ≥6 months post-stroke) negatively affects stroke survivors' interpersonal relationships, participation in wider society, emotional well-being and overall quality of life (Davidson et al., 2008; Hilari et al., 2015; Le Dorze et al., 2015). As such, speech and language therapy frequently aims to remediate naming deficits (Nickels, 2002b). Unfortunately, impairment-based behavioural therapy techniques have shown limited efficacy, especially if treatment is not provided intensively (Barthel et al., 2008; Brady et al., 2016). However, an increasing body of evidence indicates that supplementing traditional naming therapy with neurostimulation techniques, such as transcranial Direct Current Stimulation (tDCS), can enhance therapeutic effectiveness and efficiency for patients with chronic anomia (ALHarbi et al., 2017; Baker et al., 2010; Fridriksson et al., 2011; Holland & Crinion, 2012; Sandars et al., 2016; Sandars, Cloutman, & Woollams, 2017). The current study extends our previous case report that showed significant gains in noun naming accuracy following tDCS plus anomia therapy in an individual with chronic (non-fluent) Broca's aphasia (Sandars et al., 2017) by investigating the effects of combining tDCS with behavioural therapy in a total of four stroke survivors with chronic aphasia (two non-fluent and two fluent).

tDCS is a non-invasive stimulation technique that modifies neuronal resting membrane potentials by supplying weak electrical currents to the cortex via two saline-soaked electrodes applied to the scalp. To deliver unilateral stimulation, the primary electrode is positioned directly above the relevant region of interest, whilst a reference electrode is usually placed on the contralateral supra-orbit or contralateral shoulder (Fridriksson, 2011). Positive (anodal) stimulation is linked to enhanced neuronal excitability, whereas negative (cathodal) stimulation is linked to decreased neuronal excitability (Nitsche & Paulus, 2000).

At relatively low intensities (≤4mA, typically ≤1.5mA), tDCS is considered safe for both healthy individuals and stroke survivors, and is also well-tolerated, with only some participants reporting mild adverse side effects such as headaches or localised tingling (Bikson et al., 2016; Nitsche, Liebetanz, et al., 2003; Poreisz et al., 2007). Furthermore, any symptoms that do arise commonly fade within the first minute of stimulation, permitting blinded therapy studies that compare the effects of longer periods of active stimulation to sham sessions, during which the current is turned on for up to one minute before being gradually ramped down (Flöel et al., 2008; Gandiga et al., 2006; Kessler et al., 2012).

In the majority of studies involving individuals with chronic anomia, anodal stimulation has been applied to either damaged left hemisphere language regions, such as the inferior frontal gyrus (IFG), or intact neighbouring ('perilesional') sites, while patients receive concurrent behavioural therapy for their word production deficits (ALHarbi et al., 2017; Sandars et al., 2016). The rationale for attempting to increase activation in these particular sites is a wealth of research indicating that patients in the chronic stage post-stroke who, like healthy individuals, demonstrate predominantly left lateralised language functions also tend to have more favourable language recovery than those who activate a greater number of diverse regions in both hemispheres during naming tasks (Marcotte et al., 2012; Saur et al., 2005; Szaflarski et al., 2013). When left hemisphere language regions are irretrievably damaged, compensatory recruitment of perilesional areas (such as the left precentral and supramarginal gyri) is consistently linked to improvements in picture naming in people with chronic aphasia (Fridriksson, 2010; Fridriksson et al., 2010; Meinzer et al., 2008; van Hees, McMahon, Angwin, de Zubicaray, & Copland, 2014). The relationship between perilesional anodal tDCS and activation within the damaged left hemisphere has been highlighted by Datta, Baker, Bikson and Fridriksson (2011) and Darkow, Martin, Würtz, Flöel, and Meinzer (2017). Datta and colleagues modelled current flow following anodal stimulation to the left frontal cortex (BA6) of an individual with non-fluent aphasia who had responded favourably to combined tDCS and computerised anomia therapy. In this particular patient, current was found to be most concentrated in deep, perilesional regions. More recently, Darkow et al. showed that, relative to sham stimulation, anodal tDCS applied to the intact left precentral

gyrus (M1, a perilesional region functionally connected to the language network) enhanced activation in fronto-temporal language-related regions in a group of 16 patients with chronic aphasia who were scanned as they named object pictures previously named correctly during two baseline trials.

In a therapeutic context, a number of studies have reported improved picture naming after combining excitatory anodal stimulation to left perilesional regions with anomia therapy tasks (Baker et al., 2010; Fridriksson et al., 2011; Meinzer et al., 2016; Vestito et al., 2014). For instance, Baker and colleagues (2010) provided ten patients with chronic post-stroke aphasia (four with Broca's aphasia and six with anomic aphasia) with 20-minute sessions 1mA anodal tDCS daily for five consecutive days, alongside computerised noun naming therapy. All participants also completed a week of therapy plus sham stimulation, with the order of stimulation conditions counterbalanced across patients. For each individual, the active electrode was placed over the region of structurally intact perilesional cortex previously shown to be most strongly associated with correct picture naming. Thus, electrode positioning varied slightly between individuals but, for all patients, targeted either the left precentral gyrus or parts of the left frontal gyrus. Group results revealed that, compared to sham stimulation, anodal tDCS improved naming accuracy of both treated and untreated items, although increases were significant only for the treated items. The significant effect of treatment was maintained at follow-up, one week post-intervention. In line with the notion that targeting perilesional tissue is crucial to the success of therapeutic interventions in people with chronic anomia, the four participants (two non-fluent, two fluent) who responded most favourably to active treatment were those whose stimulation sites were closest to their underlying lesions. The benefits of targeting perilesional tissue with anodal stimulation do not appear to be limited to the frontal lobes. For example, Fridriksson et al. (2011) adopted the same electrode positioning protocol as Baker et al. (2010) with a cohort of eight patients with fluent aphasia. Due to their differing lesion sites, for each participant, the anode was placed more posteriorly than in Baker et al.'s study to ensure perilesional stimulation. Results showed that five, daily 20-minute sessions of anodal tDCS plus computerised speech and language therapy were significantly more effective at increasing

noun picture naming speed than the equivalent sham treatment, both immediately and three weeks after therapy.

Vestito et al. (2014) and Meinzer et al. (2016) further support the use of anodal stimulation applied to the left frontal lobe with anomia therapy, and highlight potentially long-lasting benefits on naming ability. In Vestito et al.'s (2014) study, three participants carried out a noun and verb naming task at the same time as receiving 1.5 mA anodal tDCS for 20 minutes per day, five days per week for a fortnight. Patient 1 had severe non-fluent aphasia following a fronto-temporal haemorrhagic stroke, patient 2 had very severe non-fluent aphasia associated with a frontal lobe infarct, and patient 3 had moderate anomic aphasia following a temporal lobe haemorrhage. For all patients, stimulation targeted Broca's area, identified as the crossing point between points T3 and F7 on the international 10-20 electrode positioning system. Relative to sham, active stimulation resulted in significantly greater increases in the number of items correctly named from baseline for all three participants, with therapeutic gains maintained for 16 weeks following treatment. Finally, Meinzer and colleagues (2016) reported significant treatment effects persisting for six months following an intensive two-week anomia treatment programme comprising two, 1.5 hour therapy sessions per day for eight days, with the active electrode placed over the left precentral gyrus (M1). In a between-participants design involving 26 patients representing a wide range of aphasia types and severities, 13 individuals received either 1mA anodal stimulation, whilst the remaining 13 received sham stimulation. Although all participants' naming accuracy of treated and untreated items increased significantly following intervention, therapy gains were larger, and more likely to be maintained at follow-up, for those who had received active stimulation, and for the treated items. Anodal stimulation also resulted in greater increases in everyday communicative effectiveness, as rated by participants' communication partners.

The precise mechanisms by which tDCS-plus-therapy led to enhanced naming ability in each of the four therapy studies described above are not known. However, consistent with previous imaging studies maintaining the importance of left re-lateralisation in language

recovery in the chronic stage post-stroke, all demonstrated significant benefits after attempting to increase activation in the damaged left hemisphere (Saur et al., 2005). The role of the contralesional right hemisphere in language recovery following stroke is less clear-cut (Crinion & Leff, 2015; Turkeltaub et al., 2012). Stroke survivors with chronic aphasia may show greater activation than healthy controls in right hemisphere regions (including the right IFG and right superior temporal gyrus, STG) when completing language tasks, yet such activation is not necessarily advantageous (Hamilton et al., 2011; Postman-Caucheteux et al., 2010). One theory proposes that increased activity in right hemisphere regions homologous to the left language network is the result of transcallosal disinhibition, which is said to occur when the lesioned left hemisphere no longer transmits inhibitory signals that normally suppress activation in their right homologues during language tasks, allowing these contralesional areas to become overactive (Thiel et al., 2006). In turn, inhibition stemming from the right hemisphere furthers reduce activation in the left, preventing recruitment of perilesional areas and hindering language recovery (Martin et al., 2009). Consequently, cathodal stimulation applied to the right hemisphere may inhibit undesirable right hemisphere activity, and indirectly facilitate more beneficial left hemisphere activation.

In line with this proposition, Kang and colleagues (2011) found that combining five 20-minute sessions of 2mA cathodal tDCS applied to the right Broca's homologue on consecutive days with individually tailored word retrieval therapy led to greater increases in naming accuracy over sham stimulation in a diverse group of 10 participants, although this trend was not statistically significant. There were no clear relationships between either aphasia classification or lesion profile and response to stimulation. In contrast, Rosso et al. (2014) targeted the same contralesional site in a larger cohort of stroke survivors for single 15-minute sessions of both 1mA cathodal and sham stimulation, in the absence of a concurrent therapy task. Of the 25 participants, 11 had lesions involving Broca's area (B+ participants), and 14 had lesions sparing this region (B- participants). The key finding was that, following active tDCS, naming accuracy of all B+ participants increased significantly, whilst for all but one of the B- participants, naming accuracy decreased or remained the same after receiving

identical stimulation. This result is consistent with the view that, for the B+ participants, cathodal stimulation targeting the undamaged right IFG inhibited unhelpful contralesional activation that had itself been inhibiting beneficial activation in the damaged left IFG and neighbouring tissue.

In the context of word finding difficulties, the goal of applying either anodal tDCS to the damaged left hemisphere or cathodal tDCS to the undamaged right is the same: to increase activation in left language and perilesional regions in order to improve naming ability. However, the hierarchical model (Heiss & Thiel, 2006) proposes that, for some stroke survivors, extensive left hemisphere damage may make recruitment of perilesional regions impossible, meaning that right hemisphere activation may be essential for any degree of language recovery (Schlaug, Marchina, & Wan, 2011). For these individuals, applying anodal stimulation to the *right* hemisphere or cathodal to the *left* may be the best way to improve picture naming. Recruitment of contralesional homologues may also be more beneficial for individuals with posterior lesions than those with frontal lesions. Hickok and Poeppel's (2004, 2007) dual stream model proposes that, in healthy adults, the left-lateralised dorsal stream, which extends anteriorly via the arcuate fasciculus from the parieto-temporal boundary to the posterior IFG, anterior insula and premotor cortex, is responsible for phonological speech production tasks. In contrast, semantically-mediated speech tasks such as real word repetition are said to also involve the bilaterally-organised temporo-frontal ventral stream (e.g. Crinion & Price, 2005; Saur et al., 2008). It is possible that anodal stimulation targeting right temporal regions could benefit language performance in a similar way to anodal stimulation targeting left frontal regions. Consequently, the optimal stimulation parameters for individuals with chronic post-stroke anomia may be influenced by both lesion size and site.

The potential advantages of attempting to increase activation in the contralesional hemisphere are supported by Flöel et al. (2011), who compared the effects of 1mA anodal, cathodal and sham stimulation administered to the right Wernicke's homologue of 12 stroke survivors with chronic anomia. In each of the three conditions, stimulation was applied for

the first 20 minutes of hour-long cued naming therapy sessions delivered twice daily for three days. Correct naming increased after all types of tDCS-plus-therapy. However, gains were significantly greater following right anodal stimulation and remained so two weeks post-intervention. The participants who showed the most pronounced improvements following right anodal tDCS had the most severe baseline naming impairments, with the greatest gains following right anodal stimulation relative to both right cathodal and sham stimulation observed for an individual with an extensive lesion affecting the left temporal lobe. Accordingly, the size and/or site of this participant's lesion may have rendered her reliant on increased activation of contralesional temporal regions for improved language functioning. Such activation may have been facilitated by right anodal stimulation.

The results of Kang et al.'s (2011), Rosso et al.'s (2014) and Flöel et al.'s (2011) studies indicate that both contralesional cathodal and contralesional anodal stimulation may enhance word finding in certain stroke survivors with chronic anomia. However, all of these studies, plus those discussed previously involving anodal perilesional stimulation (Baker et al., 2010; Fridriksson et al., 2011; Meinzer et al., 2016; Vestito et al., 2014) investigated the effects of just one active tDCS montage on naming ability, with the exception of Flöel et al., who included only two active conditions. Consequently, it is impossible to determine whether different types of stimulation to those provided would actually have been more beneficial for some individuals. To address this issue, Shah-Basak and colleagues (2015) trialled a comprehensive range of tDCS montages in the first step of their two-stage study initially involving 12 patients with chronic non-fluent aphasia. In the first stage, participants received five single 20-minute stimulation sessions, each incorporating a different 2mA tDCS montage (left anodal, left cathodal, right anodal, right cathodal, and either left or right sham) whilst attempting to name 20 item pictures. Electrodes targeted either F3 (located superior to the left IFG and perilesional for 11/12 participants with damage to the left frontal lobes) or its right homologue, F4. Picture naming ability was measured immediately before and after each trial session. The authors found that 7/12 participants demonstrated a significant transient improvement in naming ability after at least one form of stimulation. Of these seven individuals, five completed the second, therapy stage. During the therapy phase,

participants carried out the same picture naming task for 20 minutes per day, Monday-Friday for two weeks, alongside 2mA active stimulation, utilising the montage that had resulted in the greatest increase in naming accuracy in stage one. After treatment, all participants exhibited improvements on a range of language production scales, resulting in an overall decrease in aphasia severity rating on the WAB (Kertesz, 1982). Sham stimulation did not lead to similar benefits, although only two of the five participants received both active and sham treatment, thereby hindering within-participant comparisons between active and sham conditions.

Shah-Basak et al.'s results were extended by Norise and colleagues (2017), who used the same two-stage methodology to assess the effects of tDCS plus naming therapy on four measures of connected speech elicited via a picture description task. From a starting group of 26 patients with chronic anomia, 11 responded positively to stimulation during stage one, nine of whom completed stage two (six received both active and sham stimulation). Group results indicated that picture naming plus active tDCS was significantly correlated with increases in the number of nouns produced when describing the composite picture at the two week follow-up. No similar treatment effects were observed following sham stimulation, or on any of the remaining outcome measures (sentence length, proportion of well-formed sentences, and proportion of pronouns), indicating that the potential benefits of combining tDCS with behavioural therapy may be task-specific.

Amongst those participants who responded positively to tDCS in the first stages of Shah-Basak et al.'s (2015) and Norise et al.'s (2017) studies, different electrode montages proved beneficial for individuals with differing lesion profiles. Specifically, left anodal stimulation tended to be most effective for participants with relatively circumscribed lesions confined to the left IFG and immediately surrounding tissue, whereas left cathodal stimulation tended to be most effective for those with more extensive lesions extending superiorly and medially into the left parietal and temporal lobes. Taken together, these findings are consistent with the hierarchical model (Heiss & Thiel, 2006) and demonstrate the need to take lesion site and size into account when considering electrode placement. Norise and colleagues also

found that individuals with more severe language deficits and larger lesion volumes at baseline tended to improve most following active tDCS combined with therapy during stage two, perhaps because they had greater potential room for improvement. With regards to electrode placement, although Shah-Basak et al. (2015) and Norise et al. (2017) offered a range of electrode montages in the first stages of their studies, a single 20-minute session of each determined whether or not participants would proceed to receive 10 further, therapy sessions and, if so, which form of stimulation would be paired with therapy. It is conceivable that patients require more than one application in order to realise the true gains from a particular type of stimulation and thus, in both studies, individuals who could have gone on to benefit from a longer tDCS-plus-therapy programme may have been prematurely dropped after completing stage one. Moreover, it is important to note that, whilst tDCS was associated with significant group level increases in noun production in Norise et al.'s study, only four participants named more nouns following treatment, and two actually produced fewer nouns two weeks post-intervention than at baseline. Of the latter two individuals, one had a small fronto-parietal lesion, and received cathodal stimulation to F3, whilst the other, who had a relatively large fronto-temporo-parietal lesion, received cathodal stimulation to F4. For these patients, combining therapy with alternative electrode montages may have led to more favourable outcomes.

To directly compare the relative benefits of multiple types of tDCS combined with behavioural therapy in individuals with chronic anomia, we designed a long-term intervention programme involving six full therapy cycles, each varying the laterality and polarity of stimulation (perilesional anodal, perilesional cathodal, perilesional sham, contralesional anodal, contralesional cathodal, and contralesional sham). To minimise any potential influences of perceived differences in participants' experiences of left and right hemisphere stimulation on the results, outcomes following each form of active stimulation were directly compared to those obtained following ipsilateral sham stimulation. We recently reported results for an individual (JSc) with chronic Broca's aphasia, who was the first patient to complete the full therapy schedule (Sandars et al., 2017). In the first week of each cycle, JSc carried out a computerised noun repetition therapy task for 20 minutes per day for three

days within a working week at the same time as receiving stimulation targeting either F5 or its contralateral homologue, FC6 (as per Nicolo et al., 2016). The decision to stimulate F5 was based on high resolution structural MRI scans showing this area to be intact, and perilesional to damaged regions in JSc's left frontal lobe. Results revealed that naming accuracy of treated items improved in all conditions following treatment, but perilesional anodal stimulation resulted in the greatest gains. This effect was significantly greater than that following sham stimulation, and remained so three weeks post-intervention. There were no similar patterns following active stimulation in scores on a range of secondary outcome measures, including a picture description task, self- and carer-rated communicative effectiveness, and mood questionnaire. The finding that anodal left frontal stimulation significantly enhanced naming accuracy in this patient with chronic non-fluent aphasia is therefore consistent with the work of Baker et al. (2010), Meinzer et al. (2016), Shah-Basak et al. (2016) and Vestito et al. (2014). In contrast, JSc's results do not support studies advocating contralesional cathodal stimulation (e.g. Rosso et al., 2014), nor findings linking active tDCS plus naming therapy to increased noun production in connected speech (Norise et al., 2017).

Alongside the ability to directly compare the relative benefits of different forms of tDCS-plus-therapy, there are a number of additional advantages of the intervention programme described above. Firstly, given evidence promoting the importance of activation in intact perilesional sites for post-stroke language recovery (e.g. Fridriksson, 2010; van Hees, McMahon, Angwin, de Zubicaray, & Copland, 2014), neuroimaging data was used to determine indivdiualised perilesional stimulation sites. Secondly, the therapy schedule for each type of tDCS was considerably less intensive than those previously reported. In total, JSc received an hour of stimulation plus therapy per condition, split across three sessions within a week. This level of input can be compared with other studies that have obtained similar results following up to 16 sessions over a fortnight (Meinzer et al., 2016), and implies that it may be viable to decrease the therapeutic dosage without compromising effectiveness. Furthermore, our design included a range of secondary outcome measures. In contrast, the majority of previous studies in this field assessed the impact of tDCS-plus-

therapy on naming accuracy alone, with the notable exceptions of Meizer et al. (2016) and Norise et al. (2017). Finally, although it is not it is not possible to make any generalisations to other stroke survivors with chronic anomia on the basis of results from just one individual, we have demonstrated the feasibility of a longitudinal, repeated measures design with multiple outcome measures in this clinical population.

The primary aim of the current study was to repeat the same comprehensive treatment programme completed by JSc with three additional stroke survivors with differing behavioural and lesion profiles (one non-fluent and two fluent) to determine which of the active electrode montages would lead to the greatest improvements in picture naming ability for each individual. On the basis of previous research reporting significant language improvements following attempts to increase activation in the intact right hemisphere in patients with extensive left hemisphere damage (Norise et al., 2017; Shah-Basak et al., 2015), we hypothesised that the additional individual with severe non-fluent aphasia, who had a large lesion involving the left frontal, temporal and parietal lobes, would benefit most significantly from contralesional anodal or perilesional cathodal stimulation.

In contrast, the two fluent participants had more focal, posterior lesions. Fewer studies have examined the effects of pairing therapy with tDCS targeting posterior sites rather than the frontal lobes (Sandars et al., 2016), making predicting which electrode montage would be most likely to lead to the greatest gains in picture naming accuracy for this pair of patients more problematic. Given the volume of evidence supporting the role of perilesional activation in language recovery in patients with relatively small lesions, we anticipated that anodal stimulation applied to perilesional regions in the left hemisphere and/or cathodal stimulation applied to homologous regions in the right hemisphere may be most beneficial. Alternatively, in line with the notion that semantically-mediated language functions are represented bilaterally in more posterior regions, we also acknowledged that combining repetition therapy with contralesional anodal and/or perilesional cathodal stimulation may prove most effective. In addition, in accordance with Fridriksson and colleagues (2011), we hypothesised that perilesional anodal stimulation would result in increased naming speed for

the two participants with fluent aphasia. As a secondary aim, we sought to explore potential treatment-related effects on participants' connected speech output, and self-perceived communicative effectiveness and quality of life.

Method

Participants

Five stroke survivors with chronic anomia were initially recruited from a database of participants held by the Neuroscience and Aphasia Research Unit (NARU) at the University of Manchester, or from local communication support groups. All participants were right-handed, native English speakers who had suffered a single left hemisphere stroke at least one year before taking part in the current study. At the start of the study, no participants had severe apraxia of speech or dysarthria, a confirmed or suspected diagnosis of dementia, or history of severe psychiatric illness. None had a cardiac pacemaker or history of epilepsy. No participants were taking medications known to affect the central nervous system, aside from EBe, who was taking 20mg daily fluoxetine. Evidence demonstrates that the use of selective serotonin reuptake inhibitor (SSRI) antidepressants, such as fluoxetine, does not increase the risk of adverse side effects from tDCS in patient populations (e.g. Bikson et al., 2016; Brunoni et al., 2014; Saxena & Hillis, 2017), and these drugs are very commonly prescribed for stroke survivors. Consequently, investigating the effects of tDCS and behavioural therapy in individuals who are taking SSRI medications is likely to have high ecological validity when compared to real-life clinical situations.

One participant suffered an unrelated mild seizure during a break between his first (perilesional sham) and second therapy cycles, and was immediately removed from the study. The remaining four participants (mean age = 70.5 years, SD = 12.79; mean time post-onset = 65 months, SD = 27.04) completed the full six-cycle therapy programme. Patients did not receive any additional formal speech and language therapy during their

participation in the current study. Two participants had non-fluent aphasia (JSc and GH) and two had fluent aphasia (EBe and JSo).

JSc

JSc was an 81 year old right-handed retired engineer with 12 years of education. He had a left middle cerebral artery (MCA) infarction in November 2005, 103 months prior to recruitment to the current study. He lived with his wife and enjoyed completing sudoku and jigsaw puzzles, plus watching car restoration programmes on television. Socially, he and his wife were active members of a local stroke support group and, together, they enjoyed regular day trips by coach and longer breaks to visit their children and extended family. He was able to walk independently and drive short distances, although he had long-standing mild tinnitus. He presented with frequent word finding difficulties, telegrammatic speech and mild oral apraxia, with good comprehension of simple everyday conversation. He was classified as having Broca's aphasia.

GH

GH was a 79 year old retired joiner with 11 years of education. He had a stroke in April 2010, 63 months prior to recruitment to the current study. He lived with his wife and enjoyed watching sport on television. They both regularly attended an aphasia support group and travelled on organised day and residential coach trips. GH also spent one day per week at a respite care centre. He was a wheelchair user with a right hemiplegia affecting his upper and lower limbs, and had uncorrected mild bilateral hearing loss. GH presented with severe anomia and difficulties with auditory comprehension beyond simple words and phrases. He typically produced one word utterances, both spontaneously and in response to prompts, with occasional fluent production of conversationally appropriate learned social phrases, such as those relating to the weather. He was classified as having mixed non-fluent aphasia.

EBe

EBe was a 53 year old female with 11 years of education. She had retired early from her job as a care home manager following her stroke in August 2010, 54 months prior to recruitment to the current study. EBe lived with her husband, who also retired during the course of her participation. She was independently mobile and able to drive, and enjoyed frequent foreign holidays, socialising with friends and family, plus volunteering to support fellow stroke survivors at a nearby hospital. She presented with mild-moderate anomia, alongside very good auditory comprehension and functional conversational skills. EBe was classified as having anomic aphasia.

JSo

JSo was a 69 year old retired university professor with 19 years of formal education. She had a stroke in May 2011, 40 months prior to taking part in the current study. She lived alone and, although she had limited close interpersonal relationships, was fully mobile and able to drive, which allowed her to maintain a keen interest in academic and current affairs through her involvement in groups such as the U3A. She also enjoyed visiting restaurants and coffee shops, and keeping fit. JSo presented with good conversation skills, with word finding problems that were much less pronounced than on formal assessment, although she reported that she frequently substituted or worked around words she knew she had difficulty retrieving. She also expressed considerable frustration with her high level auditory comprehension difficulties as these diminished her ability to follow complex discussions or television show dialogue and plotlines. She was classified as having anomic aphasia.

Behavioural Assessment Battery

Prior to recruitment to the current study, all participants had completed a comprehensive range of speech, language and cognitive tests. The results of the behavioural test battery are shown in Table 4.1. The speech and language tests included the short form of the Boston Diagnostic Aphasia Examination (BDAE, Goodglass et al., 2001), including the Boston Naming Test (BNT, Kaplan et al., 2001). The BDAE provided the aphasia classification for each participant. In addition, participants completed a number of

phonological subtests from the PALPA (Kay et al., 1992): auditory discrimination of non-word minimal pairs (PALPA 1), and word minimal pairs (PALPA 2), immediate and delayed repetition of non-words (PALPA 8), and immediate and delayed repetition of words (PALPA 9). Four tests from the 64-item Cambridge Semantic Battery (Bozeat et al., 2000) were also included: the picture naming test, spoken and written word to picture matching tests, and the picture version of the Camel and Cactus Test of semantic association. The assessment battery also contained a 96-item synonym judgement task, including words presented in both spoken and written form (Jefferies, Patterson, Jones, & Lambon Ralph, 2009), and the spoken sentence comprehension task from the Comprehensive Aphasia Test (CAT, Swinburn et al., 2005). Finally, the additional cognitive tests were forward and backward digit span (Weschler, 1987), the Brixton Spatial Anticipation Test (Burgess & Shallice, 1997), and the Raven's Coloured Progressive Matrices test of non-verbal reasoning (Raven, 1962).

Neuroimaging

High resolution structural T1-weighted MRI scans (Figure 4.1) were acquired on a 3.0 Tesla Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an 8-element SENSE head coil. TR (repetition time) = 9.0ms, TE (echo time) = 3.93ms, flip angle = 8°, 150 contiguous slices, slice thickness = 1mm, acquired voxel size 1.0 x 1.0 x 1.0 x1.0 x 1.0mm^3, matrix size 256 x 256, FOV = 256mm, T1 (inversion time) = 1150ms, SENSE acceleration factor 2.5, total scan acquisition time = 575 seconds

As shown in Figure 4.1, JSc's lesion (volume = 18163 voxels) involved both inferior and medial areas of the left frontal cortex (including Broca's area), and the left insula. GH had an extensive lesion (volume = 33678 voxels) involving posterior and inferior regions of the left frontal lobe, left superior temporal lobe, plus the left supramarginal and angular gyri. EBe had a focal lesion (volume = 1526 voxels) affecting the left supramarginal gyrus. JSo's lesion (volume = 9159 voxels) involved superior and medial areas of the left STG (including Wernicke's area) and extended posteriorly into the left inferior occipital gyrus.

Table 4.1: Percentage scores for each participant on the behavioural assessment battery. Scores in bold indicate performance outside the normal range.

Name	Boston Naming Test	64-item naming	Minimal pairs (non-words)	Minimal pairs (words)	Non-word repetition (immediate)	Non-word repetition (delayed)	Word repetition (immediate)	Word repetition (delayed)	Spoken word to picture matching	Written word to picture matching	CAT Spoken sentence comprehension	96 synonym judgement	Camel and Cactus Test (pictures)	Forward digit span	Backward digit span	Brixton Spatial Anticipation Test	Raven's Coloured Progressive Matrices*
JSc	**53.33**	**71.88**	**75.00**	86.11	**36.67**	63.33	**90.00**	91.25	98.44	98.44	75.00	**76.04**	**82.81**	62.50	42.86	**43.64**	77.78
GH	**16.67**	**25.00**	**47.22**	**43.06**	**16.67**	**3.33**	**62.50**	**32.50**	**85.94**	**60.94**	**43.75**	**45.83**	**53.13**	**25.00**	**0.00**	**34.55**	61.11
EBe	**38.33**	**82.81**	93.06	98.83	66.67	**36.67**	**81.25**	**78.75**	100.00	98.44	75.00	83.33	90.63	**50.00**	**14.29**	**47.27**	66.67
JSo	**43.33**	**89.06**	**75.00**	93.06	**50.00**	**46.67**	**90.00**	88.75	100.00	100.00	81.25	96.88	95.31	**50.00**	42.86	65.45	100.00

*Norms were unavailable for this assessment

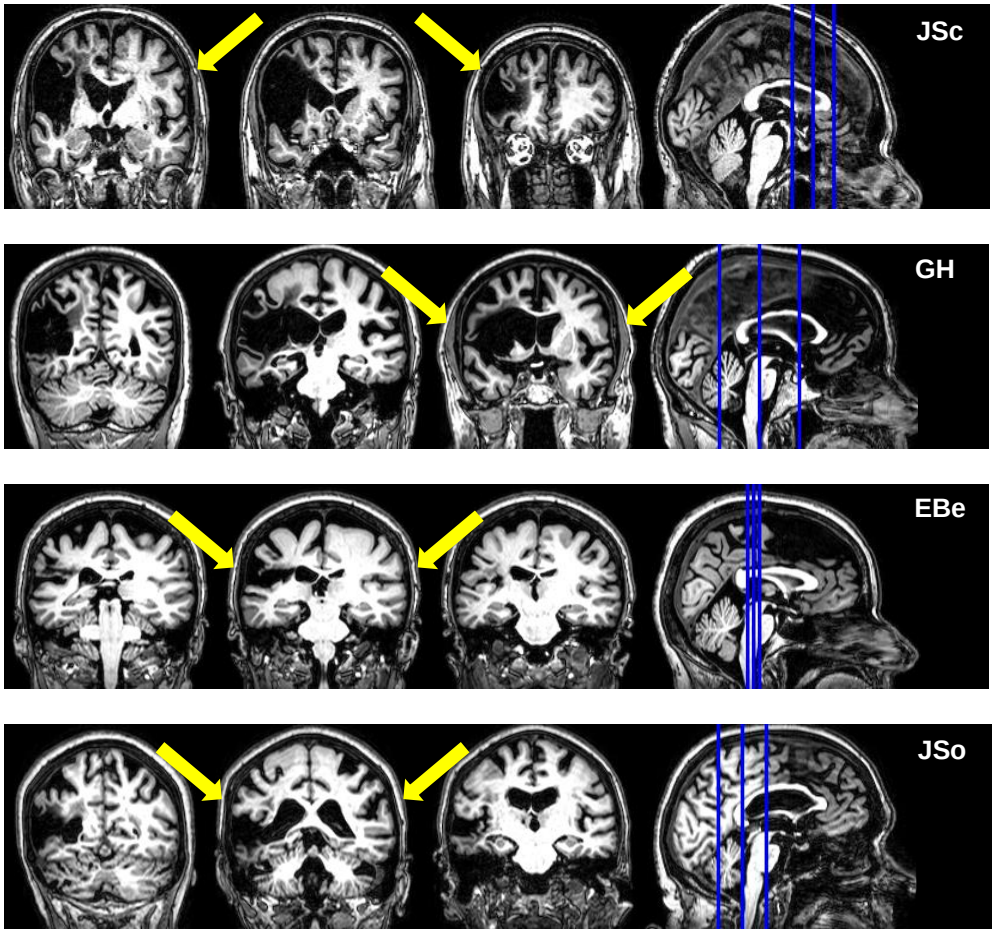


Figure 4.1: MRI images of participants' lesions, with arrows showing the location of tDCS stimulation sites.

Procedure

The design of the current study is illustrated in Figure 4.2. The study was approved by the Health Research Authority NRES Committee North West (13/NW/0844).

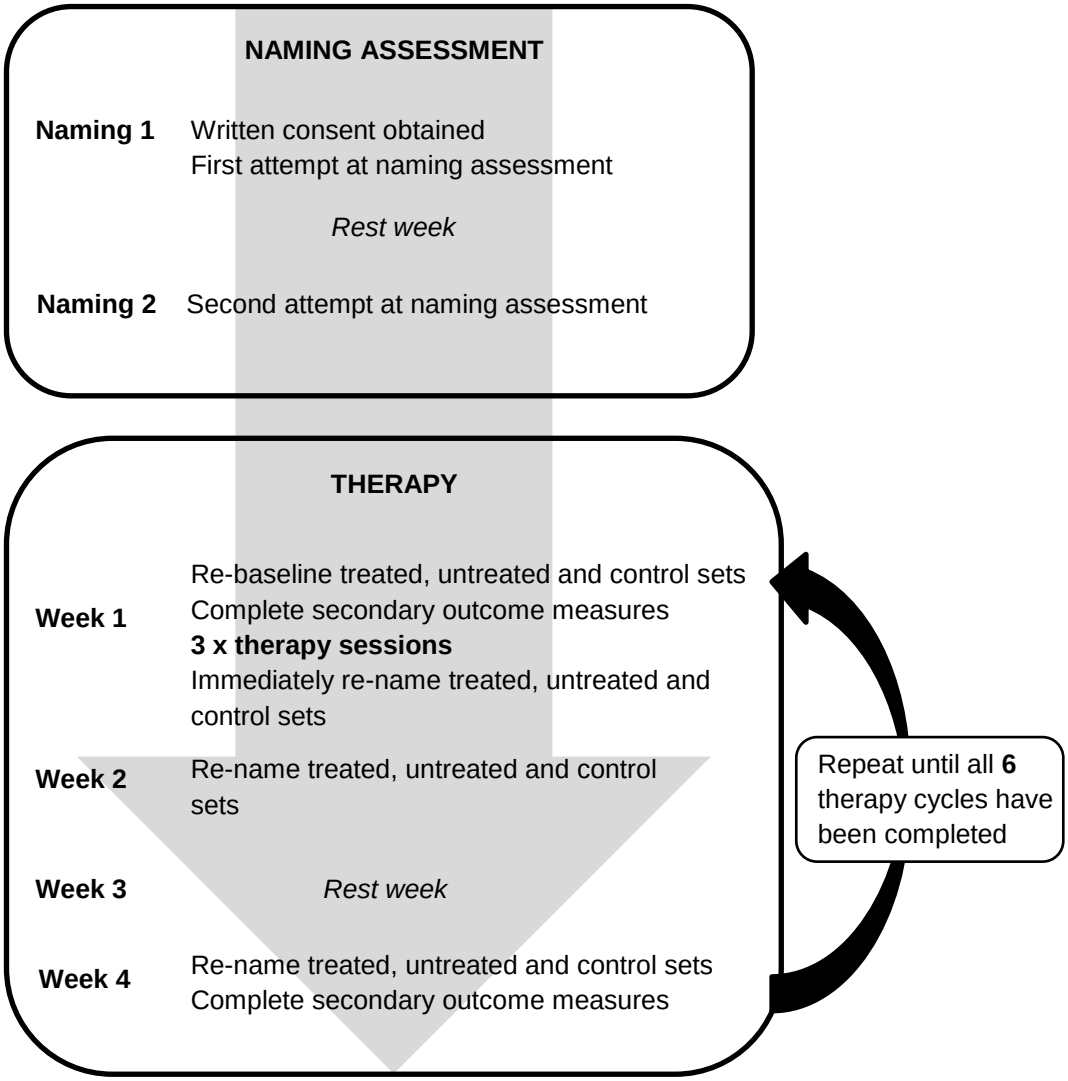


Figure 4.2: Flowchart to show the design of the current study.

Naming Assessment

All individuals gave written consent to participate in the study. Prior to commencing therapy, all participants completed a detailed naming assessment in their own homes on two occasions, at least one week apart. The stimuli were 408 black and white images taken from the International Picture Naming Project (IPNP, 2000, available at https://crl.ucsd.edu/experiments/ipnp/1stimuli.html), randomly divided into eight blocks of 51 items matched on length in phonemes, number of syllables, frequency, and age of acquisition (Appendix A). The items were presented on a laptop computer using E-Prime (Psychology Software Tools Inc., Sharpsberg, Philadephia), with the initial presentation of each image accompanied by a discreet beep sound to facilitate later measurement of

naming speed. Participants were asked to try to produce the name of each item as it appeared. No cues or specific feedback were provided, although general encouragement was given. Each image was shown for up to 10 seconds, after which time images automatically timed out if they had not yet been named correctly. Participants completed blocks 1-8 in order in the first assessment session and in the reverse order (i.e. from 8-1) in the second session. They were encouraged to take breaks between blocks, whenever required. All sessions were recorded using an Olympus VN-713PC digital voice recorder, placed to the side of the laptop computer. Participants' first naming attempts were graded as correct or incorrect. For an item to be scored as correct, participants had to produce the correct name within the ten second time limit. The correct name was defined as the target item name provided by the IPNP, an appropriate synonym (e.g. pillar → 'column') or an appropriate alternative response given the particular detail of the picture presented (e.g. house → 'bungalow'), as judged by the first author, a qualified speech and language therapist. Incorrect responses were defined as those instances in which either no naming attempt was made within the time allowed or in which the first naming attempt contained at least one error. Other verbalisations, including sighs and filler words/phrases (e.g. 'er', 'come on, think'), were ignored. The numbers of items named incorrectly and correctly by each participant during the two assessment sessions are shown in Table 4.2.

Table 4.2: Number of items named incorrectly once, incorrectly twice and correctly twice across both naming assessment sessions by each participant.

Name	Incorrectly named once	Incorrectly named twice	Correctly named twice	Total number of items*
JSc	127	116	162	405
GH	99	241	59	399
EBe	116	115	172	403
JSo	101	164	139	404

*Although 408 items were available at the start of each assessment session, items were occasionally inadvertently skipped. Therapy sets only included items attempted in both sessions.

A total of 18 personalised item sets were created for each participant, using their responses across both naming assessment sessions. For three participants (JSc, GH and JSo), 12 sets contained 20 items that they had named incorrectly on at least one occasion. EBe did not name 240 items incorrectly on at least one occasion. Therefore, to ensure that 20 items were still presented in all of her therapy sessions, each of EBe's first 12 sets contained 19 items she had named incorrectly on at least one occasion and one item she had named correctly twice. These double correct filler items were excluded from all analyses. For three participants (JSc, EBe and JSo), six further, control sets contained 20 items that they had named correctly twice. Due to the severity of GH's naming impairment, he only named 59 items correctly across both assessment sessions, meaning that five of his control sets contained 10 items he had named correctly twice and one contained nine. For each participant, the 12 incorrect sets were matched on length in phonemes, number of syllables, frequency and name agreement (see Appendix F), as were the six correct control sets (Appendix G). Six of the correct sets were randomly assigned to be treated and the remaining six were allocated to be untreated. All sets were randomly allocated to the six therapy cycles. Each therapy cycle included one treated, one untreated and one correct control set.

Computerised Naming Therapy

All therapy sessions were carried out in a designated treatment room in a large, general hospital in the North West of England. Microsoft Powerpoint slides were created for the 20 treated items to be included in each therapy cycle and presented to participants on a laptop computer. The slides included a colour Google image of each item (i.e. not the line drawings used in the assessments) and an audio video clip of a woman's mouth saying the name of the item, which were presented side by side in the centre of the slide. All images depicted typical examples of single items, with no visible brand names or other text. There was an automatic two second delay after the slide appeared to allow participants time to process the item image before the audio video clip began to play. After the audio video clip had finished playing, participants were asked to try to repeat back the item name. Once they had attempted to name the item, the next slide was revealed. Participants received

computerised therapy three times per week for 20 minutes during the first week of each therapy cycle. Each item was repeated 10 times per therapy session.

tDCS

tDCS was applied alongside computerised naming therapy. Participants completed six therapy cycles, each involving a different electrode montage. Three therapy cycles targeted perilesional regions in the left hemisphere and three targeted the homologues of these regions in the contralesional right hemisphere. Each set of three cycles involved either anodal, cathodal or sham stimulation. Individualised stimulation sites were selected on the basis of patients' MRI scans to ensure that left hemisphere stimulation targeted intact perilesional regions, and mapped onto co-ordinates as per the international 10-20 electrode positioning system. Contralesional right stimulation targeted the right homologues of these locations. The electrode placement sites for each patient are shown in Figure 4.1. For JSc, tDCS was applied to perilesional site F5 or contralesional site FC6; for GH, tDCS was applied to perilesional site F7 or contralesional site F8; for EBe, tDCS was applied to perilesional site CP3 or contralesional site CP4; and for JSo, tDCS was applied to perilesional site CP5 or contralesional site CP6.

Participants completed each therapy cycle in a different order: EBe: contralesional sham, perilesional sham, perilesional anodal, contralesional cathodal, contralesional anodal, perilesional cathodal; GH: contralesional anodal, contralesional sham, contralesional cathodal, perilesional anodal, perilesional cathodal, perilesional sham; JSc: perilesional anodal, perilesional cathodal, perilesional sham, contralesional anodal, contralesional cathodal, contralesional sham; JSo: perilesional cathodal, perilesional sham, contralesional anodal, contralesional cathodal, contralesional sham, perilesional anodal stimulation. Where possible, each cycle began the week immediately following week 4 of the preceding cycle (as per Figure 4.2). However, some adjustments were required in order to accommodate Christmas, New Year and participants' other commitments, including EBe's frequent foreign holidays. The mean and range of intervals (in days) between the offset of one type of stimulation and the onset of another for each participant were as follows: JSc: mean = 29,

range = 25-39; GH: mean = 44, range = 24-67; EBe: mean = 88, range = 46-137; JSo: mean = 30, range = 25-36. Hence, for all patients, there was a minimum 24 day wash out period between the offset of one type of stimulation and the onset of another.

In each therapy session, 1mA tDCS was delivered for 20 minutes by a NeuroConn DC Stimulator Plus device via two saline-soaked electrodes (5 x 7 cm). The active electrode was placed on the chosen location on the scalp and the second (reference) electrode was placed on the contralateral shoulder, in order to minimise the likelihood of inadvertently inducing simultaneous electrical currents in the contralateral hemisphere (Datta et al., 2011). To blind participants to whether they were receiving active or sham stimulation, during sham sessions, the stimulation was turned on for one minute to invoke the initial tingling sensation of tDCS before being gradually ramped down to nil over a further 30 seconds (Flöel et al., 2008; Gandiga et al., 2006; Kessler et al., 2012). All tDCS-plus-therapy sessions were carried out by the lead author. Although she was not blinded to the type of stimulation administered, the same protocol was strictly followed during every session. This included placing the tDCS display screen out of participants' sight in order to further minimise the risk of them distinguishing between active and sham stimulation conditions.

Outcome Measures

Naming

The primary outcome measure was naming accuracy. This was measured before the start of the first therapy session in each cycle in order to re-establish baseline accuracy for all of the treated, untreated and correct control items within that cycle. Naming ability was assessed again immediately after the third therapy session, at one week post-therapy and at three weeks post-therapy. On each occasion, participants was presented with black and white line drawings (the same images used in the initial naming assessment) of all treated, untreated and correct control items used in the current therapy cycle on a laptop screen. As in the initial naming assessment sessions, they were asked to try to produce the name of each item without any cues and images automatically timed out after 10 seconds if they had

not yet been named correctly. To investigate any effects of treatment on participants' naming speed, the time they took to correctly name the correct control items was measured at the same four time points. The time from initial item presentation (signified on the recording by the accompanying beep) to the onset of the first naming attempt was calculated manually for each item, in milliseconds, using Audacity 2.0.0 (available at http://audacity.sourceforge.net/).

Secondary Outcome Measures

Secondary outcome measures were collected prior to the first therapy session in each cycle, and at one week and three weeks post-therapy. To assess the extent of generalisation of therapy to connected speech, all four participants completed a picture description task ('Cookie Theft', Goodglass et al., 2001). Verbal responses on each occasion were transcribed and timed. The following measures were calculated: 1) total number of real words or 'tokens' per sample, which indicated quantity of speech output, 2) mean length of utterance (MLU) in morphemes, which indicated grammatical complexity and speech fluency, and 3) type/token ratio (TTR, calculated by dividing the number of unique words per sample by the total number of tokens), which indicated lexical diversity (as per Borovsky et al., 2007). In addition, the number of silent pauses (of at least one second duration) per response were recorded, and the number of tokens per minute (TPM) was calculated for each sample. Both measures provided further indications of speech fluency.

In addition to the picture description task, three of the participants (JSc, EBe and JSo) also completed the validated 20-item Communication Outcome After Stroke (COAST) scale (Long et al., 2008) to examine any effects of therapy on participants' self-perceptions of functional communication and quality of life. Total scores for each administration of the scale were converted to percentages, with higher percentages indicating better outcomes. GH was unable to complete the COAST due to the severity of his associated cognitive difficulties.

Results

Participants completed all planned sessions across the six therapy cycles. tDCS was well-tolerated by all four participants. Although EBe experienced mild, short-lived, localised itching during the majority of sessions, regardless of whether active or sham stimulation had been applied, no serious adverse effects were noted or reported during or after any of the therapy plus tDCS sessions (such as scalp reddening or headaches). When debriefed at the end of the study, all participants confirmed that they had not perceived any difference between active and sham conditions, although JSc felt that all of the cycles involving stimulation to the right hemisphere had been more beneficial and more comfortable.

To facilitate comparisons between patients with more similar behavioural and lesion profiles, results are displayed pairwise based on aphasia subtype (non-fluent: JSc and GH; fluent: EBe and JSo).

Naming Accuracy

Raw naming accuracy data for all four participants is provided in Appendix H. To assess changes in naming accuracy, the percentage change from baseline (at the start of each cycle) in the number of items named correctly immediately post-therapy, one week post-therapy and three weeks post-therapy were calculated for each stimulation condition, for each participant.

Treated Items

Percentage changes in naming accuracy from baseline for all treated items in each stimulation condition, at each time point, for both pairs of participants are depicted in Figure 4.3 (non-fluent) and Figure 4.4 (fluent). McNemar tests were used to determine the statistical significance of any changes in raw naming accuracy scores within the six stimulation conditions.

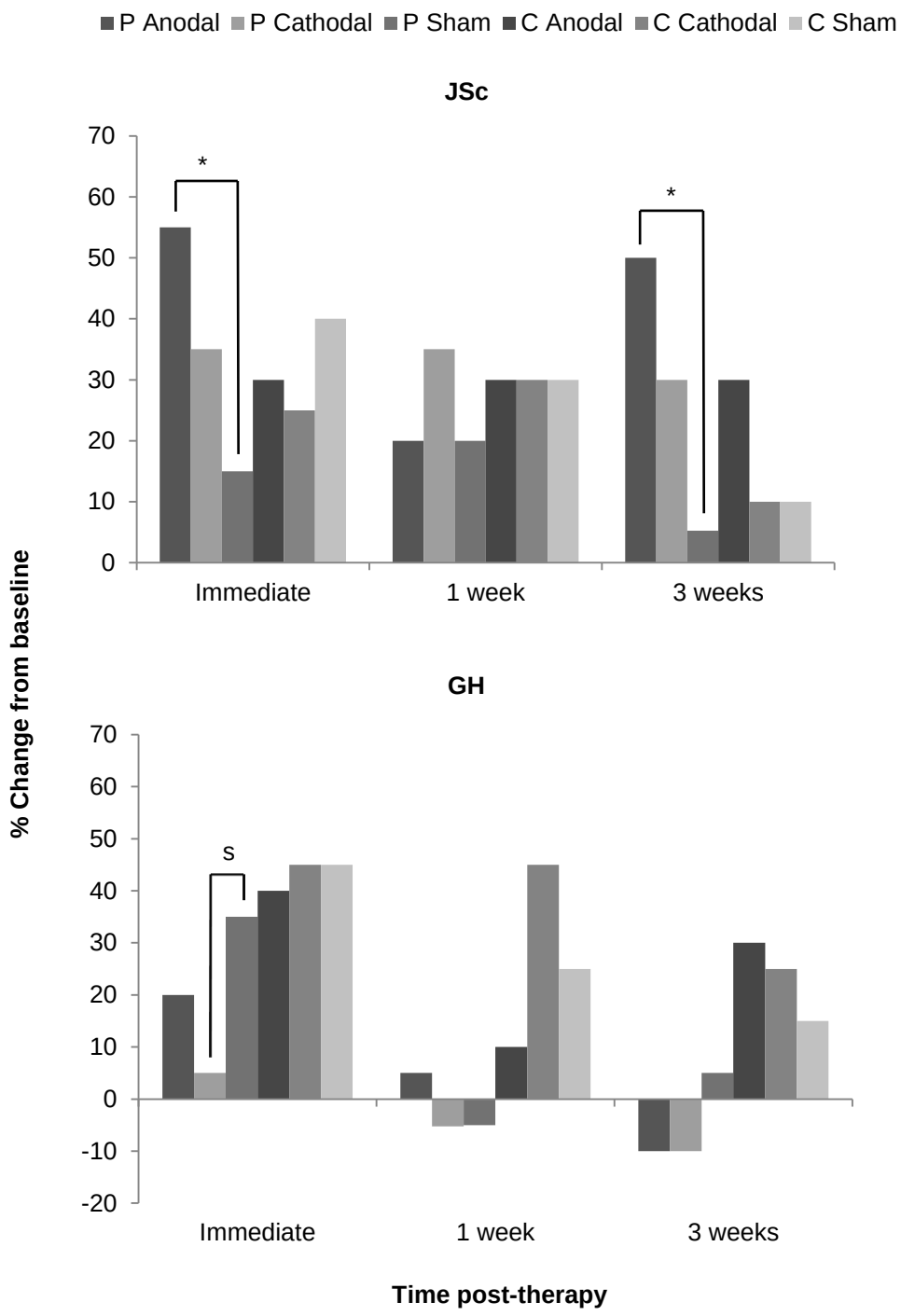


Figure 4.3: Percentage changes in naming accuracy from baseline for all treated items for JSc and GH. Asterisks indicate significantly greater gains for active than sham stimulation. 's' indicates a significantly greater gain for sham than active stimulation.

Non-Fluent Participants

Figure 4.3 shows that JSc's naming accuracy increased numerically from baseline in all stimulation conditions, at all three time points, indicating a strong overall beneficial effect of therapy. Perilesional anodal stimulation resulted in the greatest increases immediately post-therapy (55%) and three weeks post-therapy (50%). These increases were significant at both time points (immediate: χ^2=6.67, p=0.007; 3 weeks: χ^2=6.75, p=0.006). Increases in JSc's naming accuracy were also significant in the perilesional cathodal condition at all three time points (immediate: χ^2=5.14, p=0.016; 1 week: χ^2=7.11, p=0.004; 3 weeks: χ^2=6.13, p=0.008), and in the contralesional sham condition immediately post-therapy (χ^2=4.90, p=0.021). Chi square tests (again based on raw naming accuracy scores) indicated that the effect of perilesional anodal stimulation was significantly greater than that for perilesional sham, both immediately post-therapy (χ^2=4.57, p=0.032), and three weeks later (χ^2=6.99, p=0.008). The effect of perilesional cathodal stimulation was not significantly greater than that for perilesional sham, at any time point (immediate: χ^2=1.31, p=0.253: 1 week: χ^2=0.43, p=0.510; 3 weeks: χ^2=3.01, p=0.083).

Like JSc, GH's naming accuracy also increased numerically from baseline in all stimulation conditions immediately post-therapy. However, rather than perilesional anodal stimulation, contralesional cathodal and contralesional sham stimulation resulted in the greatest increases (both 45%) at this time point, both of which were significant (contralesional cathodal: χ^2=4.92, p=0.022; contralesional sham: χ^2=7.11, p=0.004). Increases in naming accuracy were also significant immediately post-therapy in the perilesional sham (χ^2=4.00, p=0.039) and contralesional anodal conditions (χ^2=6.13, p=0.008), with the gain following perilesional sham stimulation significantly greater than that following perilesional cathodal stimulation (χ^2=5.56, p=0.018). At one week post-therapy, gains were significant only in the contralesional cathodal condition (χ^2=7.11, p=0.004), although this effect was not significantly greater than that for contralesional sham stimulation (χ^2=0.38, p=0.536). In contrast to JSc, whose naming accuracy increased from baseline at all three time points, at one week following treatment, GH's naming accuracy was lower than at baseline in the perilesional cathodal and sham conditions and, at three weeks post-therapy, his naming

accuracy was lower than at baseline in the perilesional anodal and perilesional cathodal conditions.

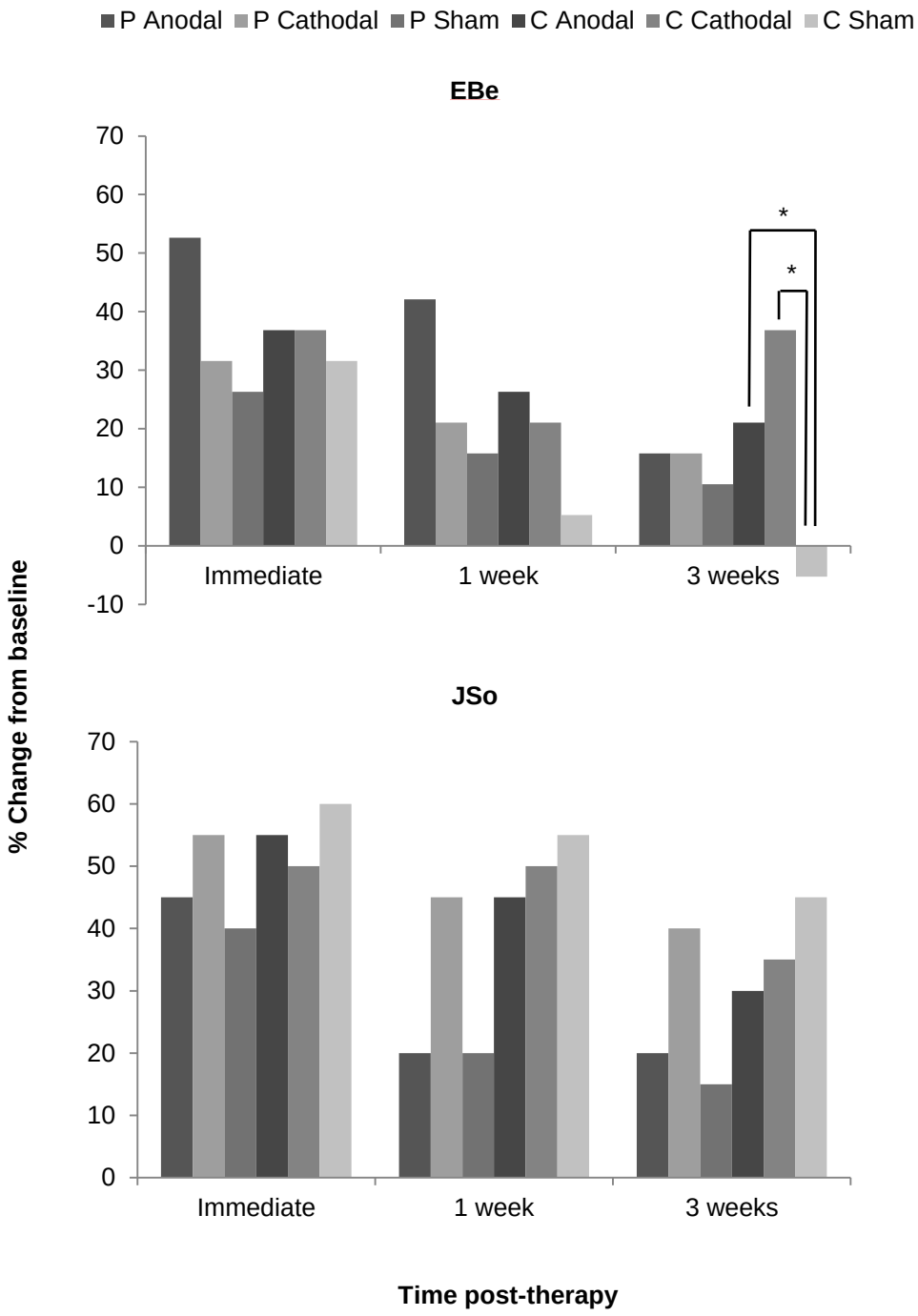


Figure 4.4: Percentage changes in naming accuracy from baseline for all treated items for EBe and JSo. Asterisks indicate significantly greater gains for active than sham stimulation.

Fluent Participants

Figure 4.4 shows that, aside from EBe's three week follow-up in the contralesional sham condition, both EBe's and JSo's naming accuracy increased numerically from baseline in all stimulation conditions, at all three time points, indicating an overall beneficial effect of therapy for the two participants. For EBe, perilesional anodal stimulation resulted in the greatest increases immediately post-therapy (53%) and one week post-therapy (42%). These increases were significant at both time points (immediate: χ^2=8.10, p=0.002; 1 week: χ^2=4.08, p=0.039), although chi square tests indicated that the effect of perilesional anodal stimulation was not significantly greater than that for perilesional sham either immediately post-therapy (χ^2=2.25, p=0.134) or one week later (χ^2=2.36, p=0.125). Increases in EBe's naming accuracy were also significant immediately post-therapy in the perilesional cathodal (χ^2=4.17, p=0.031), contralesional anodal (χ^2=5.14, p=0.016), contralesional cathodal (χ^2=5.14, p=0.016) and contralesional sham (χ^2=4.17, p=0.031) conditions, and three weeks post-therapy in the contralesional cathodal condition (χ^2=5.14, p=0.016). Chi square tests indicated that, at the three week follow-up, the effects of both contralesional anodal (χ^2=4.15, p=0.042) and contralesional cathodal stimulation (χ^2=6.47, p=0.011) were significantly greater than that for contralesional sham stimulation.

Therapy effects following active stimulation were less selective for JSo than for EBe, with the greatest significant increases at all three time points noted following cathodal sham stimulation (immediate: 60%, χ^2=10.08, p=0.000; 1 week: 55%, χ^2=9.09, p=0.001; 3 weeks: 45%, χ^2=5.82, p=0.012). Increases in JSo's naming accuracy were also significant immediately post-therapy in all five remaining conditions (perilesional anodal: χ^2=7.11, p=0.004; perilesional cathodal: χ^2=9.09, p=0.001; perilesional sham: χ^2=4.90, p=0.021; contralesional anodal: χ^2=9.09, p=0.001; contralesional cathodal: χ^2=8.10, p=0.002), one week post-therapy in three additional conditions (perilesional cathodal: χ^2=7.11, p=0.004; contralesional anodal: χ^2=5.82, p=0.012; contralesional cathodal: χ^2=8.10, p=0.002) and three weeks post-therapy in two additional conditions (perilesional cathodal: χ^2=4.90,

p=0.021; contralesional cathodal: χ^2=4.00, p=0.039). Active tDCS did not increase therapy gains above those observed for sham at any time point, irrespective of laterality or polarity.

Untreated Items

Figures 4.5 (non-fluent) and 4.6 (fluent) show the percentage changes in naming accuracy from baseline for all untreated items in each stimulation condition, at each time point, for the pairs of participants. McNemar tests were used to determine the statistical significance of any changes in raw naming accuracy scores within the six stimulation conditions.

Non-Fluent Participants

As per Figure 4.5, JSc's naming accuracy increased numerically at all three time points following perilesional cathodal stimulation, immediately post-therapy following contralesional cathodal stimulation and at three weeks post-therapy following perilesional anodal and contralesional anodal stimulation. GH's naming accuracy increased numerically immediately post-therapy in the perilesional cathodal condition, one week post-therapy in the perilesional anodal, contralesional anodal, contralesional anodal, contralesional cathodal and contralesional sham conditions, and three weeks post-therapy in the perilesional anodal and contralesional anodal conditions. For both JSc and GH, within the remaining conditions/at the remaining time points, naming accuracy remained the same or decreased following therapy. None of the post-therapy increases or decreases in naming accuracy for the untreated items were significant for either participant.

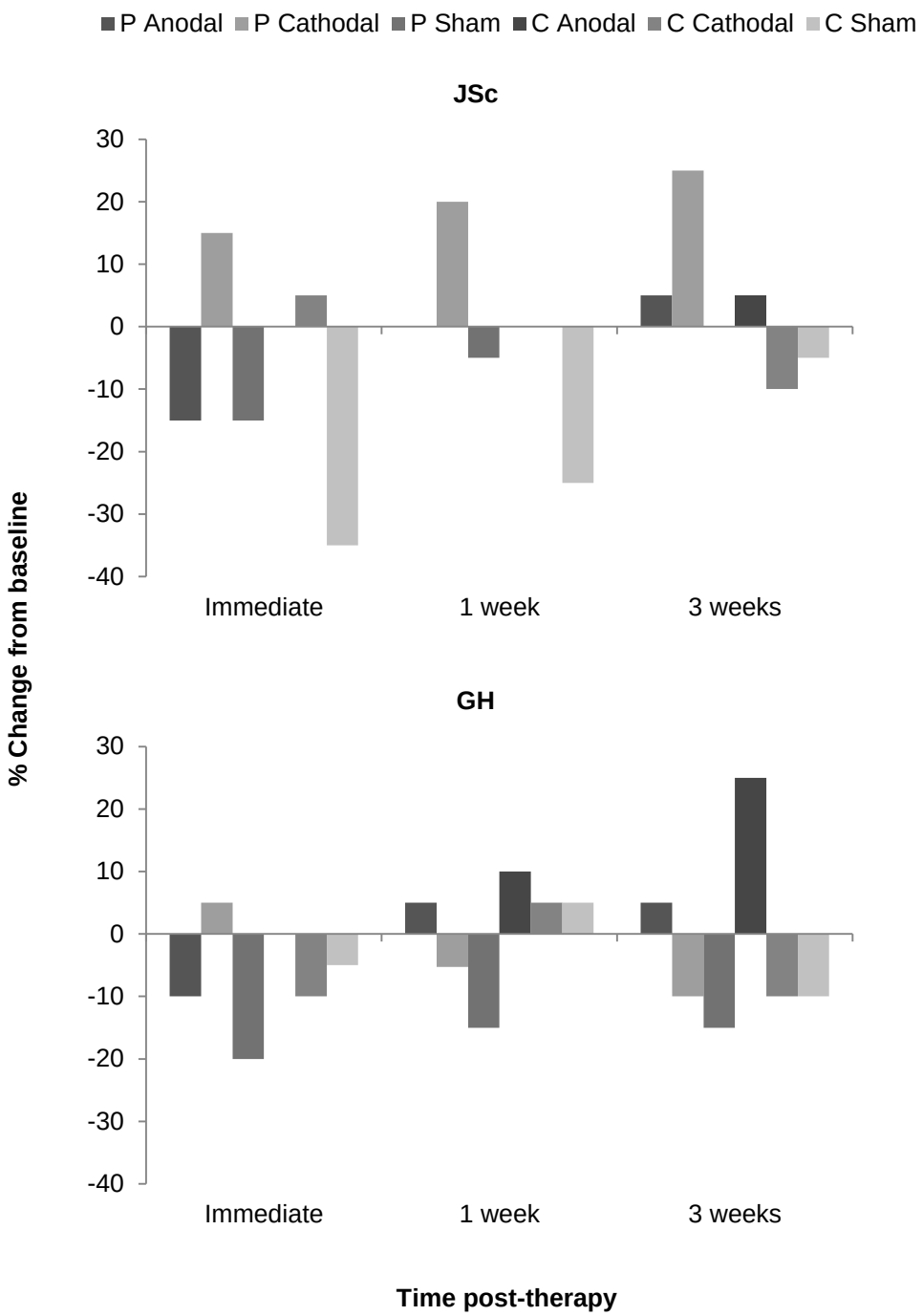


Figure 4.5: Percentage changes in naming accuracy from baseline for all untreated items for JSc and GH.

Fluent Participants

Figure 4.6 shows that EBe's naming accuracy remained the same as at baseline immediately post-therapy following perilesional anodal and perilesional cathodal stimulation, one week post-therapy following perilesional sham stimulation, and three weeks post-therapy following perilesional anodal stimulation. In addition, her naming accuracy decreased numerically from baseline to one week post-therapy in both the perilesional anodal and contralesional cathodal conditions. For JSo, naming accuracy following perilesional sham stimulation remained the same immediately post-therapy and three weeks later, and decreased numerically following contralesional anodal stimulation. In all remaining conditions, EBe's and JSo's accuracy increased numerically at all three time points following treatment. As for the non-fluent participants, none of the post-therapy increases or decreases in naming accuracy for the untreated items were significant for either of the fluent participants.

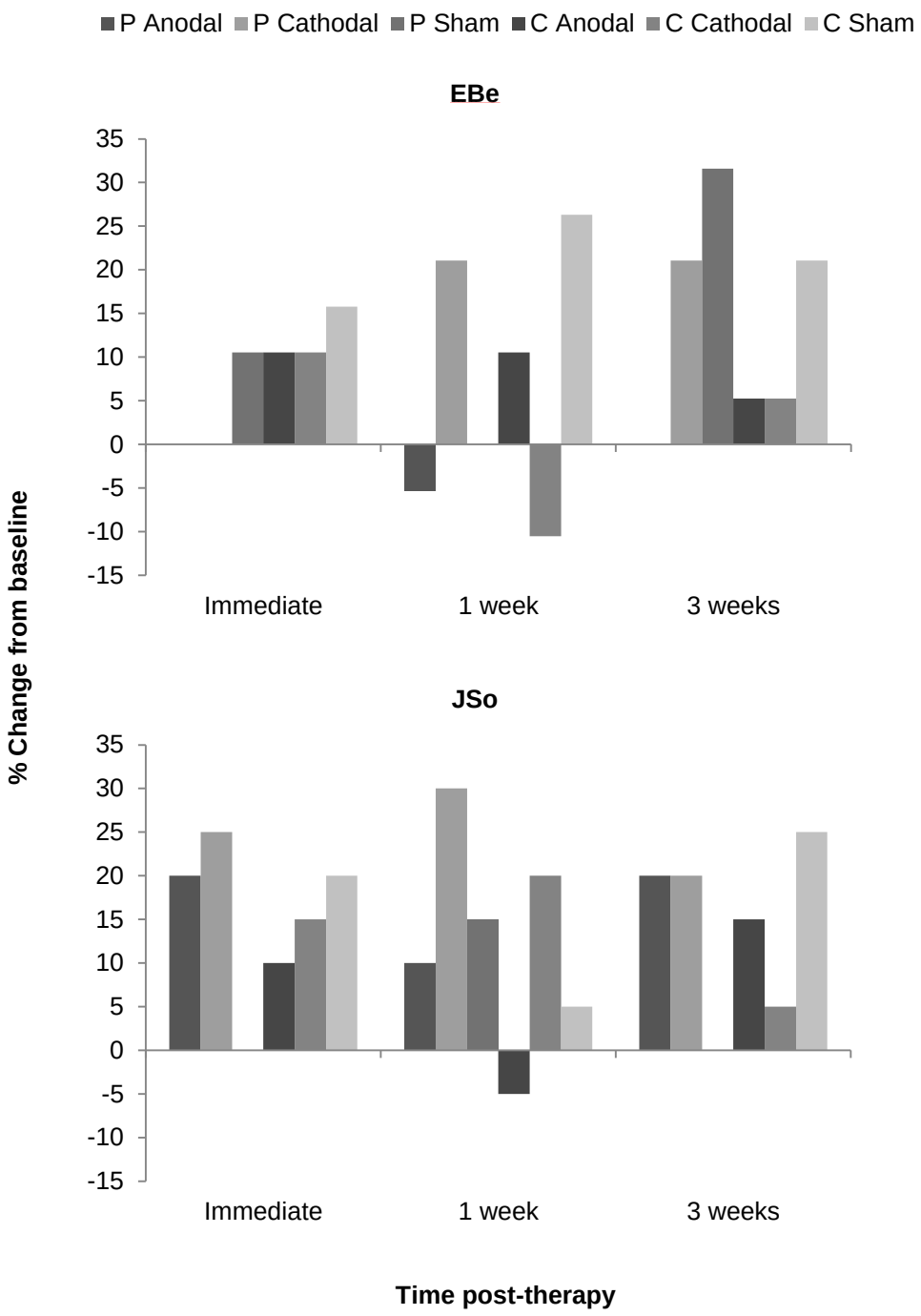


Figure 4.6: Percentage changes in naming accuracy from baseline for all untreated items for EBe and JSo.

Speed of Naming

Figures 4.7 (non-fluent) and 4.8 (fluent) show the mean time each participant took to name the double correct items correctly at baseline, immediately post-therapy, one week post-therapy and three weeks post-therapy.

Non-Fluent Participants

Figure 4.7 shows that there were no consistent patterns in the mean length of time JSc took to name the 20 correct control items within each therapy cycle. GH's mean naming speed was more variable than JSc's, particularly at the one week follow-up. However, due to the severity of his naming impairment, he failed to name many control items at any of the time points, and only had 10 (nine in the cathodal sham condition) correct control items per condition rather than 20. As a result, naming just one item particularly quickly or slowly would have had a relatively larger effect on mean naming speed for GH than JSc. Wilcoxon Signed Ranks tests showed that there were no significant changes from baseline in the length of time taken by either of the participants with non-fluent aphasia to correctly name the control items following therapy in any of the six conditions, at any of the follow-up points.

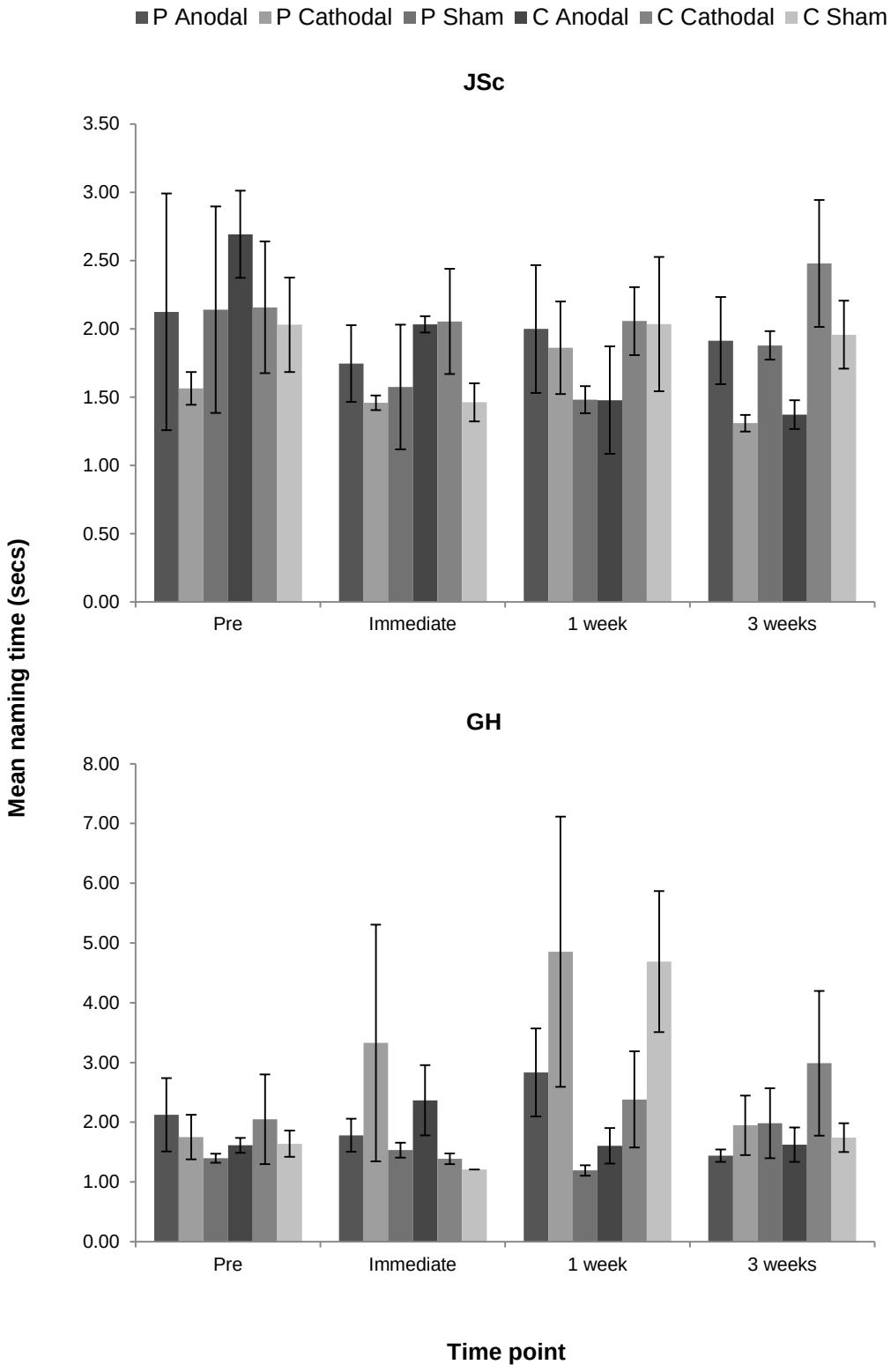


Figure 4.7: *Mean time (secs) taken by JSc and GH to correctly name control items. Error bars show +/-1 standard error.*

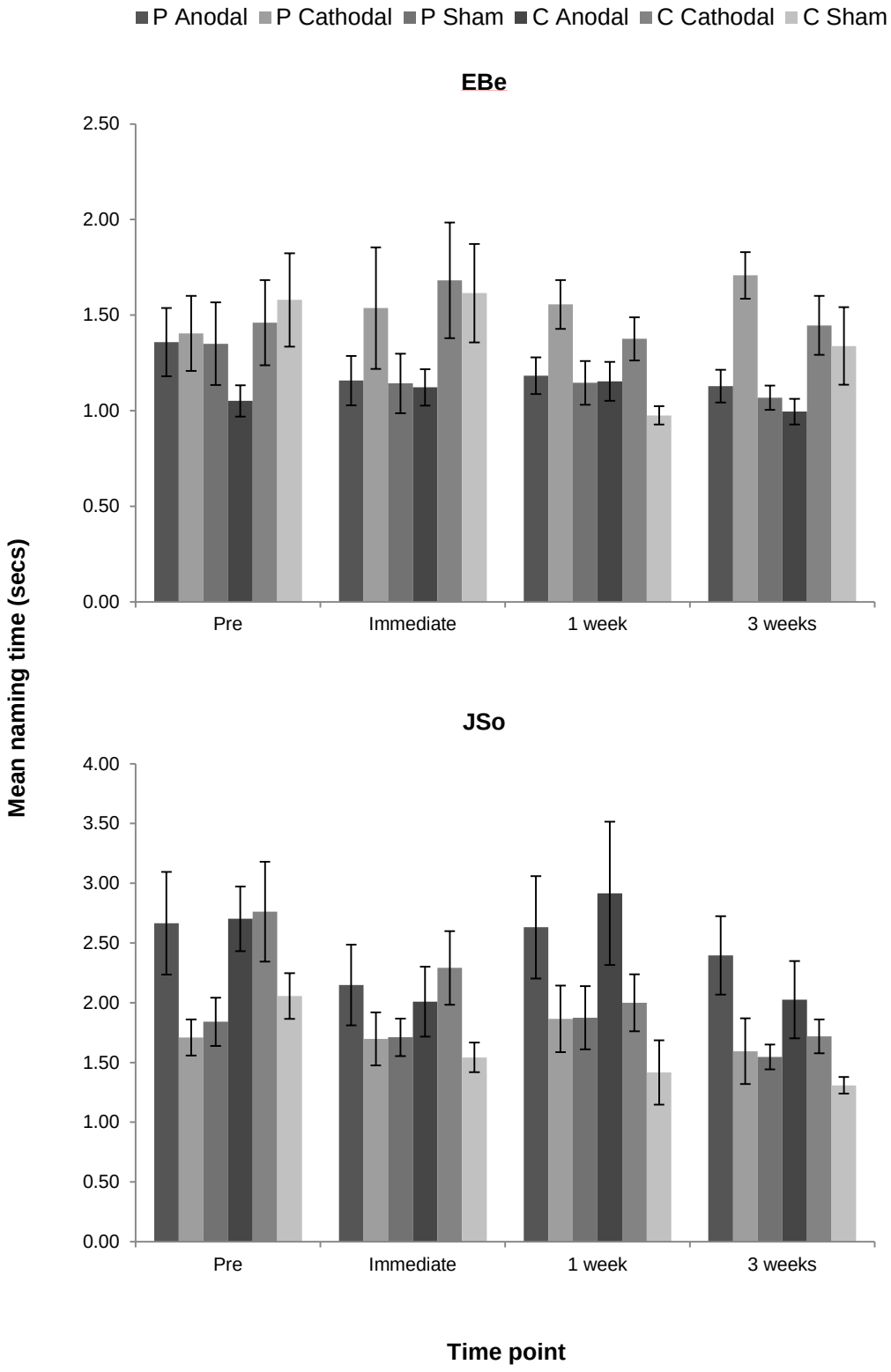


Figure 4.8: *Mean time (secs) taken by EBe and JSo to correctly name control items. Error bars show +/-1 standard error.*

Fluent Participants

For the two patients with fluent aphasia (Figure 4.8), Wilcoxon Signed Ranks tests showed that EBe's mean naming speed was significantly faster immediately post-treatment than pre-treatment (z=-2.64, p=0.008) in the perilesional sham condition. For JSo, there were significant increases in mean naming speed from baseline to immediately post-therapy in the perilesional anodal (z=-2.90, p=0.004), contralesional anodal (z=-2.78, p=0.005) and contralesional sham (z=-2.55, p=0.011) conditions, from baseline to one week post-therapy in the contralesional sham condition (z=-2.65, p=0.008), and from baseline to three weeks post-therapy in the contralesional anodal (z=-2.09, p=0.036), contralesional cathodal (z=-2.50, p=0.013) and contralesional sham (z=-3.02, p=0.003) conditions. The increase in JSo's mean naming speed from baseline to immediately post-therapy in the perilesional anodal condition was not significantly greater than the corresponding increase in the perilesional sham condition (z=-1.24, p=0.215). There were no further significant changes from baseline in the length of time taken by either EBe or JSo to correctly name the control items following therapy for the remaining conditions/time points.

Secondary Outcome Measures

Picture Description Task

The total response length (in seconds), number of pauses, total number of tokens, mean length of utterance (MLU) in morphemes, type to token ratio (TTR, expressed as a percentage) and number of tokens per minute (TPM) were calculated for the responses all participants gave when asked to describe the Cookie Theft image before therapy, one week post-therapy and three weeks post-therapy in each of the six stimulation conditions. These values are shown in Table 4.3 (non-fluent) and Table 4.4 (fluent).

During six of her picture description attempts (all three time points in the first, perilesional cathodal condition, at baseline in the contralesional cathodal condition, and at baseline and three weeks post-therapy in the contralesional sham condition), JSo became very frustrated when she was unable to retrieve a particular word. On these occasions, the lead author provided the verbal name for the appropriate item, which JSo repeated back several times before continuing to describe the Cookie Theft image. These segments of non-spontaneous speech were excluded from analysis. No prompts were required or provided for the three remaining participants. On one further occasion (at the three week follow-up in the contralesional cathodal condition), the doorbell interrupted JSo's picture description attempt and she did not wish to continue after a short delay. Consequently, this particular recording was considerably shorter and contained fewer tokens than her other attempts.

Table 4.3: Total response length (secs), number of pauses, number of tokens, MLU, TTR, and TPM for the picture description task for JSc and GH.

		JSc						GH					
Condition	**Time point**	**Length**	**Pauses**	**Tokens**	**MLU**	**TTR**	**TPM**	**Length**	**Pauses**	**Tokens**	**MLU**	**TTR**	**TPM**
P Anodal	Pre	107.8	15	78	6.3	43.6	43.4	146.8	19	21	1.6	85.7	8.6
	1 Week	73.9	10	41	4.6	63.4	33.3	135.8	10	7	1.7	71.4	3.1
	3 Weeks	89.6	10	60	7.1	56.7	40.2	132.0	14	16	2.0	62.5	7.3
P Cathodal	Pre	68.9	10	47	6.5	67.0	40.9	100.9	10	10	1.9	80.0	5.9
	1 Week	110.2	17	57	3.7	52.6	31.0	186.8	21	16	1.4	75.0	5.1
	3 Weeks	68.7	10	55	5.9	60.0	48.0	152.9	16	21	2.0	85.7	8.2
P Sham	Pre	63.8	10	43	4.9	48.8	40.4	178.0	20	21	2.1	90.5	7.2
	1 Week	94.8	18	74	6.3	55.4	46.8	151.2	12	14	2.2	78.6	5.6
	3 Weeks	46.0	9	48	5.8	62.5	62.6	194.4	22	20	1.9	75.0	6.2
C Anodal	Pre	68.5	17	63	4.3	52.4	55.2	33.7	8	8	1.6	100.0	14.2
	1 Week	38.2	5	51	10.2	72.6	80.1	148.7	21	20	1.6	65.0	8.1
	3 Weeks	59.7	8	64	10.4	59.4	64.3	142.3	15	15	1.6	80.0	6.3
C Cathodal	Pre	47.5	10	64	6.6	59.4	80.8	86.6	15	8	1.2	87.5	5.5
	1 Week	47.5	10	63	6.4	54.0	79.6	100.5	16	13	1.4	84.6	7.8
	3 Weeks	64.7	9	62	8.8	59.7	57.5	110.7	13	12	1.9	91.7	6.5
C Sham	Pre	29.2	3	46	12.8	67.4	94.5	68.4	12	8	1.5	100.0	7.0
	1 Week	50.1	7	52	8.6	55.8	62.3	149.9	17	16	1.9	81.3	6.4
	3 Weeks	50.9	6	50	8.7	72.0	58.9	100.1	15	14	2.5	92.9	8.4

Table 4.4: Total response length (secs), number of pauses, number of tokens, MLU, TTR, and TPM for the picture description task for EBe and JSo.

		EBe						JSo					
Condition	**Time point**	**Length**	**Pauses**	**Tokens**	**MLU**	**TTR**	**TPM**	**Length**	**Pauses**	**Tokens**	**MLU**	**TTR**	**TPM**
P Anodal	Pre	56.7	2	96	38.0	53.1	101.5	117.2	9	218	29.7	41.7	111.6
	1 Week	37.5	0	66	86.0	68.2	105.6	192.2	13	280	24.0	45.7	87.4
	3 Weeks	49.1	5	73	14.5	61.6	89.1	87.2	17	113	7.8	57.5	77.8
P Cathodal	Pre	40.4	0	64	86.0	60.9	95.1	108.3	8	199	27.0	48.7	110.2
	1 Week	42.6	2	77	31.3	58.4	108.4	130.5	9	197	24.3	49.2	90.6
	3 Weeks	35.7	0	68	82.0	58.8	114.4	215.7	24	340	19.8	44.4	94.6
P Sham	Pre	40.0	1	61	37.5	57.4	91.5	188.3	2	304	17.9	42.4	96.9
	1 Week	48.2	2	81	32.0	58.0	100.8	146.2	15	222	19.9	40.1	91.1
	3 Weeks	40.0	3	49	16.3	75.5	73.1	202.2	28	312	14.4	38.8	92.6
C Anodal	Pre	39.6	3	60	19.0	65.0	91.0	128.5	10	197	24.1	44.2	92.0
	1 Week	58.0	3	92	28.8	65.0	95.1	167.3	14	310	25.1	40.0	111.2
	3 Weeks	35.5	1	63	39.5	57.1	106.6	201.6	26	277	15.5	43.3	82.4
C Cathodal	Pre	47.7	2	73	29.7	39.7	91.8	210.4	28	33	16.2	38.0	100.7
	1 Week	45.3	1	82	51.0	53.7	108.6	171.8	21	240	16.4	44.2	83.8
	3 Weeks	53.4	3	73	22.8	60.3	82.1	119.3	8	189	28.1	51.3	95.1
C Sham	Pre	37.6	3	43	19.7	69.8	68.6	224.0	26	335	17.3	40.3	89.7
	1 Week	48.9	3	80	33.3	60.0	98.1	175.0	19	239	16.2	46.4	81.9
	3 Weeks	37.4	1	70	45.0	60.0	112.3	196.0	20	324	21.0	43.5	99.2

Non-Fluent Participants

Table 4.3 indicates that both JSc's and GH's scores on all six measures varied across the eighteen assessment sessions. For JSc, there were no consistent patterns of improvement or reduction in performance on any of the measures with each stimulation condition from baseline to one week or three weeks post-therapy. However, between the conditions, four trends emerged over time from the first cycle (perilesional anodal) to the last (contralesional sham), namely, the total length of JSc's responses and the number of pauses he made tended to decrease over time, whilst his MLU and TPM increased, consistent with a cumulative improvement in fluency over the course of repeated cycles of behavioural therapy. There were no obvious trends between stimulation conditions with regards to JSc's total number of tokens and TTR. Relative to JSc's productions, GH's picture naming attempts were longer in total duration, but with more pauses and fewer tokens, and correspondingly lower MLU and TPM values. These differences between JSc and GH's responses are commensurate with GH's greater aphasia severity and fluency impairment. Within each stimulation condition, the number of tokens GH produced increased from baseline to one week post-therapy in all of the therapy cycles except the perilesional anodal and perilesional sham conditions, both of which had the highest baseline values. At the same times, total response length also increased in all but the perilesional anodal and perilesional sham conditions, plus, in all six conditions, his TTR decreased from baseline to one week post-intervention. Taken together, these findings imply that at the one week follow-up, the quantity of GH's speech increased relative to immediately pre-therapy, but his attempts were more repetitive. In contrast to JSc, there were no consistent patterns in GH's responses between stimulation conditions from the first (contralesional anodal) to the final (perilesional sham) therapy cycles on any of the connected speech measures.

Fluent Participants

Table 4.4 shows that the total length of EBe's responses increased from baseline to one week post-therapy in all but the perilesional anodal and contralesional cathodal cycles (both of which had highest baselines). The number of tokens she produced also increased from baseline to the one week follow-up in five of the stimulation conditions, with the exception of

the perilesional anodal condition, which again had the highest baseline value. Furthermore, her TPM values increased from baseline to one week post-intervention in all six conditions and increased further by the three week follow-up in the perilesional cathodal, contralesional anodal and contralesional sham conditions. These figures suggest that EBe spoke for longer and produced more words, more quickly after therapy, with these effects persisting for a further fortnight in the perilesional cathodal, contralesional anodal and contralesional sham conditions before diminishing by the start of the next therapy cycle. For EBe, there were no further consistent trends within or between the six therapy cycles on any of the connected speech measures and, in particular, her MLU was highly variable across the eighteen assessment sessions. This is likely to be because she made very few pauses (range = 0 - 5), meaning that a small change in the number of pauses between different attempts resulted in a relatively large change in MLU. Compared to EBe's responses, JSo's picture description attempts were generally much longer. However, as she produced correspondingly more tokens and pauses, her TPM values were very similar to EBe's. There were no apparent trends involving any of the six connected speech measures either within or between cycles, although the three week follow-up for the final (perilesional anodal) cycle differed noticeably from all of JSo's previous attempts (including her interrupted attempt at the three week follow-up in the contralesional cathodal cycle): it was relatively very short with fewer tokens and more pauses, resulting in correspondingly lower MLU and TPM values, signalling that, on this particular occasion, her language production was less prolific and less fluent than usual.

COAST

Table 4.5 shows the total percentage scores on the COAST before therapy, one week post-therapy and three weeks post-therapy, in each of the six stimulation conditions, for the three participants who completed this measure (JSc, EBe and JSo).

Table 4.5: Total percentage scores on the COAST for JSc, EBe and JSo.

Condition	Time point	Participant		
		JSc	EBe	JSo
P Anodal	Pre	52.5	83.8	73.6
	1 Week	37.5	83.3	84.2
	3 Weeks	41.3	81.6	74.3
P Cathodal	Pre	47.5	81.6	67.1
	1 Week	42.5	81.6	58.3
	3 Weeks	42.5	85.5	63.2
P Sham	Pre	36.5	78.8	77.6
	1 Week	45.0	78.8	77.8
	3 Weeks	42.5	85.6	76.3
C Anodal	Pre	43.8	80.6	67.1
	1 Week	46.3	82.5	78.8
	3 Weeks	46.3	81.6	77.5
C Cathodal	Pre	46.3	85.0	84.2
	1 Week	55.0	85.0	80.3
	3 Weeks	43.8	88.2	82.9
C Sham	Pre	52.5	66.3	77.6
	1 Week	65.0	75.0	71.3
	3 Weeks	51.3	78.8	77.5

Non-Fluent Participant

JSc's total percentage scores on the COAST fluctuated both within and between stimulation conditions (total range = 36.5% - 65.0%). Wilcoxon Signed Ranks tests showed that the decrease in percentage score from the start of the perilesional anodal therapy cycle to one week post-therapy was significant (z=-2.97, p=0.003), and persisted at the three week post-therapy mark (z=-2.07, p=0.038), although the pre-therapy percentage score in this cycle was numerically higher than in all the other conditions other than the contralesional sham condition. In contrast, his increased ratings from baseline to one week post-therapy in the perilesional sham (z=2.33, p=0.020), contralesional cathodal (z=2.65, p=0.008) and contralesional sham (z=2.89, p=0.004) conditions were also significant. Overall, there was a trend for JSc to score more highly on the COAST as he continued to participate in the study:

his average percentage score across the three measurement points within the final stimulation condition (contralesional sham, 56.3%) was significantly greater than his average percentage score across the three measurement points within the first stimulation condition (perilesional anodal, 43.8%) (z=3.76, p=0.000).

Fluent Participants

EBe's total percentage scores on the COAST varied throughout her participation in the current study (total range = 66.3% - 88.2%). Wilcoxon Signed Ranks tests showed that the increases in percentage scores from baseline to three weeks post-therapy seen in the perilesional sham (z=2.05, p=0.040) and contralesional sham (z=2.14, p=0.032) conditions were significant, although these two conditions had the lowest baseline values. Between therapy cycles, there was a significant increase in average percentage score between the first therapy cycle (contralesional sham, 73.3%) and the second (perilesional sham 81.0%) (z=2.63, p=0.008). Following this, EBe's average scores remained high through to the final cycle (perilesional cathodal, 82.9%), peaking during the fourth therapy condition (contralesional cathodal, 86.05%).

JSo's total percentage scores on the COAST also varied within and between stimulation conditions (total range = 58.3% - 84.2%). There was a significant increase in percentage score in the perilesional anodal condition from pre- to one week post-therapy (z=2.31, p=0.021), and a decrease in percentage score in the perilesional cathodal condition from baseline to the one week follow-up (z=-2.00, p=0.046), when her score was especially low (58.3%). Between therapy cycles, JSo demonstrated the same pattern as EBe, with an initial significant increase in average score from the first (perilesional cathodal, 62.87%) to second (perilesional sham, 77.2%) cycles (z=4.46, p=0.000) that remained high as she progressed through the study to the sixth, perilesional anodal cycle (78.1%). The average percentage score within JSo's fourth therapy cycle (82.5%), which coincidentally involved contralesional cathodal stimulation, was also her highest.

Discussion

We have previously shown the feasibility of a comprehensive, longitudinal therapy schedule that systematically varied the laterality and polarity of tDCS paired with computerised repetition therapy in an individual (JSc) with chronic Broca's aphasia (Sandars et al., 2017). The primary aim of the current study was to extend our findings by completing the same intervention programme with three additional participants (one with non-fluent aphasia and two with fluent aphasia) in order to investigate which of the electrode montages would lead to the greatest improvements in noun naming ability in each patient. For our initial participant, JSc, augmenting behavioural anomia therapy with anodal stimulation applied to intact perilesional tissue in his left frontal lobe resulted in a significant increase in his immediate picture naming accuracy over and above the therapy gains achieved following perilesional sham stimulation. The same effect was also evident at the final follow-up, three weeks post-treatment. The finding that delivering excitatory anodal stimulation to perilesional regions in the damaged left frontal lobe of this patient with chronic non-fluent aphasia led to significant improvements in noun naming accuracy relative to sham stimulation is in line with existing group studies that have investigated the effects of left anodal stimulation on confrontation naming ability in individuals with left frontal lesions (Baker et al., 2010; Meinzer et al., 2016; Shah-Basak et al., 2015; Vestito et al., 2014). This result is also consistent with neuroimaging research highlighting the importance of activation in left perilesional regions for post-stroke language recovery (Fridriksson, 2010; Fridriksson et al., 2010; Meinzer et al., 2008; van Hees, McMahon, Angwin, de Zubicaray, & Copland, 2014).

For the second participant with non-fluent aphasia, GH, we anticipated that his extensive left hemisphere damage may preclude recruitment of perilesional regions to facilitate language recovery, in accordance with the hierarchical model (Heiss & Thiel, 2006). Consequently, we hypothesised that contralesional anodal or perilesional cathodal rather than perilesional anodal stimulation would lead to the greatest therapy gains. This hypothesis was not confirmed. None of the active stimulation montages resulted in significant increases in GH's

naming accuracy over and above the effects of sham stimulation. Instead, there was a significantly greater increase in performance immediately following perilesional sham stimulation than following perilesional cathodal stimulation, although this effect had disappeared by one week post-therapy. The observation that applying neither cathodal stimulation to the left hemisphere nor anodal stimulation to the right hemisphere significantly enhanced the effects of behavioural anomia therapy in this particular patient is at odds with results reported by Shah-Basak et al. (2015) and Flöel et al (2011), and is also inconsistent with tDCS-plus-therapy studies showing greater improvements in picture naming for individuals with more severe language deficits (Flöel et al., 2011; Volpato et al., 2013).

With regards to the two participants with fluent aphasia arising from relatively small, posterior lesions, we posited that applying perilesional anodal stimulation to intact posterior regions and/or cathodal stimulation to their contralesional homologues may result in the greatest treatment gains in noun picture naming accuracy, in line with our findings with JSc. For EBe, this hypothesis was partly confirmed in that, three weeks post-treatment, there was a significantly greater increase in her naming accuracy following contralesional cathodal stimulation than after contralesional sham stimulation. However, at the same time point, there was also a significantly greater increase from baseline in EBe's naming accuracy in the contralesional anodal condition than in the contralesional sham condition. Thus, EBe's results also support the alternate hypothesis that posterior contralesional anodal and/or perilesional cathodal stimulation would prove most beneficial. For JSo, none of the active tDCS montages led to significantly greater improvements than those obtained following sham stimulation, at any of the three time points, contrary to our expectations.

Overall, in contrast to our previous finding that perilesional anodal stimulation led to significant improvements in picture naming over perilesional sham stimulation for JSc, we did not find a clear benefit of one particular form of active tDCS compared to sham on the same outcome measure in three further participants with chronic anomia. There are several potential reasons why both GH and JSo failed to demonstrate any significant gains in naming accuracy following active, rather than sham, stimulation. For example, our

intervention programme included only three 20-minute sessions of anomia plus tDCS treatment per therapy cycle, compared to previous studies in which participants received between five (Baker et al., 2010; Fridriksson et al., 2011) and 16 (Meinzer et al., 2016) sessions in each treatment condition. Reducing the number of therapy sessions in each stimulation condition in the current study was largely motivated by a desire to minimise patient burden, as well as trying to avoid any ceiling effects from therapy that would obscure differences between stimulation conditions. However, it is plausible that most stroke survivors require more than three treatment sessions to achieve similar increases in naming accuracy following active stimulation to those seen for JSc. Relatedly, we administered 1mA tDCS in the present study. Others have found significant improvements in picture naming performance using stronger currents, specifically 1.5mA (Vestito et al., 2014) or 2mA (Shah-Basak et al., 2015). Although currents up to and including 4mA do not appear to lead to harmful side effects in patient populations, using higher current intensities than 1mA raises the risk that participants will readily distinguish active from sham stimulation, making direct comparisons between the two types of conditions more problematic (Bikson et al., 2016; Kessler et al., 2012). Nevertheless, 1mA may have been insufficient to produce both immediate and lasting naming improvements following active tDCS combined with anomia therapy for GH and JSo. Future studies could use a within-participants design to explore the effects of varying stimulation intensity on therapeutic outcomes.

EBe demonstrated significant gains in picture naming accuracy compared to sham following both contralesional anodal and contralesional cathodal stimulation three weeks post-treatment. Such incongruent results may be explained in a number of ways. Firstly, her naming accuracy in the cathodal sham condition at the three week follow-up was the only instance across all six conditions that her percentage of correctly named items was below baseline at any time point following therapy. It is not known why EBe's naming accuracy was especially low on this particular occasion. However, the significant interactions between the contralesional sham and both the contralesional anodal and cathodal conditions could reflect the outlying decrease in performance in the sham condition rather than increased performance following either contralesional anodal or contralesional cathodal tDCS. This

suggestion is supported by the observation that, whilst gains were relatively larger following contralesional anodal and contralesional cathodal stimulation than in the remaining conditions at three weeks post-treatment, EBe demonstrated numerically greater increases in naming accuracy from baseline in alternative conditions both immediately post-therapy and at the one week follow-up. Specifically, gains were greater in the perilesional anodal condition both immediately and one week post-therapy than three weeks after treatment in the contralesional cathodal condition. Gains were also equal or greater immediately post-therapy in all remaining conditions, and one week post-intervention in all but the perilesional sham and contralesional sham conditions, than three weeks after treatment in the contralesional anodal condition. In comparison, when JSc's therapy gains were significantly greater following perilesional anodal stimulation than perilesional sham stimulation (immediately and three weeks post-treatment), his percentage increases in naming accuracy in the perilesional anodal condition were markedly higher than in any of the other conditions. This observation supports the notion that, for JSc, treatment led to enhanced performance after anodal stimulation rather than depressed performance following sham treatment.

An alternative explanation for the apparently contradictory significant increases in EBe's naming accuracy three weeks after both contralesional anodal and contralesional cathodal stimulation compared to sham is her use of fluoxetine. SSRI antidepressants are commonly prescribed for stroke survivors to improve mood, and may have additional benefits for physical recovery when administered in the acute and sub-acute stages post-stroke (e.g. Mead et al., 2012). In addition, evidence suggests that combining tDCS with SSRI antidepressants in stroke survivors does not increase the risk of serious adverse reactions (e.g. Saxena & Hillis, 2017). However, lasting effects following tDCS are believed to rely on changes in synaptic strength, which are facilitated by neurotransmitters and neuromodulators, including serotonin and dopamine (Stagg & Nitsche, 2011). Studies involving healthy individuals have shown that SSRIs can alter the typical excitatory or inhibitory effects of stimulation on neural activation by altering concentrations of such neurochemicals. For instance, Nitsche and colleagues (2009) found that administering citalopram to increase serotonin levels enhanced and prolonged the excitatory after effects

of anodal tDCS, and switched the inhibitory after effects of cathodal tDCS to produce excitation.

In EBe's case, it is possible that the presence of fluoxetine reversed the inhibitory effects of contralesional cathodal stimulation, meaning that both contralesional anodal and contralesional cathodal tDCS acted to increase neural activation in her undamaged right hemisphere. This explanation is in accordance with the notion that certain language abilities are distributed bilaterally in posterior regions in healthy individuals (e.g. Hickok & Poeppel, 2004, 2007) and, consequently, improvements in picture naming may be anticipated to follow from increased contralesional activation. Conversely, other researchers have shown that increased dopamine levels can switch the excitatory after effects of anodal stimulation to produce inhibition and prolong the inhibitory effects of cathodal stimulation (Kuo, Paulus, et al., 2007). Unlike citalopram, fluoxetine can affect reuptake of additional neurochemicals to serotonin, including dopamine and norepinephrine (Bymaster et al., 2002). Thus, it is also conceivable that, in the present study, fluoxetine reversed the excitatory effects of contralesional anodal stimulation, leading to decreased neural activation in EBe's right hemisphere. This chain of events is consistent with the prior expectation that a patient with a small left hemisphere lesion may experience the greatest therapeutic benefits from increasing perilesional and/or decreasing contralesional activation.

It is impossible to confirm whether or not fluoxetine altered typical neural activity following anodal or cathodal stimulation and, if so, whether facilitating excitation or inhibition in contralesional tissue was most beneficial for EBe. However, the fact that picture naming accuracy in both the contralesional anodal and contralesional cathodal conditions was significantly greater than sham only at three weeks post-therapy lends some support to the notion that fluoxetine was involved. Altering synaptic strength does not occur instantaneously, so it may be that a consolidation period is required following tDCS before the effects of this process are evident (e.g. Reis et al., 2009). In contrast, immediate, more transient effects of tDCS are believed to stem from short-lived changes in membrane polarity (Stagg & Nitsche, 2011). Different mechanisms for short and long term potentiation could

also explain why JSc showed significant benefits from perilesional anodal stimulation immediately and three weeks post-therapy but failed to do so one week after treatment. Repeating the current protocol with larger numbers of patients, including those taking SSRIs (who are typically excluded from participating in tDCS-plus-therapy studies), may confirm whether delayed responses to tDCS are common to a wider population of stroke survivors under the same stimulation conditions.

With regards to the untreated items, all participants showed some numerical increases in naming accuracy from baseline throughout their involvement in the current study. This trend was particularly marked for JSo, who named more untreated items following all therapy cycles than at baseline at all points post-treatment except the one week follow-up in the contralesional anodal condition, although none of the post-therapy increases in naming accuracy for any of the four participants were significant. Such increases may be indicative of 'repetition priming', whereby simply asking patients to repeatedly name the same items on a number of occasions provides retrieval practice and increases the probability that items will be produced correctly on subsequent naming attempts (Nickels, 2002a). If repetition priming had occurred, one would expect any gains in patients' naming accuracy to rise within each therapy cycle. For JSc, this was indeed the case within the contralesional cathodal condition and, for GH, this was true for the contralesional anodal cycle. However, for the two fluent participants, and within all other cycles for JSc and GH, therapy gains did not show an increasing trend over time, reducing the likelihood that repetition priming was chiefly responsible for increased naming accuracy for the untreated items across the four patients. Instead, increases in participants' naming accuracy of untreated items may provide some evidence of generalisation, as also noted in previous tDCS plus anomia therapy studies (Baker et al., 2010; Meinzer et al., 2016).

Speech production needs to be both correct and timely to be functional (Conroy et al., 2009b; Conroy, Sotiropoulou Drosopoulou, Humphreys, Halai, & Lambon Ralph, 2018). Thus, increasing naming speed in individuals with anomia may help to enhance everyday interactions. We predicted that the patients with fluent aphasia would name the correct

control items significantly faster following perilesional anodal tDCS. EBe named items significantly faster immediately post-treatment relative to baseline only in the perilesional sham cycle. In contrast, JSo's naming was significantly faster immediately after treatment in the perilesional anodal condition, in accordance with both our hypothesis and the work of Fridriksson et al. (2011). The effects of the intervention programme on JSo's naming speed were, however, rather indiscriminate, with additional significantly faster naming noted in a number of conditions, including the contralesional sham condition, at all three time points post-therapy, and her naming speed following perilesional anodal stimulation was not significantly faster than after perilesional sham stimulation. Whilst it is possible that repetition priming may account for improvements over time in the contralesional sham and the contralesional cathodal condition, JSo's naming speed tended to fluctuate more randomly within the remaining conditions. One plausible reason for the different patterns of improvement following stimulation found in the current study relative to Fridriksson et al.'s study is that our control items were untreated. Consequently, treatment-related effects may have been more unstable and less predictable than if the control items had been targeted in therapy.

With regards to the two non-fluent participants, there were no significant effects of any type of stimulation on naming speed. This finding was not entirely unexpected since previous studies have not demonstrated any effects of frontal stimulation on speed of correct naming in patients with chronic non-fluent aphasia (Kang et al., 2011; Monti et al., 2008; Volpato et al., 2013). It is possible that naming speed is best facilitated via stimulation to posterior cortical regions, such as Wernicke's area in the temporal lobe, for both fluent and non-fluent patients (Fiori et al., 2011; Fridriksson et al., 2011). It is also conceivable that, irrespective of lesion site, posterior stimulation is more effective for increasing naming speed in individuals whose anomia is the result of breakdown during semantically-mediated word retrieval rather than phonologically-focused speech production. Overall, the potential effects of tDCS on speed of correct noun naming in individuals with fluent and non-fluent aphasia remain unclear, but could be investigated further in the future by adapting the current study design to include treatment for double correct items, and by considering varying electrode

placement according to whether the primary focus of treatment is improved naming accuracy or speed, also taking patients' underlying functional impairments into account.

An additional aim of the current study was to investigate treatment-related effects on participants' connected speech output (elicited via a picture description task), and self-perceived communicative effectiveness and quality of life. With respect to the picture description task, Norise and colleagues (2017) found that combining active tDCS and a noun naming task led to increased noun production in connected speech two weeks post-treatment in a group of individuals with non-fluent aphasia. Norise et al.'s participants described the same Cookie Theft image used in the present study, providing an opportunity to compare our results to their findings. The first non-fluent participant, JSc, did not demonstrate consistent patterns of improvement on any of the included measures within each of the stimulation conditions, indicating that his productions did not alter following any particular tDCS montage. There was, however, a growing improvement in fluency over the course of his involvement in the study, which was likely due to amassed retrieval practice for the same lexical items over 18 attempts. In contrast, the number of tokens (including nouns) GH produced increased from baseline to one week post-therapy in all but the perilesional anodal and perilesional sham cycles, which had the highest baseline values, although this effect was no longer evident two weeks later. This finding provides some support for Norise et al. and is in agreement with their observation that individuals who, like GH, had more severe pre-therapy language and fluency deficits showed the greatest improvements in elicited noun production following treatment. However, as GH's word production increases were not linked to any particular type of active or sham stimulation, it is likely that a more general therapy effect was responsible for these increases. For example, being able to successfully complete the errorless repetition therapy task may have temporarily increased GH's word finding confidence and encouraged him to say more. As he was unable to complete the COAST, links between increased word production and enhanced self-perceptions of communicative competence cannot be confirmed. GH showed no similar trends to JSc in performance from the first to the final cycle on any of the connected speech

measures, indicating that repeated attempts at the same task did not have any cumulative effects on GH's picture description skills.

As with JSo and GH, we did not find any specific treatment benefits following only active stimulation for the two individuals with fluent aphasia. Although EBe, like GH, produced a greater number of tokens one week post-therapy than at baseline in every cycle except the perilesional anodal cycle (which had the highest value at baseline), with further increases at the three week follow-up in the perilesional cathodal, contralesional anodal and contralesional sham conditions, this finding is again most likely due to a therapy effect common to all cycles. Furthermore, there were no trends in JSo's picture description abilities either within or between the six therapy cycles on any of the connected speech measures. One potential explanation why treatment had no effects on JSo's performance is that her capabilities could have been at ceiling at the start of the current study. She had already described the Cookie Theft picture on many prior occasions as part of her involvement in other research projects within the same university department and, overall, was competent at completing this task. Asking patients to describe an additional, unfamiliar composite image in the present study may have increased the possibility of finding significant treatment effects, especially for JSo.

In addition to completing the picture description task, three participants (JSc, EBe and JSo) self-rated their communicative competence and quality of life using the COAST. To date, no studies have explored the effects of unilateral tDCS on such a measure. This means that our results cannot be directly compared with previous findings, but provide some interesting insights. All participants shared a common tendency to score more highly on the COAST in their second and later cycles than in their first cycles. JSc's ratings became more positive as he progressed through the six cycles. This finding may be due to a cumulative effect of therapy. Alternatively, it could be linked to his belief that the later three cycles targeting his undamaged right hemisphere had been more beneficial. Whilst this perception was not reflected in JSc's naming data, there was a corresponding trend for his picture description fluency to also increase throughout his involvement in the current study. The two fluent

participants, EBe and JSo, had the highest average percentage scores on the COAST within their fourth, contralesional cathodal, cycles. For EBe, this increase corresponded to a significant gain in naming treated items three weeks following contralesional cathodal stimulation, although there was no matching peak in COAST score associated with the contralesional anodal condition. Similarly, there were no associations between changes in JSo's COAST ratings and her performance on any of the primary or secondary outcome measures. Consequently, it is possible that the rise in COAST scores within the fourth cycle seen for both EBe and JSo was simply coincidental, and further reflected variability in perceptions unrelated to the present project. Overall, few studies have examined the effects of tDCS-based therapy programmes on outcomes other than picture naming ability in patients with chronic fluent and non-fluent aphasia. Whilst we found improvements in 3/4 participants' picture description abilities and 3/3 participants' ratings of their own communicative skills and quality of life following treatment, there was limited evidence that these gains were the result of any particular type/s of active stimulation. Going forward, there is a need for studies to include additional measures to further investigate the effects of combining active tDCS and anomia therapy on everyday communication skills, well-being and quality of life in this target population.

A case series design facilitates in-depth exploration of individual patients' results. A common theme within the current study was considerable between-participant variability in observed treatment gains. Examining previous results reveals that certain patients also responded more favourably to tDCS plus anomia therapy than others, such as those with more severe aphasia, or particular lesion profiles (Flöel et al., 2011; Rosso et al., 2014; Volpato et al., 2013). Substantial inter-individual differences in response to stimulation may also be apparent even when treating relatively homogeneous groups of patients. For example, Lifshitz Ben Basat, Gvion, Vatine and Mashal (2016) recruited seven stroke survivors (two with Broca's aphasia and five with anomic aphasia) who had all been diagnosed with a chronic severe post semantic-lexical naming deficit. Prior to treatment, participants received eight single sessions that varied the polarity (anodal vs. cathodal), laterality (left vs. right hemisphere) and site (IFG vs. STG) of stimulation in order to

determine which montage led to the greatest increase in correct picture naming for each individual. Following identification of their optimal stimulation parameters, all participants received a total of six, 10-minute sessions of 2mA tDCS, delivered thrice weekly for a fortnight, followed by six sham stimulation sessions. The group level results showed that, despite a lack of a concurrent therapy task, active, but not sham, stimulation resulted in significantly greater picture naming accuracy relative to baseline at three follow-up points: immediately, one month, and three months post-stimulation. Nevertheless, the individual level analysis showed that disparate tDCS montages, which varied as a function of both aphasia classification and lesion site, proved optimally effective for different participants in the first stage of the study, and some patients' naming did not improve following the additional stimulation sessions. For instance, two participants (one fluent, one non-fluent) with fronto-temporal lesions responded transiently to perilesional cathodal STG stimulation. However, whilst the fluent patient demonstrated significant gains one month and three months post-treatment, naming accuracy for the non-fluent participant did not improve significantly at any of the three follow-up points, and was actually lower than at baseline at the one month follow-up. Consequently, despite the two patients sharing similar lesion profiles, underlying naming deficits and initial responses to the same form of tDCS, one individual responded to further active tDCS sessions and the other did not.

In other investigations, relatively large numbers of participants also failed to respond significantly to tDCS. For example, in the first stage of their studies, only 7/12 of Shah-Basak et al.'s (2015) participants and 11/26 of Norise et al.'s (2017) patients demonstrated a significant transient improvement in naming following any form of active tDCS. These results suggest that approximately fifty percent of patients with chronic aphasia may not benefit from tDCS-plus-therapy programmes, which is compatible with the finding that none of the active tDCS montages resulted in significantly greater increases in naming ability than sham stimulation for two of the four participants in the current study.

The question remains why some individuals with chronic anomia do not respond equally, if at all, to tDCS-based language interventions. The most probable explanation is that there

are critical differences between their lesions, both in terms of structural damage and deficits in white matter connectivity. This hypothesis is supported by studies linking poor responses to tDCS with lesions involving the basal ganglia, insula, superior and inferior longitudinal fasciculi (Campana, Caltagirone, & Marangolo, 2015), and lesions to both Broca's area and the arcuate fasciculus (Rosso et al., 2014). Similarly, although all of the participants in Lifshitz Ben Basat and colleagues' (2016) study had comparable language profiles, their lesions spanned a variety of cortical regions across the left frontal, temporal and parietal lobes, as well as the left basal nuclei and corona radiata. Diverse lesion sites may have led to different patterns of neural reorganisation for each individual that, in turn, led to variation in the optimal stimulation parameters to facilitate language recovery. When applying tDCS, the effects of stimulation may extend from regions directly under the active electrode to functionally and/or structurally connected brain regions via excitatory and inhibitory neural pathways (Zheng et al., 2011). Consequently, when white matter tracts are irreversibly damaged, stimulation may not be directed to the same sites as it would be if these pathways were intact, leading to unpredictable results. Targeting perilesional tissue is also physically more difficult to achieve in individuals with lesions concentrated in white rather than grey matter.

In the present study, left hemisphere stimulation targeted cortical regions within the normal language network shown by structural MRI scans to be intact and perilesional. Such scans do show damage to white matter, but do not accurately reflect the degree of disruption to structural connectivity. Future studies could utilise technologies such as diffusion tensor imaging (DTI) to better understand the effects of white matter damage on treatment success or failure following tDCS combined with anomia therapy. Additional neuroimaging research may also investigate treatment-induced changes in functional connectivity by scanning patients before and after they complete tDCS-plus-therapy intervention programmes. Following previous studies involving varying aspects of stroke rehabilitation, this work could reveal both task-based and resting-state white matter connectivity changes as a result of treatment (Kiran, 2012; Sandberg, Bohland, & Kiran, 2015; van Hees, McMahon, Angwin, de Zubicaray, Read, et al., 2014). It is, however, important to note that detailed imaging data is

not typically available in mainstream clinical settings. Therefore, in order to facilitate the adoption of tDCS into everyday practice, subsequent research could build on imaging findings to discover potential behavioural markers that can quickly predict whether or not an individual patient is likely to benefit from stimulation.

Conclusions

Previous studies have combined behavioural speech and language therapy with only one or two active tDCS montages. In comparison, we have shown that it is feasible to complete a relatively long-term tDCS plus repetition therapy programme that systematically varies the laterality and polarity of stimulation with four patients with chronic post-stroke anomia. Although it is not possible to generalise from just four participants to the wider population of stroke survivors with chronic aphasia, our case series design permitted detailed analysis of how these four individuals responded to the treatment provided. In line with previous findings, combining anodal tDCS applied to perilesional regions in the left frontal lobe with behavioural speech and language therapy was significantly more effective than therapy alone in increasing naming accuracy for one individual with chronic non-fluent aphasia, with treatment effects still evident three weeks post-therapy. In addition, combining both anodal and cathodal tDCS applied to contralesional regions in the right parietal lobe with naming treatment was significantly more effective than therapy alone in increasing naming accuracy for one individual with chronic fluent aphasia. Participants in the current study received a total of just one hour of each form of active stimulation over the course of a week, indicating that supplementing more traditional behavioural treatments with tDCS may be an efficient way to enhance therapy outcomes for certain individuals. The two remaining patients did not experience any additional gains in language performance as a result of receiving tDCS alongside therapy than they did from receiving therapy alone. Consequently, our results confirm the considerable between-participant variability in response to stimulation also noted in previous studies, although it is not yet clear why these two particular participants failed to benefit directly from tDCS. Future research is required in order to identify behavioural and neurological characteristics common to good responders to tDCS-based therapy schedules,

as well as determine which stimulation parameters lead to maximal therapeutic gains for each of these individuals.

Chapter 5

How, and why, is Oral Picture Naming Inconsistent in Chronic Post-Stroke Aphasia?

Abstract

Oral picture naming in people with aphasia is known to be inconsistent across multiple trials, yet the reason for such within-participant variability is unclear. The current study aimed to describe observed patterns of naming response inconsistency, and use a range of demographic, behavioural and psycholinguistic data to investigate potential explanations why some individuals are more inconsistent than others. Fifteen right-handed stroke survivors with chronic anomia named 408 black and white object images twice, with at least a week between attempts. All participants demonstrated considerable naming response inconsistency across the two trials (mean = 25.98%, range = 16.54% - 34.15%), with both incorrect-then-correct and correct-then-incorrect naming response patterns displayed. Degree of naming response inconsistency was not related to age, years of education, time post-onset, type of aphasia, lesion size, or overall anomia severity, nor to participants' scores on a wide range of cognitive and linguistic assessments, although limited support for roles of repetition priming (5/15 participants) and mild apraxia of speech (3/15 participants) was found. Six psycholinguistic variables (number of phonemes, number of syllables, frequency, name agreement, age of acquisition and phonological neighbourhood density) were important predictors of consistently correct or incorrect naming for all participants. However, the same variables played a reduced part in explaining inconsistent incorrect-then-correct naming for only 5/15 participants and inconsistent correct-then-incorrect naming for 7/15 participants. The findings have broad clinical implications for the assessment and treatment of chronic anomia. Further research is required to elucidate the underlying cognitive and neuroanatomical bases of naming response inconsistency.

Introduction

Anomia, or word finding difficulty, is the most common symptom across all types of post-stroke aphasia (Postman-Caucheteux et al., 2010). Anomia often persists long into the chronic stage (Pedersen et al., 2004), impacting significantly on the daily functioning and quality of life of both stroke survivors and their communication partners (Grawburg et al., 2014; Hilari et al., 2015). Consequently, improving word finding is a frequent aim in post-stroke language rehabilitation (Nickels, 2002b). Whilst individuals with anomia also have difficulties with sentence production and conversation, word finding difficulties are commonly measured clinically at single word level via confrontation naming tasks: patients are presented with a series of pictures of objects or actions and asked to produce the spoken name of each item (Raymer, 2011). Following assessment, therapy typically targets words that were not named correctly, with the number of such words named correctly following therapy taken as a measure of treatment effectiveness .

One issue with treating items that have been named incorrectly during just one assessment session is that naming in many people with aphasia has been known for some time to be inconsistent (Howard, Patterson, Franklin, Orchard-Lisle, & Morton, 1985). Anecdotally, patients often report that on occasion they produce a particular word with ease whilst at other times are unable to do so. In line with this, studies in which people with aphasia were asked to name the same pictures on multiple occasions have shown considerable variation in some participants' naming performance across trials, even with very short intervals between presentations (e.g. Freed et al., 1996; Laiacona, Allamano, & Capitani, 1996). The reason for such variability is unclear. There is some evidence for 'repetition priming', whereby asking participants to attempt to name the same items repeatedly strengthens existing mapping between the semantic and phonological representations of these items, making successive naming attempts more likely to be correct than earlier ones (Nickels, 2002a). However, repetition priming can only explain instances when the total number of items named correctly increases over time. For other individuals, the total number of correctly named items may be similar between trials, but *within* items there is considerable

inconsistency, with certain pictures named incorrectly then correctly and others named correctly then incorrectly in subsequent trials (Capitani et al., 2012; Freed et al., 1996). Other potential explanations for naming response inconsistency include varying levels of fatigue, motivation and mood, and the overall severity of an individual's naming impairment. It is also possible that correct naming may vary within and between items as a function of the psycholinguistic properties of the item name. A growing body of research indicates that naming success for some individuals with aphasia is influenced by various psycholinguistic variables, including frequency, imageability, word length, age of acquisition, name agreement and phonological neighbourhood density (Cuetos, Aguado, Izura, & Ellis, 2002; Kittredge, Dell, Verkuilen, & Schwartz, 2008; Laiacona, Luzzatti, Zonca, Guarnaschelli, & Capitani, 2001; Middleton & Schwartz, 2010; Nickels & Howard, 1995, 2004). However, potential relationships between psycholinguistic variables and inconsistency have yet to be investigated in individuals with chronic aphasia.

Clinically, it is important to acknowledge and understand inconsistency in picture naming for a number of reasons. Firstly, one may report significant therapeutic benefits following treatment of items incorrectly named on a single occasion when, in actuality, patients may have named some or all of these words successfully on a second attempt even if they had not received therapy (Freed et al., 1996). Secondly, therapists are presumably less likely to choose to treat items which are correctly named following a single assessment session. However, this may not be a true reflection of the patient's ability to consistently produce the item, and patients may not be able to produce these words on further occasions. Targeting these items in therapy may help to ensure their production is more consistent (Laiacona et al., 1996). Related to this point, it is possible that different therapy techniques may be optimally effective for items individuals inconsistently fail to name correctly and items that they are consistently unable to name. For instance, in line with some psycholinguistic models of lexical access in aphasia, within-item naming inconsistency may reflect incomplete or unstable representations that require strengthening, whilst items consistently named incorrectly may require complete relearning (e.g. Dell et al., 1997; Levelt et al., 1999).

The present study examined the consistency of naming performance in a group of individuals with chronic post-stroke aphasia, with the aim of elucidating the nature of consistent versus inconsistent responding, and potential explanatory factors. To do this, participants were asked to name a large corpus of object pictures on two occasions, separated by at least one week. Patterns of consistent and inconsistent responding were identified, and a range of demographic, behavioural and psycholinguistic data examined to investigate potential reasons why naming response inconsistency varies between individuals.

Method

Participants

Fifteen stroke survivors were recruited via presentations at stroke support groups in the North West of England, as well as from a database of participants already known to the Neuroscience and Aphasia Research Unit (NARU) at the University of Manchester. All participants were right-handed, native English speakers, and had suffered a single left hemisphere stroke at least one year prior to taking part in the study. Individuals with a suspected or confirmed diagnosis of an additional neurological condition that may affect speech and language abilities (e.g. dementia), or those with moderate to severe apraxia of speech, were excluded. High resolution structural MRI scans were acquired for each participant as part of their involvement in other studies within the department. Participant demographic and lesion volume information is shown in Table 5.1. The mean (SD) age was 64.33 (13.88) years, time spent in formal education was 12 (2.62) years, time post-onset was 67.53 (62.48) months, and lesion volume was 14715.33 (9381.8) voxels. The study was approved by the Health Research Authority NRES Committee North West (13/NW/0844). All individuals gave written consent to participate in the study.

Table 5.1: Participant demographic and lesion volume information.

Name	Sex	Age (years)	Education (years)	Time post-onset (months)	BDAE classification	Lesion volume (voxels)
AB	M	51	13	82	Anomic	22948
DF	F	50	11	67	Anomic	6975
DM	M	52	17	80	Broca's	11915
EBe	F	53	11	53	Anomic	1526
EBo	M	44	11	42	Anomic	8437
GH	M	79	11	63	Mixed non-fluent	33678
GL	M	50	12	52	Broca's	26218
JSc	M	81	12	103	Broca's	18163
JSo	F	69	19	40	Anomic	9159
JW	M	82	10	20	Broca's	12131
KA	M	68	11	23	Anomic	3311
MaD	F	57	11	277	Anomic	12699
MD	M	73	11	26	Mixed non-fluent	22732
PR	F	72	11	47	Transcortical motor	23863
RL	M	84	9	38	Anomic	6975

Behavioural Assessment Battery

All participants completed a comprehensive battery of speech, language and cognitive tests prior to recruitment to the current study. The results of these assessments are shown in Table 5.2. As part of this assessment battery, participants completed the short form of the Boston Diagnostic Aphasia Examination (Goodglass et al., 2001), which incorporated the Boston Naming Test (BNT, Kaplan et al., 2001). In addition, the battery of tests included a number of subtests from the PALPA (Kay et al., 1992): auditory discrimination of non-word minimal pairs (PALPA 1), and word minimal pairs (PALPA 2), immediate and delayed repetition of non-words (PALPA 8), and immediate and delayed repetition of words (PALPA 9). Four tests from the 64-item Cambridge Semantic Battery (Bozeat et al., 2000) were also included: the picture naming test, spoken and written word to picture matching tests, and the

picture version of the Camel and Cactus Test of semantic association. Patients also completed a 96-item synonym judgement task, including words presented in both spoken and written form (Jefferies et al., 2009), and the spoken sentence comprehension task from the Comprehensive Aphasia Test (CAT, Swinburn et al., 2005). Finally, the additional cognitive tests included forward and backward digit span (Weschler, 1987), the Brixton Spatial Anticipation Test (Burgess & Shallice, 1997), and the Raven's Coloured Progressive Matrices test of non-verbal reasoning (Raven, 1962).

Table 5.2: Percentage scores for each participant on the behavioural assessment battery. Scores in bold indicate performance outside the normal range.

Name	Boston Naming Test	64-item naming	Minimal pairs (non-words)	Minimal pairs (words)	Non-word repetition (immediate)	Non-word repetition (delayed)	Word repetition (immediate)	Word repetition (delayed)	Spoken word to picture matching	Written word to picture matching	CAT Spoken sentence comprehension	96 synonym judgement	Camel and Cactus Test (pictures)	Forward digit span	Backward digit span	Brixton Spatial Anticipation Test	Raven's Coloured Progressive Matrices*
AB	**41.67**	**76.56**	80.56	87.50	**26.67**	**13.33**	**86.25**	**63.75**	**95.31**	98.44	75.00	**75.00**	**79.69**	**37.50**	**14.29**	88.89	88.89
DF	**50.00**	**87.50**	90.28	95.83	**53.33**	**10.00**	**93.75**	**41.25**	100.00	**96.88**	**62.50**	**78.13**	92.19	**37.50**	**14.29**	**43.64**	88.89
DM	**71.67**	**75.00**	80.56	93.06	**60.00**	**10.00**	**73.75**	**68.75**	98.44	98.44	**56.25**	95.83	98.44	**37.50**	**0.00**	**50.91**	91.67
EBe	**38.33**	**82.81**	93.06	98.83	66.67	**36.67**	**81.25**	**78.75**	100.00	98.44	75.00	**83.33**	90.63	**50.00**	**14.29**	**47.27**	66.67
EBo	**55.00**	**89.06**	98.61	97.22	100.00	90.00	100.00	100.00	100.00	100.00	87.50	**90.63**	90.63	**50.00**	42.86	69.09	97.22
GH	**16.67**	**25.00**	**47.22**	**43.06**	**16.67**	**3.33**	**62.50**	**32.50**	**85.94**	**60.94**	**43.75**	**45.83**	**53.13**	**25.00**	**0.00**	**34.55**	61.11
GL	**31.67**	**68.75**	98.61	97.22	93.33	63.33	100.00	**81.25**	**96.88**	**95.31**	**65.63**	**75.00**	**73.44**	**37.50**	28.57	58.18	91.67
JSc	**53.33**	**71.88**	**75.00**	86.11	**36.67**	63.33	**90.00**	91.25	98.44	98.44	75.00	**76.04**	**82.81**	62.50	42.86	**43.64**	77.78
JSo	**43.33**	**89.06**	**75.00**	93.06	**50.00**	**46.67**	**90.00**	88.75	100.00	100.00	81.25	96.88	95.31	**50.00**	42.86	65.45	100.00
JW	**38.33**	**65.63**	86.11	**81.94**	**33.33**	**16.67**	**65.00**	**66.25**	**96.88**	98.44	90.63	**85.42**	**81.25**	87.50	**14.29**	61.82	88.89
KA	**61.67**	**84.38**	95.83	95.83	83.33	70.00	96.25	96.25	100.00	100.00	78.13	**79.17**	**84.38**	87.50	**14.29**	65.45	77.78
MaD	**76.67**	**84.38**	81.94	91.67	**60.00**	**56.67**	**95.00**	93.75	98.44	98.44	81.25	**88.54**	**82.81**	62.50	**0.00**	63.64	83.33
MD	**38.33**	**46.88**	98.61	98.61	**26.67**	**16.67**	**50.00**	**61.25**	**96.88**	**93.75**	**12.50**	**57.29**	**59.38**	**37.50**	**14.29**	58.18	38.89
PR	**38.33**	**60.94**	81.56	94.44	**56.67**	**43.33**	**85.00**	91.25	100.00	100.00	87.50	**83.33**	**84.38**	75.00	**0.00**	**50.91**	80.56
RL	**63.33**	**84.38**	**56.94**	89.72	**13.33**	**16.67**	**61.25**	**53.75**	**96.88**	98.44	**62.50**	**93.75**	95.34	62.50	42.86	72.73	80.86

*Norms were unavailable for this assessment

Naming Assessment

The stimuli for the naming assessment were 408 black and white object images taken from the International Picture Naming Project (IPNP, 2000, available at https://crl.ucsd.edu/experiments/ipnp/1stimuli.html). Psycholinguistic variable data were also taken from the IPNP. Across all 408 items, mean (SD) length in phonemes was 4.54 (1.78), and number of syllables was 1.73 (0.81). Mean frequency (as per the CELEX lexical database, Baayen, Piepenbrock, & Gulikers, 1995) was 2.87 (1.35), and name agreement (name, 'H statistic', following Snodgrass & Vanderwart, 1980, where '0' represents perfect name agreement and increasing values indicate lower name agreement), was 0.57 (0.56). Phonological neighbourhood density (PND) was estimated for each item using the unstressed, unweighted values provided by the Irvine Phonotactic Online Dictionary (Vaden, Halpin, & Hickok, 2009) and had a mean value of 15.16 (13.79). Finally, values were obtained from the IPNP for the ordinal variable, age of acquisition (AoA, as per the MacArthur Communicative Development Inventories, CDI, Fenson et al., 1994). This variable had three categories, each representing ranges in the average age of acquisition: 1 = 8-16 months, 2 = 17-30 months, 3 = >30 months. The frequencies of each category were as follows: 1 = 114, 2 = 41, 3 = 253. A series of Spearman's rho signed ranked tests showed that the psycholinguistic properties of the items were significantly intercorrelated (Table 5.3).

The 408 images were randomly divided into eight blocks of 51 items (Appendix A). Across all blocks, items were matched with respect to length in phonemes ($F(7,400)=0.252$, $p=0.971$), number of syllables ($F(7,400)=0.628$, $p=0.733$), frequency ($F(7,400)=1.857$, $p=0.075$) and name agreement ($F(7,400)=1.206$, $p=0.298$). The items were entered into scripts in E-Prime (Psychology Software Tools Inc., Sharpsberg, Philadephia) and loaded onto a laptop computer, with the initial presentation of each image accompanied by a beep sound.

Table 5.3: Correlations between the psycholinguistic properties of the naming assessment items.

	Phonemes	Syllables	Frequency	Name	AoA	PND
Phonemes		0.828**	-0.464**	0.163**	0.298**	-0.880**
Syllables	0.828**		-0.437**	0.115*	0.227**	-0.801**
Frequency	-0.464**	-0.437**		-0.216**	-0.401**	0.508**
Name	0.163**	0.115*	-0.216**		0.279**	-0.101*
AoA	0.298**	0.227**	-0.401**	0.279**		-0.250**
PND	-0.880**	-0.801**	0.508**	-0.101*	-0.250**	

* = p<0.05 ** = p<0.01

Procedure

Participants completed the naming assessment in their own homes on two occasions, at least one week apart. Participants were asked to try to produce the name of each item as it appeared. No cues or specific feedback were provided, although general encouragement was given. Each image was shown for up to 10 seconds, after which time images automatically timed out if they had not yet been named correctly. Participants completed blocks 1-8 in order in the first assessment session and in the reverse order (i.e. from 8-1) in the second session. They were encouraged to take breaks between blocks, whenever required. All sessions were recorded using an Olympus VN-713PC digital voice recorder, placed to the side of the laptop computer. Participants' first naming attempts were graded as correct or incorrect. For an item to be scored as correct, participants had to produce the correct name within the ten second time limit. The correct name was defined as the target item name provided by the IPNP, an appropriate synonym (e.g. pillar → 'column') or an appropriate alternative response given the particular detail of the picture presented (e.g. house → 'bungalow'), as judged by the first author, a qualified speech and language therapist. Incorrect responses were defined as those instances in which either no naming attempt was made within the time allowed or in which the first naming attempt contained at

least one error. Other verbalisations, including sighs and filler words/phrases (e.g. ‘er’, ‘come on, think’), were ignored.

Results

All participants completed both naming assessment sessions. The numbers of items named incorrectly and correctly by each participant during the two assessment sessions are shown in Table 5.4. Naming response inconsistency, expressed as a percentage, is also shown. This was calculated as a function of the total number of items incorrectly named in either one of the assessment sessions divided by the total number of items attempted, with higher values indicating greater inconsistency. Mean (range) naming response inconsistency was 25.98% (16.54% - 34.15%). The proportions of items named incorrect-then-correct, correct-then-incorrect, incorrect twice and correct twice by each participant are also depicted in Figure 5.1.

Table 5.4: Number of items named incorrectly once, incorrectly twice and correctly twice across both naming assessment sessions by each participant, plus percentage inconsistency.

Name	Incorrectly named once		Total number of inconsistent items	Incorrectly named twice	Correctly named twice	Total number of consistent items	Total number of items*	% Naming response inconsistency
	Incorrect then correct	Correct then incorrect						
AB	63	52	115	162	127	289	404	28.47
DF	54	46	100	95	210	305	405	24.69
DM	37	35	72	51	280	331	403	17.87
EBe	59	57	116	115	172	287	403	28.78
EBo	38	29	67	58	280	338	405	16.54
GH	46	53	99	241	59	300	399	24.81
GL	66	43	109	146	147	293	402	27.11
JSc	78	49	127	116	162	278	405	31.36
JSo	71	30	101	164	139	303	404	25.00
JW	63	54	117	170	110	280	397	29.47
KA	63	76	139	86	182	268	407	34.15
MaD	55	34	89	47	271	318	407	21.87
MD	57	40	97	204	100	304	401	24.19
PR	79	58	137	94	175	269	406	33.74
RL	52	36	88	83	235	318	406	21.67
Mean (SD)	59 (13)	46 (13)	105 (21)	122 (58)	177 (68)	299 (21)	404 (3)	25.98 (5.22)

*Although 408 items were available at the start of each assessment session, items were occasionally inadvertently skipped. Any items not attempted in both sessions were excluded from any further analysis.

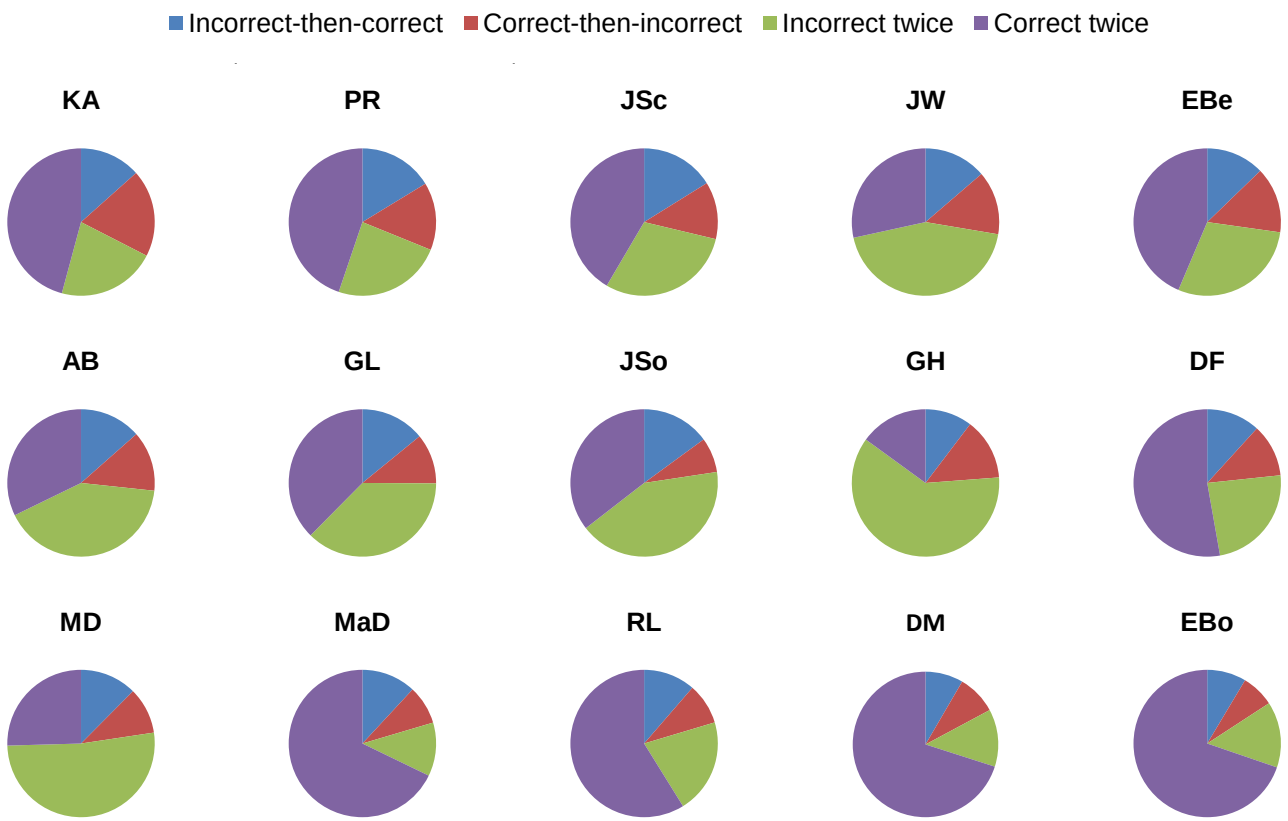


Figure 5.1: Pie charts showing the proportion of incorrect-then-correct, correct-then-incorrect, incorrect twice and correct twice items for each participant, ordered by degree of naming response inconsistency (from highest to lowest).

Demographic and Behavioural Variables

To investigate the relationship between severity of naming impairment and degree of naming response inconsistency, BNT score was correlated with naming response inconsistency for each participant (Figure 5.2). A Spearman's rho signed ranked test indicated that there was a weak, non-significant negative correlation between BNT score and naming response inconsistency (rs=-0.396, p=0.144).

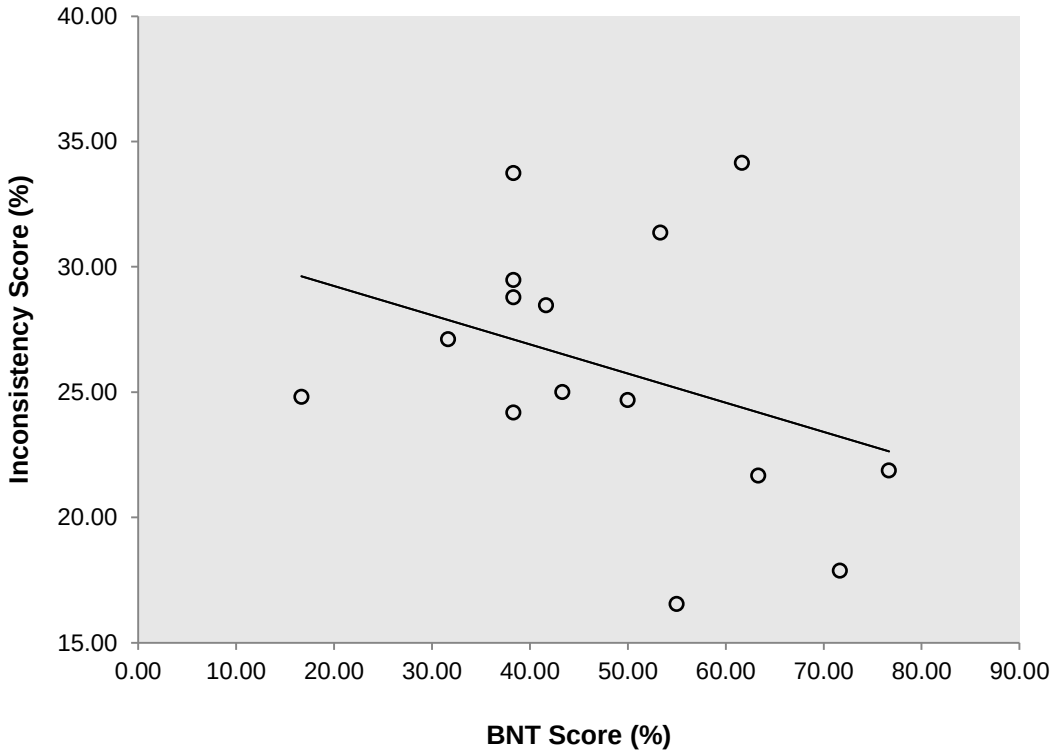


Figure 5.2: Scatterplot to show the relationship between BNT score and naming response inconsistency score.

Spearman's rho signed ranked tests also showed a non-significant correlation between lesion volume and naming response inconsistency (rs=0.100, p=0.723), although there was a significant negative correlation between lesion volume and BNT score (rs=-0.598, p<0.05). Patients with larger lesions tended to have lower BNT scores, indicating more severe naming deficits. There were no significant correlations between any patient demographic characteristics and naming response inconsistency (age in years: rs=0.270, p=0.331, years

of education: rs=0.029, p=0.918), months post-onset: rs=-0.157, p=0.576). There were also no observed trends in naming response inconsistency according to BDAE classification, with both the most (KA) and least (EBo) inconsistent participants classified as having anomic aphasia.

Further Spearman's rho signed ranked tests were used to investigate potential relationships between naming response inconsistency and scores on the remaining subtests included in the behavioural assessment battery. None of these correlations were significant: 64 item naming (rs=-0.310, p=0.260), non-word minimal pairs (rs=0.181, p=0.518). word minimal pairs (rs=-0.106, p=0.708), immediate non-word repetition (rs=0.030, p=0.914), delayed non-word repetition (rs=0.233, p=0.402), immediate word repetition (rs=0.098, p=0.727), delayed word repetition (rs=0.216, p=0.439), SWPM (rs=0.138, p=0.623), WWPM (rs=0.232, p=0.405), spoken sentence comprehension (rs=0.367, p=0.179), synonym judgement (rs=-0.340, p=0.215), Camel and Cactus written test (rs=-0.304, p=0.270), forward digit span (rs=0.471, p=0.076), backward digit span (rs=-0.051, p=0.857), Brixton Spatial Anticipation Test (rs=-0.183, p=0.514), and Raven's Coloured Progressive Matrices (rs=-0.326, p=0.221).

Practice Effects

To investigate whether inconsistent patterns of naming responses could be attributed to the effects of repeated naming practice, a series of one-tailed McNemar tests were carried out to compare the number of items each participant named incorrectly then correctly with the number they named correctly then incorrectly. There were no significant differences in the number of incorrect-then-correct items and correct-then-incorrect items for 10 participants, indicating no practice effects: AB (χ^2=0.870, p =0.176), DF (χ^2=0.490, p=0.242), DM (χ^2=0.014, p=0.453), EBe (χ^2=0.009, p=0.463), EBo (χ^2=0.955, p=0.164), GH (χ^2=0.364, p=0.273), JW (χ^2=0.547, p=0.230), KA (χ^2=1.036, p=0.155), MD (χ^2=2.639, p=0.052) and RL (χ^2=2.557, p=0.055), although the difference approached significance for the latter two participants. The remaining five participants named significantly more incorrect-then-correct

items than correct-then-incorrect items, indicating potential practice effects: GL (χ^2=4.440, p<0.05), JSc (χ^2=6.173, p<0.01), JSo (χ^2=15.842 p<0.001), MaD (χ^2=4.494, p<0.05), and PR (χ^2=2.920, p<0.05). Due to the significant differences observed for some participants, items named correctly once in the first or the second sessions were considered separately for all participants for the purposes of further analysis rather than combining items named inconsistently in either session.

A binomial logistic regression was performed to further investigate whether the degree of naming response inconsistency influenced the likelihood of a participant exhibiting any evidence of repetition priming effects. The logistic regression model was not significant (χ^2=1.032, p=0.310). The model explained 9% of the variance in categorising individuals as showing evidence of repetition priming effects or not.

Psycholinguistic Variables

Group Level

The percentages of participants who named each item incorrect-then-correct, correct-then-incorrect, incorrect twice or correct twice were calculated, adjusted for the number of participants who attempted to name each item twice. The mean (SD) percentage of participants with any item incorrect-then-correct was 14.6% (9.6%), correct-then-incorrect 11.5% (8.0%), incorrect twice 30.3% (21.1%), and correct twice 43.8% (22.0%). Spearman's rho signed ranked tests were used to investigate whether the percentages of participants who named each item in/consistently were related to the psycholinguistic properties of the item. The results of these correlations are shown in Table 5.5.

Table 5.5: Correlations between the percentage of participants with each pattern of naming response on each item and item psycholinguistic properties.

Response pattern / Psycholinguistic property	Incorrect-then-correct	Correct-then-incorrect	Incorrect twice	Correct twice
Phonemes	0.002	0.096	0.446**	-0.462**
Syllables	0.033	0.073	0.396**	-0.423**
Frequency	-0.062	-0.129*	-0.513**	0.549**
Name	0.001	0.089	0.453**	-0.456**
AoA	0.046	0.074	0.470**	-0.473**
PND	-0.038	-0.137**	-0.419**	0.442**

* = $p<0.05$ ** = $p<0.01$

There were highly significant correlations between all six psycholinguistic variables and the percentage of participants naming an item consistently correctly or consistently incorrectly across the two assessment sessions. Incorrect twice items tended to be those that were long, infrequent, typically acquired late, with low name agreement and small phonological neighbourhood density. The reverse pattern was observed for the correct twice items. With regards to inconsistent naming, only frequency and phonological neighbourhood density correlated significantly with the percentage of participants with correct-then-incorrect items. The lower the frequency or phonological neighbourhood density of an item, the higher the percentage of participants who named it correct-then-incorrect. No similar relationships were observed between the percentage of participants with incorrect-then-correct items and any of the psycholinguistic properties.

Four multiple regressions were performed to examine whether any of the psycholinguistic variables could predict a significant proportion of the variance in the percentage of participants producing a particular naming response. Phonemes, frequency, name agreement, AoA and PND were entered into each regression. All of the psycholinguistic variables were (naturally) intercorrelated (Table 5.3). Due to the interaction between

number of phonemes and length in syllables, length in syllables was excluded from the regression analyses. In order to determine with some degree of clarity which, if any, of the five remaining variables uniquely predicted naming performance, unique sums of squares were used. This method does mean that shared variance was discarded, but using sequential sums of squares would have required unsupported assumptions to be made regarding the relative priority of all predictors.

As per Figure 5.2, there was no evidence of a nonlinear relationship between severity of naming impairment and degree of naming response inconsistency. Visual inspection of scatterplots between each of the predictors and rates of consistent/inconsistent responses also showed no evidence of nonlinear relationships, and a comparison of relationships assessed via Spearman's and Pearson's tests did not show differing patterns of significance. Consequently, linear regression was adopted. A key aim of the regression analyses was to investigate differing patterns of significance of the predictors for each naming response pattern. Carrying out individual regressions for each of the four naming response patterns was considered the most straightforward way to achieve this aim.

For incorrect-then-correct responses, the regression model was not significant ($F(5,359)=0.765$, $p=0.575$). None of the independent variables predicted the percentage of participants naming an item incorrectly then correctly (phonemes: $\beta=-0.056$, $p=0.506$, frequency $\beta=-0.068$, $p=0.285$, name agreement: $\beta=-0.007$, $p=0.902$, AoA: $\beta=0.064$, $p=0.288$, PND: $\beta=-0.024$, $p=0.775$). For correct-then-incorrect responses, the regression model was significant ($F(5,359)=2.419$, $p=0.036$), although none of the variables independently predicted the percentage of participants naming an item correctly then incorrectly (phonemes: $\beta= -0.062$, $p=0.456$, frequency: $\beta=-0.090$, $p=0.155$, name agreement: $\beta=0.045$, $p=0.406$, AoA: $\beta=0.017$, $p=0.771$, PND $\beta=-0.146$, $p=0.076$).

For the incorrect twice responses, the regression model was highly significant ($F(5,359)=58.071$, $p<0.001$). Four variables predicted 44% of the variance in the percentage of participants naming an item incorrectly on both attempts (phonemes: $\beta=0.292$, $p<0.001$,

frequency: β=-0.253, p<0.001, name agreement: β=-0.307, p<0.001, AoA: β=0.187, p<0.001). PND was not a significant predictor (β=0.059, p=0.343). For the correct twice responses, the regression model was also highly significant (F(5,359)=69.22, p<0.001). Four independent variables predicted 48% of the variance in the percentage of participants naming an item correctly on both attempts (phonemes: β=-0.222, p<0.001, frequency: β=0.296, p<0.001, name agreement: β=-0.296 p<0.001, AoA: β=-0.208, p<0.001), but PND was again not a significant predictor (β=0.012, p=0.837).

Individual Level

A series of binomial logistic regressions were performed for each individual participant to determine the percentage of variance in their production of a particular response pattern explained by each of the six psycholingustic variables. For the items named inconsistently, these percentages are shown in Figures 5.3 (incorrect-then-correct) and 5.4 (correct-then-incorrect).

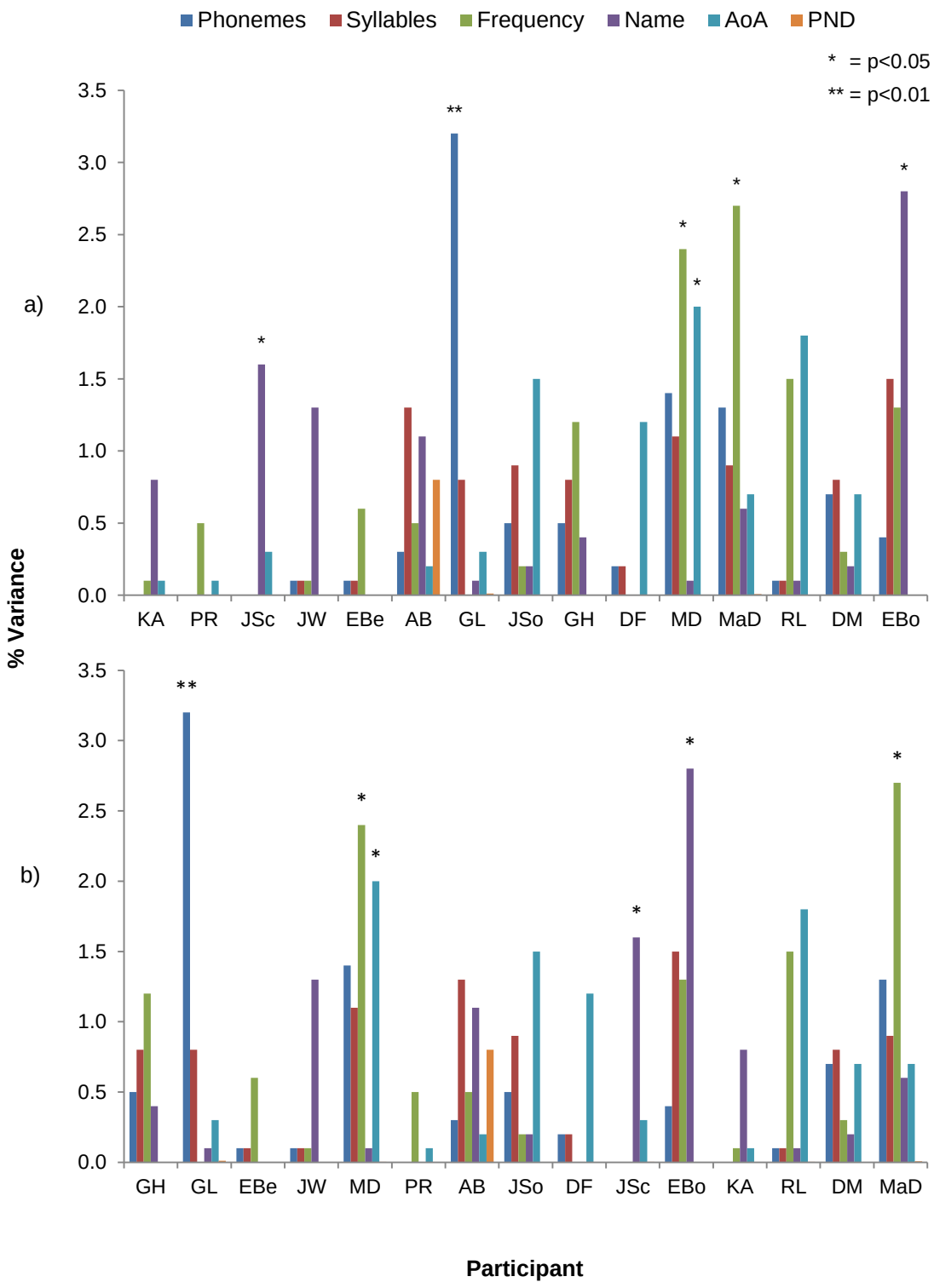


*Figure 5.3: Percentage of variance in **incorrect-then-correct** response pattern explained by each psycholinguistic variable, for each participant. Results are shown ordered a) by naming response inconsistency (greatest degree of inconsistency first) and b) by BNT score (greatest severity of naming impairment first).*

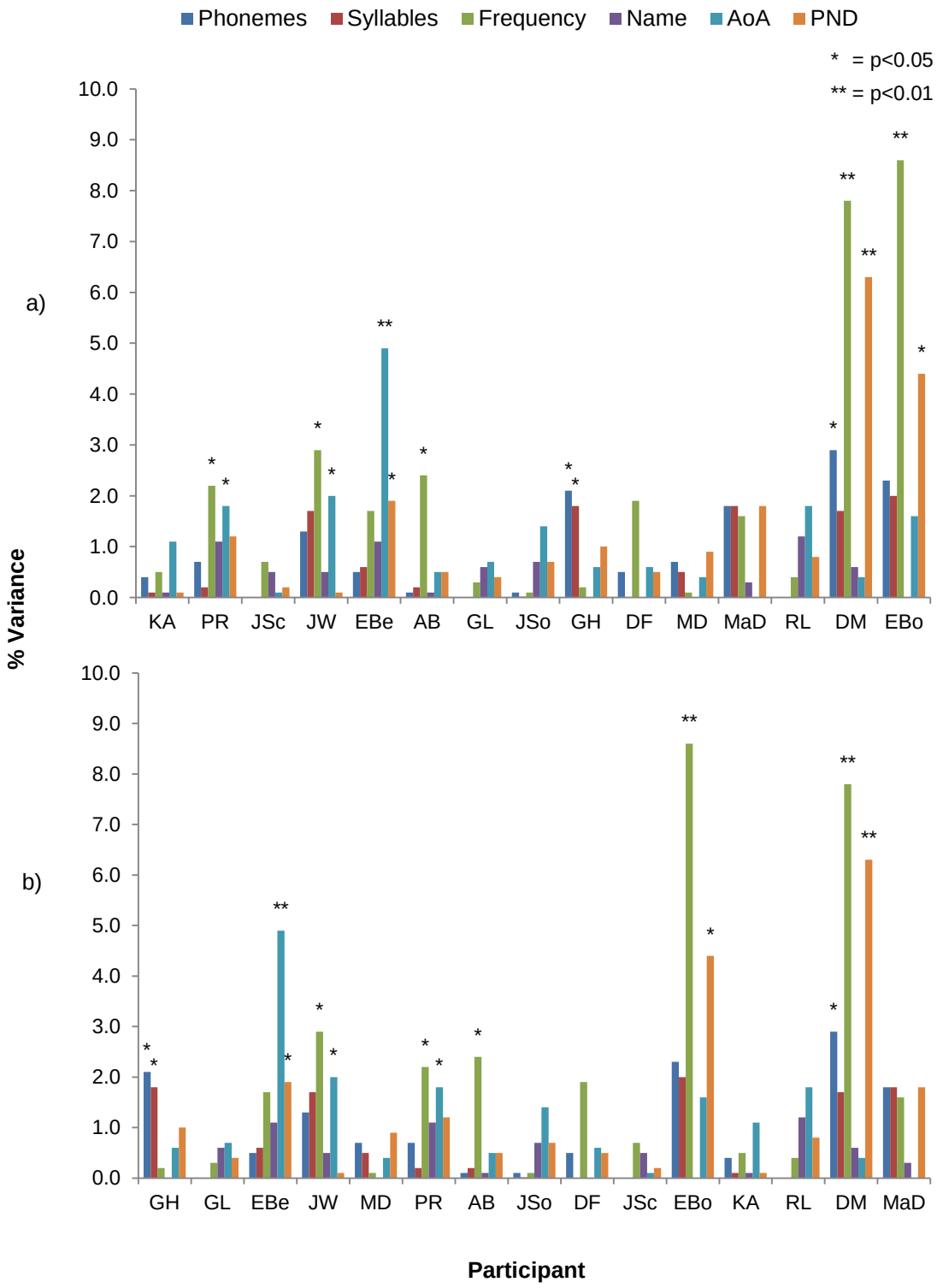


*Figure 5.4: Percentage of variance in **correct-then-incorrect** response pattern explained by each psycholinguistic variable, for each participant. Results are shown ordered a) by naming response inconsistency (greatest degree of inconsistency first) and b) by BNT score (greatest severity of naming impairment first).*

Figure 5.3 shows that four psycholinguistic variables explained small, but significant, percentages of the variance in naming an item incorrect-then-correct for 5/15 participants: length in phonemes (GL: χ^2=7.560, R^2=0.032, p<0.01), frequency (MaD: χ^2=5.568, R^2=0.027, p<0.05; MD: χ^2=4.893, R^2=0.024, p<0.05), name agreement (EBo: χ^2=5.364, R^2=0.028, p<0.05; JSc: χ^2=4.168, R^2=0.041, p<0.05), and AoA (MD: χ^2=4.458, R^2=0.024, p<0.05). There were no obvious trends in the extent to which psycholinguistic variables were able to explain variance in naming an item incorrectly then correctly when participants were ranked by either degree of inconsistency (Figure 5.2a), or severity of naming impairment (Figure 5.2b).

Figure 5.4 shows that five of the six psycholinguistic variables explained small, but significant, percentages of the variance in naming an item correct-then-incorrect for 7/15 participants: length in phonemes (DM: χ^2=-5.269, R^2=0.029, p<0.05; GH: χ^2=4.552, R^2=0.021, p<0.05), number of syllables (GH: χ^2=4.014, R^2=0.018, p<0.05), frequency (AB: χ^2=4.614, R^2=0.024, p<0.05; DM: χ^2=12.493, R^2=0.078, p<0.001; EBo: χ^2=12.210, R^2=0.086, p<0.001; JW: χ^2=5.917, R^2=0.029, p<0.05; PR: χ^2=4.518, R^2=0.022, p=<0.05), AoA (EBe: χ^2=11.265, R^2=0.049, p<0.01; JW: χ^2=4.315, R^2=0.020, p<0.05; PR: χ^2=4.030, R^2=0.018, p<0.05), and PND (DM: χ^2=10.962, R^2=0.063, p<0.01; EBe: χ^2=4.128, R^2=0.019, p<0.05; EBo: χ^2=6.898, R^2=0.044, p<0.05). For DM and EBo, the two most consistent participants, frequency and PND were able to explain much larger percentages of the variance in naming an item correct-then-incorrect than any of the other psycholinguistic variables, although absolute percentage values remained small (<9%). Aside from this observation, there were no trends noted with regards to the extent to which psycholinguistic variables were able to explain variance in naming an item correct-then-incorrect when participants were ranked by either degree of inconsistency (Figure 5.3a), or severity of naming impairment (Figure 5.3b). Overall, psycholinguistic variables exerted a greater influence on correct-then-incorrect items than incorrect-then-correct items, although the variables linked to inconsistent naming were not the same for the two response patterns and, for individual participants, the two response patterns were not influenced similarly by psycholinguistic properties.

For the items named consistently across both assessment sessions, the percentage of variance associated with each participant producing a particular response pattern explained by each of the psycholinguistic variables are shown in Figures 5.5 (incorrect twice) and 5.6 (correct twice).

Figures 5.5 and 5.6 show that the percentage of variance in both incorrect twice and correct twice response patterns explained by item psycholinguistic properties was generally much greater for all participants than for the inconsistent naming patterns. All six psycholinguistic variables predicted significant amounts of variance in incorrect twice naming for all participants (Figure 5.5), with the exception of name agreement for GH (χ^2=1.121, R^2=0.004, p=0.293), and PND for JSc (χ^2=3.370, R^2=0.013, p=0.072). Similarly, all six psycholinguistic variables predicted significant amounts of variance in correct twice naming for all participants (Figure 5.6), except number of phonemes for KA (χ^2=1.874, R^2=0.006, p=0.173), number of syllables for GL (χ^2=2.632, R^2=0.009, p=0.109) and KA (χ^2=1.802, R^2=0.006, p=0.182), frequency for JSc (χ^2=2.940, R^2=0.011, p=0.088), name agreement for JSc (χ^2=0.613, R^2=0.002, p=0.433), and PND for GL (χ^2=3.564, R^2=0.013, p=0.059), JSc (χ^2=3.764, R^2=0.013, p=0.053) and KA (χ^2=1.851, R^2=0.006, p=0.174).

These results indicate that consistent correct naming for two of the three most inconsistent participants (KA and JSc) was influenced by specific psycholinguistic variables to a lesser extent than for the other participants. However, there were no further apparent trends with regards to the extent to which psycholinguistic variables were able to explain variance in naming an item either incorrect twice or correct twice when participants were ranked by either degree of inconsistency (Figures 5.5a and 5.6a), or severity of naming impairment (Figures 5.5a and 5.6b). At the individual level, the influence of the different psycholinguistic variables on participants' incorrect twice naming tended to follow a similar pattern to the influence of the variables on their correct twice naming.

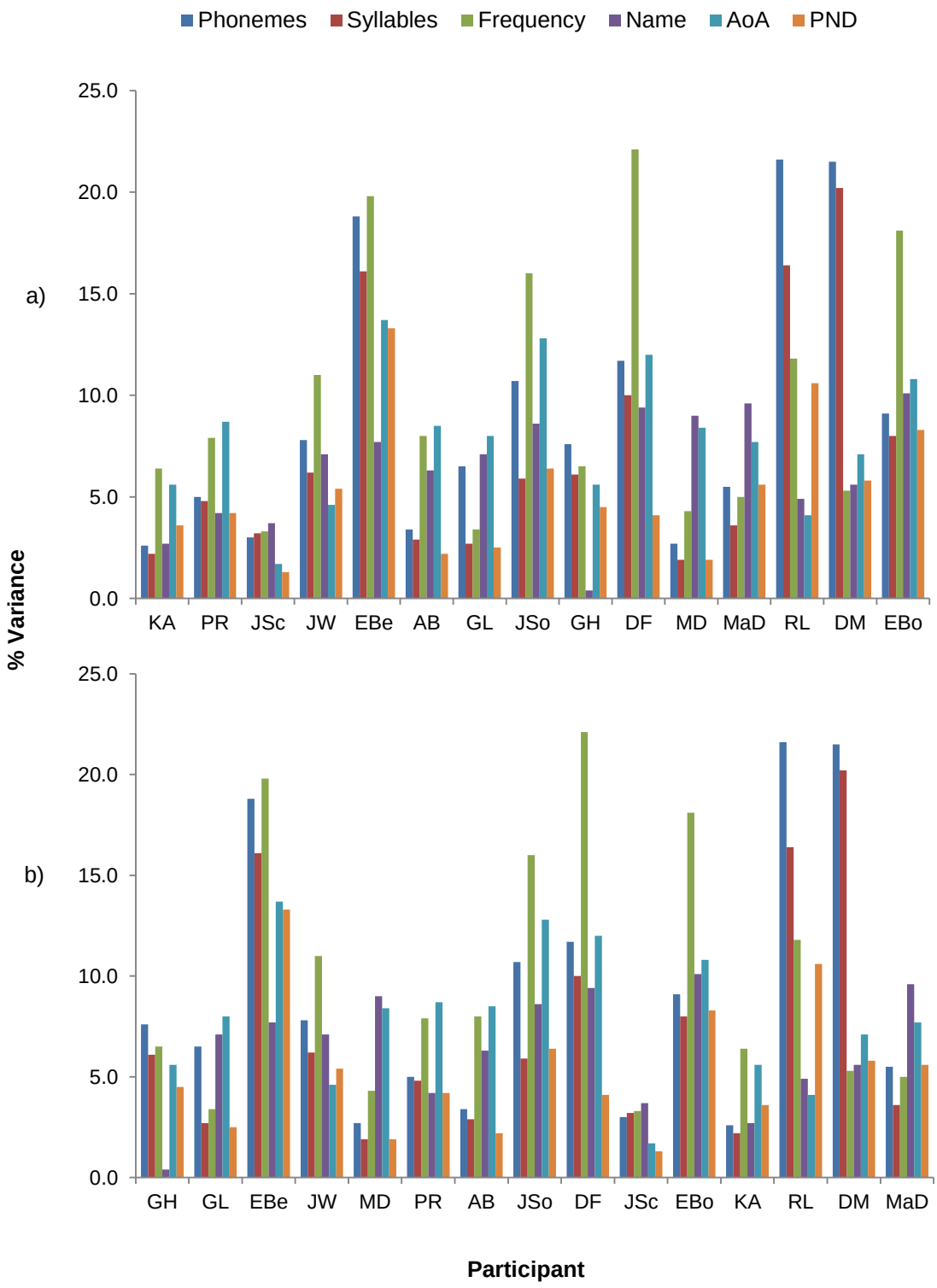


*Figure 5.5: Percentage of variance in **incorrect twice** response pattern explained by each psycholinguistic variable, for each participant. Results are shown ordered a) by naming response inconsistency (greatest degree of inconsistency first) and b) by BNT score (greatest severity of naming impairment first).*

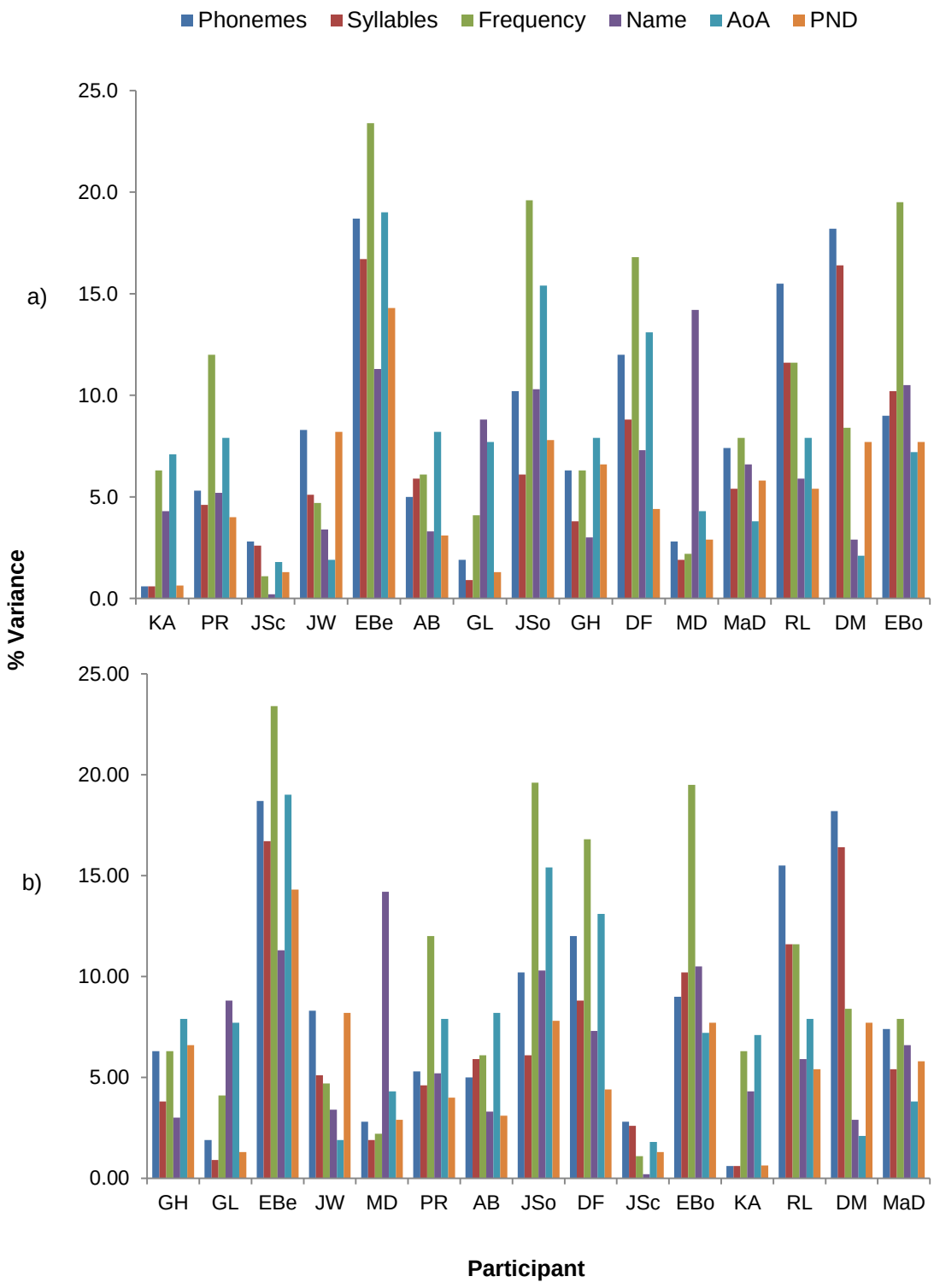


*Figure 5.6: Percentage of variance in **correct twice** response pattern explained by each psycholinguistic variable, for each participant. Results are shown ordered a) by naming response inconsistency (greatest degree of inconsistency first) and b) by BNT score (greatest severity of naming impairment first).*

Discussion

The purpose of the current study was to describe patterns of picture naming response inconsistency in a diverse group of 15 stroke survivors with chronic anomia, and to use a range of demographic, behavioural and psycholinguistic data to investigate potential reasons why some individuals may be more inconsistent than others. We began by examining the extent of naming response inconsistency for each participant. Our results showed that, when asked to name a large number of object pictures twice, all participants demonstrated substantial inconsistency in their naming responses, although there was considerable individual variation. The most inconsistent participant (KA) named over a third of items (34.15%) correctly on one attempt and incorrectly on another, whilst the most consistent individual (EBo) failed to name almost a sixth of items (16.54%) consistently correctly or incorrectly across the two trials. These findings are congruent with previous studies in which people with aphasia have displayed varying levels of inconsistent naming performance across multiple trials (Freed et al., 1996; Laiacona et al., 1996).

However, it is still unclear why individual participants were particularly consistent or inconsistent relative to others. There were no significant relationships found between degree of inconsistency and age, years of education, time post-onset, lesion volume, or scores on any of the wide-ranging speech, language or cognitive tests, ruling these factors out in explaining why some participants were more consistent than others. Interestingly, naming response inconsistency was also unrelated to overall severity of naming impairment, as measured by the BNT, although this finding may not be entirely unexpected. Whilst some form of relationship between naming response inconsistency and degree of anomia may be anticipated, it is unclear what this relationship may be. It could be suggested that those with less severe anomia may be more consistent, given that these individuals have less overall difficulty with lexical access and phoneme production than those with greater naming impairments (e.g. Dell et al., 1997). Conversely, it could be expected that those with greater naming impairments may be more consistent if they have access to fewer correct lexical items. This lack of explanatory relationship between severity of impairment and other

demographic and cognitive factors suggests that successful one off retrieval may rely on different processes to successful, consistent, repeated retrieval.

One potential explanation that has been posited to explain why some people with aphasia may produce inconsistent naming responses is repetition priming, or practice effects. In support of Nickels (2002a), five participants (GL, JSc, JSo, MaD, PR) did indeed name significantly more items correctly only on the second attempt (incorrect-then-correct) compared to items correctly produced only on the first attempt (correct-then-incorrect), indicating that, for these patients, greater exposure to the stimulus images increased the likelihood that they would be named correctly. However, importantly, the remaining 10 participants were equally likely to name items correctly followed by incorrectly as incorrectly followed by correctly. For example, DM and EBe, two patients with highly dissimilar naming response inconsistency scores (DM = 17.87% vs. EBe = 28.78%), each named almost identical numbers of items correctly only on the first presentation as only on the second presentation. Furthermore, KA named more items correctly only on his first attempt (76 items) than his second (63 items). These findings confirm that repetition priming cannot account for inconsistency in oral picture naming for the majority of participants in the current study. The finding that degree of response inconsistency did not predict the likelihood of an individual displaying practice effects further suggests that the two variables are not directly linked. There are no discernible demographic or linguistic similarities between the five patients who demonstrated evidence of repetition priming, meaning that it is not possible at this time to predict which individuals will be susceptible to the benefits of repeated naming practice.

A further intrinsic factor that has not yet been considered, but which may lead to increased naming response inconsistency for some patients, is apraxia of speech. Individuals with this disorder display 'groping' articulatory gestures when attempting to produce particular phonemes, plus characteristic naming errors that increase with word length, such as perseverations and lengthened and distorted phonemes, especially consonants (Ballard, Granier, & Robin, 2000; McNeil, Weismer, Adams, & Mulligan, 1997). They also tend to

make inconsistent errors across multiple productions (Ballard et al., 2000). Apraxia of speech commonly co-occurs with non-fluent aphasia rather than as a stand-alone, primary speech production deficit (Fridriksson, Hubbard, et al., 2012). Although apraxia was not formally assessed in the current study, the lead author (a qualified speech and language therapist) used clinical judgement to exclude potential participants with moderate to severe apraxia. Of the included individuals, three were deemed to have mild apraxia: JSc, JW and PR. These participants' naming response inconsistency scores (JSc: 31.36%, JW: 29.47%, PR: 33.74%) were above average (mean = 25.98%). However, the most inconsistent participant (KA) did not have apraxia. Therefore, apraxia cannot be the only reason why some participants in the present study were more inconsistent than others.

In order to elucidate which psycholinguistic factors may be linked to naming response inconsistency, the psycholinguistic properties of the 408 items included in the present study were examined. With regards to consistent performance (i.e. incorrect twice or correct twice), the group level analyses identified significant relationships between the percentage of participants naming items consistently and all six included psycholinguistic variables (length in syllables, number of phonemes, frequency, name agreement, PND and AoA). A greater number of participants named items that had fewer phonemes and syllables, a lower age of acquisition, and higher frequency, name agreement and phonological neighbourhood density correctly during both testing sessions. Correspondingly, a larger proportion of participants named items incorrectly on both naming attempts if these items had a greater number of phonemes and syllables, a higher age of acquisition, and lower frequency, name agreement and phonological neighbourhood density. These findings were supported by individual level analyses, with all psycholinguistic variables significantly linked to incorrect twice and correct twice naming for the majority of participants. These results are in keeping with previous research highlighting the importance of psycholinguistic variables for accurate picture naming in many people with aphasia (Cuetos et al., 2002; Kittredge et al., 2008; Laiacona et al., 2001; Middleton & Schwartz, 2010; Nickels & Howard, 1995, 2004). As also noted in previous studies is the current finding of individual differences in the extent to which psycholinguistic properties predicted consistent correct, or incorrect, naming. For example,

correct twice naming was influenced to a lesser degree by psycholinguistic properties for GL, JSc and KA than the remaining participants' naming, although these three patients do not appear to share any common demographic or language features. It is therefore not apparent why psycholinguistic variables had a reduced effect on consistently correct picture naming in these particular individuals.

With respect to items named inconsistently (incorrect-then-correct or correct-then-incorrect), interestingly, a much weaker relationship was found between psycholinguistic properties and inconsistent naming than between the same properties and consistent naming, at both group and individual levels. At the group level, two variables (frequency and PND) were independently correlated with the percentage of participants first naming items correctly followed by incorrectly, with patients more likely to show this pattern of naming response for items with lower frequency and/or lower PND. Taking number of phonemes, frequency, name agreement, AoA and PND into account, the regression model was also significant in predicting the percentage of participants first naming items correctly followed by incorrectly. In contrast, none of the psycholinguistic variables were linked to incorrect followed by correct naming. At the individual level, psycholinguistic variables again exerted a greater influence on correct-then-incorrect naming compared to incorrect-then-correct naming, with individual participants differentially affected. Specifically, correct-then-incorrect naming of seven participants (AB, DM, EBe, EBo, GH, JW and PR) was significantly influenced by either length in phonemes, number of syllables, frequency, AoA and PND, or a combination of these five variables, whilst incorrect then correct naming of only five participants (EBo, GL, MaD, MD and JSc) was significantly influenced by length in phonemes, frequency, name agreement and/or AoA. Thus, the relationship between psycholinguistic variables and inconsistent responding is not a straightforward one, and common factors that may be anticipated to influence naming success, such as length and frequency, may not exert a predictive influence on inconsistent naming.

As mentioned previously, practice effects may explain, in part at least, some participants' tendency to produce incorrect followed by correct responses. Consequently, it is possible

that there may be less of a role for psycholinguistic variables to account for this production pattern than for correct-then-incorrect naming. However, incorrect-then-correct naming of 3/5 individuals who exhibited practice effects was also influenced by psycholinguistic variables (GL, JSc and MaD), making this hypothesis unlikely. There were no trends for incorrect-then-correct naming of more or less inconsistent individuals, or those with particular demographic characteristics or language profiles, to be influenced in particular ways by psycholinguistic properties. With regards to correct-then-incorrect naming, psycholinguistic variables explained a greater total percentage of the variance in this response pattern for the two most consistent participants (DM and EBo) than for the remaining patients. This finding suggests that item properties may play a lesser role in incorrect followed by correct naming for more inconsistent participants than for more consistent individuals, although it is not clear why this should be the case.

Overall, our results indicate that, although psycholinguistic properties play an important role in consistent naming, such properties cannot adequately explain naming response inconsistency. In the present study, psycholinguistic variables linked to correct-then-incorrect naming differed from those linked to incorrect-then-correct naming, and, for individual participants, the two response patterns were not affected in the same way by psycholinguistic variables. These results suggest that the reasons why individuals name items correctly only on a first attempt may differ from the reasons they name items correctly only on a second attempt. This is an issue for further investigation in future studies.

Conclusions

The current study aimed to describe observed patterns of response inconsistency in a group of 15 stroke survivors with chronic anomia. In achieving this aim, we showed that all patients failed to name a number of the same pictures correctly across both trials, confirming that confrontation object naming in this population is often inconsistent. Our results also highlight between-participant variation in degree of naming inconsistency, both in terms of the overall degree of inconsistency and the number of items correctly named on either the

first or second attempt. These findings are clinically important as they imply that reported therapy gains may be over- or under-estimated if inherent inconsistency across repeated naming attempts is not considered. In the present study, patients named an average of 25.98% of items inconsistently across two trials, suggesting that an apparent mean pre- to post-therapy gain of 25.98% in this group may potentially be unconnected to the provided intervention. In contrast, a small and apparently non-significant therapy effect may in fact reflect a large improvement in an individual who typically names fewer items correctly on a second than first naming attempt if no treatment is given. To accurately identify true therapy gains, it is essential to understand how particular patients naturally tend to name items presented to them on multiple occasions. Knowing which items individuals consistently and inconsistently name incorrectly may also help to inform personalised item selection and/or therapy methods. Consequently, it may be prudent to complete at least two baseline naming assessments with each patient prior to commencing therapy.

Whilst item inconsistency was found across the range of participants examined in the current study, we cannot yet fully explain why certain individuals are more inconsistent than others. For the five participants who named an increased number of items correctly on the second attempt relative to the first, repetition priming may provide an incomplete account. Mild apraxia of speech may also be partly responsible for inconsistent naming in three patients, two of whom also showed practice effects. In contrast, psycholinguistic properties appear to play a far greater role in consistent rather than inconsistent naming for all of the participants in the present study. There is a clear need for future studies to investigate additional factors in order to clarify why some stroke survivors with chronic aphasia are more inconsistent than others, and elucidate the underlying reasons why individuals name particular items correctly-then-incorrectly or incorrectly-then-correctly. A potential next step may be to use a voxel-based lesion symptom mapping approach in an attempt to identify the specific components of the language network damaged in patients with highly inconsistent or consistent oral picture naming. Alternatively, future studies could include fine-grained analysis of error types across trials to determine whether there are differences between the patterns of

paraphasias produced by the most, and least, inconsistent individuals, or explore the relative contributions of mood, motivation or attention to degree of inconsistency.

Chapter 6

Rethinking Repetition in the Presence of a Picture: Exploring the Relative Importance of Visual Speech Articulation in Repetition Therapy for Chronic Post-Stroke Anomia

Abstract

Repetition of auditory speech in the presence of a picture (RIPP) is a popular behavioural speech and language treatment for post-stroke anomia. Nevertheless, research indicates that therapeutic gains may be enhanced by the inclusion of a visual speech articulation component. In the current case series, six individuals with chronic anomia (three non-fluent and three fluent) received three different types of therapy: repetition in the presence of a picture and articulation (RIPPA), repetition in the presence of articulation but no picture (ARTIC), and RIPP. Five participants demonstrated significant increases in treated item naming accuracy following at least one type of therapy and did not respond to at least one further type of therapy. RIPPA resulted in the greatest gains for three participants and ARTIC resulted in the greatest gains for the remaining two responders, highlighting the importance of a speech articulation input component for optimising repetition therapy success. In contrast, only two individuals (both with fluent aphasia) required the presence of a picture to realise significant therapy gains, and, for two non-fluent individuals, providing semantic, auditory and articulatory cues was detrimental to naming performance. Exploratory lesion analysis work revealed that different left hemisphere regions appeared to mediate the effects of each type of therapy (RIPPA: premotor cortex (BA6); RIPP: inferior temporal and fusiform gyri; ARTIC: medial anterior insula), although neuroimaging findings are limited by the small sample size. The final participant had conduction aphasia following a lesion involving the arcuate and longitudinal fasciculi, and failed to respond to any of the three types of therapy. The results have important clinical implications for maximising treatment success when providing repetition therapy to individuals with chronic post-stroke anomia.

Introduction

The most common and persistent symptom of post-stroke aphasia is anomia, or word finding difficulty (Pedersen et al., 2004; Postman-Caucheteux et al., 2010). Anomia is frustrating for people with aphasia and may adversely affect all aspects of their daily life, including relationships with their communication partners (e.g. Davidson et al., 2008; Hilari et al., 2015). Correspondingly, improving word finding is a frequent aim of behavioural speech and language therapy for stroke survivors. Impairment-based anomia therapy techniques focus on helping patients to 're-learn' words they have difficulty naming. A popular method is repetition in the presence of a picture (RIPP), which involves presenting the individual with a picture of an item along with its verbal name, and asking him/her to repeat the name back (Nickels, 2002b). RIPP can significantly improve noun picture naming of treated items in people with chronic anomia (e.g. Mason et al., 2011; Morris et al., 2014; Nickels, 2002b), and has a number of additional advantages in the clinical setting. Firstly, it requires no specialist materials, making it a straightforward technique for therapists to administer. Secondly, for some patients with expressive language difficulties, providing the full item name for immediate repetition is less linguistically demanding than tasks requiring more independent recall, such as confrontation picture naming. As a result, RIPP may be associated with fewer production errors than alternative treatments, and subsequently prove more enjoyable and rewarding for patients (Conroy, Sage, & Lambon Ralph, 2009a; Fillingham, Hodgson, Sage, & Lambon Ralph, 2003; Fillingham, Sage, & Lambon Ralph, 2006).

Current theoretical models of language production propose that successful word retrieval relies on multiple, interrelated sub-tasks, involving processing at semantic and phonological levels (Dell & O'Seaghdha, 1992; Indefrey, 2011; Levelt et al., 1999). According to these models, when asked to name an object, individuals must activate the stored conceptual representation of the item within the semantic system, select its lexical name, retrieve its phonological form, then create a motor sequence ready for articulation. Ease of word retrieval relies on the strength of links between the semantic and phonological systems.

Models differ in whether processes are considered to occur concurrently or sequentially, however, all explain anomia as the result of incorrect or incomplete activation of semantic and/or phonological information (Dell et al., 1997; Indefrey, 2011; Schwartz et al., 2004). Analysing the types of naming errors made by individuals with aphasia may highlight the faulty process/es responsible for their underlying naming deficits and consequently guide therapy (Abel, Weiller, Huber, & Willmes, 2014; Best & Nickels, 2000; Howard & Gatehouse, 2006; Kiran & Bassetto, 2008; Maher & Raymer, 2004; Nickels, 2002b). In line with Hebbian learning theory (Hebb, 1949), RIPP aims to alleviate word finding difficulties in patients with a range of apparent deficits by strengthening mappings between phonological and semantic representations when both are active at the same time (Howard, 2000). The picture of the item to be named is thought to provide a semantic cue, whilst repetition targets phonology.

The extensive neural network believed to underpin word production in healthy individuals has been conceptualised by the dual stream framework offered by Hickok and Poeppel (2004, 2007). Two distinct pathways are said to link language-related regions: the dorsal stream and the ventral stream. The left-dominant dorsal stream extends anteriorly via the arcuate fasciculus from area Spt within the Sylvian fissure at the parieto-temporal boundary, to the posterior inferior frontal gyrus (IFG, incorporating Broca's area), anterior insula and premotor cortex. The dorsal stream is responsible for mapping sensory input and phonological information onto the articulatory network. In contrast, semantic processing relies more heavily on the ventral stream, which encompasses bilateral structures in the temporal lobes, including the middle temporal gyrus and the inferior temporal sulcus (ITS). The dorsal and ventral pathways are both linked to additional cortical regions, including the left superior temporal gyrus (STG) and superior temporal sulcus (STS). In support of the dual stream model, imaging studies have revealed recruitment of the left STG, IFG (in particular, pars opercularis, BA44, and pars triangularis, BA45), and premotor cortex (BA6) during phonological tasks such as non-word repetition. Conversely, increased activation in the left MTG, inferior temporal gyrus (ITG) and bilateral temporal poles has been noted during semantic speech comprehension tasks (Price, 2010, 2012; Saur et al., 2008). In stroke survivors with chronic aphasia, lesion mapping techniques have localised

phonological deficits to damage to dorsal stream structures (including the left insula and arcuate fasciculus), as well as the left mid to posterior MTG and STG, and semantic difficulties to lesions affecting ventral stream regions in the left anterior temporal lobe (MTG, ITG and fusiform gyrus) (Butler et al., 2014; Halai et al., 2017).

To explore how RIPP influences activity in brain regions involved in phonological and semantic processing, Heath and colleagues (2012) asked 21 healthy older adults to repeat the names of 20 noun pictures presented with their auditory names (long-term facilitated items) a total of six times across two treatment sessions. Two days later, participants were asked the name the same pictures whilst undergoing fMRI. During the fMRI phase, a further 20 untreated items were provided for naming, and an additional 20 noun pictures were presented once with their auditory names for immediate repetition and then alone for naming (short-term facilitated items). Results showed that naming accuracy was greatest and reaction time fastest for short-term facilitated items, followed by long-term facilitated items, then untreated items. These results indicate that RIPP was effective in enhancing confrontation naming, both immediately and in the longer term, and that different neurological mechanisms were involved in immediate and longer term facilitation of picture naming. The group level analysis revealed that naming of long-term items was associated with lesser activity in the left posterior STG and left MTG relative to naming of short-term facilitation items. The authors propose that this pattern of results is best explained by so-called 'repetition suppression' in regions associated with phonological and semantic processing, with decreased activity in these areas in the days following RIPP said to reflect greater processing efficiency due to strengthening of the links between phonology and semantics.

Heath et al.'s (2012) findings reveal how RIPP may modulate brain activity in healthy controls, resulting in enhanced noun picture naming. However, stroke survivors with anomia have damage to structures within the language network, meaning that successful RIPP-based therapy for these individuals may involve alternative brain regions to those found in non-brain damaged adults. To investigate this possibility, Heath et al. (2013) carried out a

similar treatment protocol as in their previous study with six individuals with chronic post-stroke anomia. For the people with aphasia, each item set (short-term facilitated, long-term facilitated, and untreated) contained 25 items, with the 50 treated nouns selected from a pool of items consistently named incorrectly during pre-treatment testing. Following RIPP treatment, all participants demonstrated significant gains in naming accuracy for both short- and long-term facilitated items, again demonstrating the effectiveness of RIPP as a therapy method. Moreover, treatment gains remained significant at a further follow-up session one week after the fMRI phase. There were no significant changes in naming untreated items. Imaging data showed that the brain regions involved in successful naming did not mirror those found in healthy participants, and there was considerable individual variation. For the stroke survivors, post-treatment naming was associated with a range of regions in the left hemisphere language network and homologous areas in the undamaged right. For example, one participant (P02) had greater activation in the left ITG left pars triangularis, right MTG pole and right pars orbitalis when naming short- than long-term facilitated items, whilst another (P05) showed activation only in the right MTG, angular gyrus and pars opercularis for the same contrast. Consequently, although Heath et al.'s (2013) study supports the use of RIPP to enhance word finding in people with chronic post-stroke anomia, the neural correlates of short- and long-term language relearning remain unclear.

A potential explanation for observed differences in activation patterns for the same contrasts between patients in Heath et al.'s (2013) study is that their lesions did not affect the same areas of the normal language network. Re-activation of left lateralised language areas is typically linked to more favourable language outcomes in the chronic stage post-stroke (Bonilha et al., 2016; Fridriksson, 2010; Saur et al., 2005; Szaflarski et al., 2013). However, particularly for individuals with extensive left hemisphere lesions, such re-activation may not always be possible, making recruitment of right homologous regions necessary in order to regain a degree of language functioning (Heiss & Thiel, 2006; Turkeltaub et al., 2011). Relative to healthy participants, all six patients showed activation changes in right hemisphere homologous areas or a combination of these and spared left hemisphere

language related regions, indicating varying patterns of neural reorganisation in the stroke survivors.

Nardo and colleagues (2017) also revealed neural activation changes in the left and right hemispheres linked to RIPP treatment in a group of 18 individuals with chronic stroke-induced anomia, who were scanned before and after they completed an six-week intensive home-based intervention programme. Patients repeated noun picture names presented alongside three different forms of auditory cues: whole words (RIPP), initial phonemes and final phonemes. Behavioural results showed that, as a group, participants' naming accuracy and speed significantly increased relative to baseline following therapy, with significantly greater gains noted for treated than for untreated items, further indicating the potential therapeutic benefits of RIPP. During fMRI sessions, patients completed the same cued naming task, which included a subset of words targeted during therapy (long-term facilitated items) as well as some untreated ones (immediate facilitated items). Like Heath et al. (2013), Nardo et al. found bilateral regions implicated in both immediate and long-term facilitation of picture naming, including the right anterior insula, right IFG and left premotor cortex (BA6). Immediate naming following RIPP, but not initial or final phoneme cueing, was also associated with activity in the right angular gyrus, an area previously linked to semantic processing in individuals with extensive left hemisphere damage (Sims et al., 2016).

It is important to note that none of the patients in either Heath et al.'s (2013) or Nardo et al.'s (2017) studies named all treated items correctly following intervention, and therapeutic gains were not equal across participants. For instance, although precise figures are unavailable, in Heath et al.'s study the mean percentage of long-term facilitated items named correctly at the fMRI stage was approximately 70%, with a range of approximately 30% - 95%. Such variability in therapeutic response is to be expected when treating individuals with aphasia (e.g. Lambon Ralph et al., 2010), and has also been found in further studies providing RIPP therapy (e.g. Morris et al., 2014). Nevertheless, it may be possible to increase RIPP's effectiveness by adding a visual speech articulation component when presenting pictures and their auditory names. This suggestion is based on studies that have shown a number of

common neural regions to be involved in speech perception and speech production tasks in healthy individuals (Campbell et al., 2001; Fridriksson, Moser, et al., 2009; Fridriksson et al., 2008; Ojanen et al., 2005; Skipper et al., 2005). For instance, Fridriksson and colleagues (2008) scanned a group of 20 adults whilst they were shown pairs of silent video clips showing only the lower part of a speaker's face, who produced either speech or non-speech (such as tongue protrusion or lip biting) oral movements. As well as type of oral movements, task difficulty was manipulated by reducing the frame rate in half of the video clip pairs from 30 to three frames per second, thereby degrading the visual signal. Participants were asked to decide whether paired clips were identical or not in four conditions: standard speech, standard non-speech, degraded speech, and degraded non-speech. The authors hypothesised that blood flow would increase most in areas directly involved in visual speech perception in the degraded speech condition, as a consequence of increased processing demands. In line with expectations, the degraded speech condition was coupled with significantly greater neural activity in the left pars opercularis and inferior premotor cortex than the non-speech and standard speech conditions: two areas also implicated in speech production tasks.

One disadvantage of Fridriksson et al.'s (2008) study is that observing silent presentations of speech movements bears limited resemblance to real-life situations. Unless an individual has a hearing impairment, they frequently receive audio as well as visual information when another is speaking, and communication partners usually produce spoken words rather than just oral movements. These concerns were addressed by Skipper and colleagues (2005) presented nine university students with audio-only, AV and video-only clips of an adult speaker telling engaging stories. In the audio-only condition, participants listened to spoken stories; in the AV condition, participants watched and listened to AV clips of the same stories, with the storyteller's whole head in shot; and in the video-only condition, participants watched the same video clips, minus the sound track. All sessions were carried out in an fMRI scanner. Scans showed increased activation in different regions associated with each condition. Thus, whilst the audio-only condition activated areas including the left pars triangularis, STG and STS, the video-only condition activated the left middle frontal gyrus

(MFG) and right pars opercularis. Moreover, compared to processing of either audio-only or video-only speech, processing of AV speech was associated with relatively greater increases in activation across the wider language network and beyond, comprising the left pars opercularis, pars triangularis, posterior STG, and premotor cortex, as well as somatosensory cortex, the mouth area of primary motor cortex, and the cerebellum.

Fridriksson et al.'s (2008) and Skipper et al.'s (2005) studies indicate that simply observing either audio-only, visual-only or AV speech activates neural regions believed to also be involved in speech production. Skipper et al.'s (2005) results also reveal greater, more widespread activation of the language network when passively processing AV rather than audio-only speech, at least in non-brain damaged individuals. However, neither of these two studies directly examined potential differences in activation patterns during speech perception and overt speech production. In contrast, Fridriksson, Moser et al. (2009) presented 13 healthy adults with AV clips of a speaker producing nonsense consonant-vowel syllables. As in Fridriksson et al.'s (2008) study, only the lower portion of the face was shown, and all participants were scanned as they completed the study protocol. In the first condition, participants were instructed to observe the speech movements and press a button whenever the speaker's tongue was visible (a task intended to maintain participants' attention) whilst, in the second condition, participants were instructed to repeat the syllables out loud, as they were produced. Both conditions led to increased activation across an extensive network of bilateral posterior neural regions, including the right and left occipital lobes, posterior temporal lobes, and inferior parietal lobes. Higher levels of activation were also recorded in the posterior portion of Broca's area. In addition, the authors found significantly greater activity in the bilateral pre- and post-central gyri and premotor cortex as participants completed the second condition compared to when they completed the first condition. These results suggest that, although speech production tasks recruit a larger number of cortical regions than speech perception tasks, speech production and speech perception share a number of common neural substrates.

Taken together, the above findings may have important implications for stroke survivors with word finding difficulties if therapeutic effectiveness can be increased via the use of AV rather than audio-only speech alongside active therapy tasks. In support of this hypothesis, Fridriksson, Baker, Whiteside et al. (2009) recruited 10 individuals with chronic Broca's aphasia to a within-participants crossover study with two therapy phases: audio-only and AV. Eighteen high frequency nouns were selected for treatment in each therapy phase. During therapy, images of each item were presented for three seconds, followed by either an audio clip or AV clip of a male's mouth saying the name of a noun. In half of the trials, the name of the noun matched the image, whilst in the remaining trials the name provided was that a different target in the therapy set. On each trial, participants were instructed to press buttons to indicate whether the named noun matched the image or not, and were provided with immediate non-verbal feedback on their responses. Participants completed five x 30-minute, self-directed therapy sessions per week in their own homes for a minimum of six weeks. The group level analysis showed that, after therapy, the number of treated items named correctly increased numerically in both conditions, although the increase was only significant in the AV condition. There was also some evidence of treatment generalisation to untreated nouns, which was again only significant in the AV condition.

The results of Fridriksson, Baker and Whiteside et al.'s (2009) study confirm the potential for greater therapeutic gains when therapy tasks include an additional visual speech articulation component rather than audio-only speech. However, since speech production was not required on the part of the people with aphasia, it is not possible to generalise the results to alternative therapies, such as RIPP, that ask patients to repeat words. Similarly, participants were not scanned, meaning that one cannot draw any conclusions about the neural mechanisms involved in facilitating word finding via AV versus audio-only speech. Although all participants were classified as having Broca's aphasia, their language profiles varied substantially, as did individual participants' responses to therapy, which were masked by the group level analysis. At the individual level, two patients with the most severe naming deficits responded very poorly to both audio-only and AV therapy, and three further participants showed greater increases in confrontation naming ability following audio-only

than following AV therapy. It is not obvious why AV speech led to greater naming improvements than audio-only speech for some participants whilst the reverse pattern was true for others. This issue was addressed in the current study by utilising a case series approach with participants with differing lesions and aphasia diagnose in order to elucidate the patient characteristics associated with better responses to varying forms of speech input provided during repetition therapy.

Behavioural speech and language therapy for anomia is increasingly delivered via computer, in both research and real-world contexts (Brady et al., 2016; Palmer et al., 2012). Treatment may be fully clinician-led, or self-directed, whereby the therapist devises an appropriate therapy programme for patients to carry out more independently in their own homes, as in Fridriksson, Baker and Whiteside et al. (2009) and Nardo et al. (2017). Whilst conventional RIPP treatment involves the therapist presenting a tangible image of an item and its auditory name before asking the patient to repeat the name back, it is also possible to provide the same treatment using a computer, tablet or mobile telephone. A number of software applications are commercially available that fulfil this function. One such programme, StepbyStep (available at http://www.aphasia-software.com), also includes a word repetition task in which the user is presented with a picture of an item alongside an AV clip of a female's mouth saying the name of the item. This task therefore increases the input provided by RIPP through the addition of a visual speech articulation component. Completing word production exercises through StepbyStep, including repetition of AV item names presented in the presence of a picture, has been shown to improve both naming accuracy and speed in stroke survivors with chronic anomia (Palmer et al., 2012). However, to our knowledge, no study to date has compared the potential benefits of including a visual speech articulation component with those obtained following typical RIPP therapy in this target patient population.

The purpose of the present study was to explore the relative importance of visual speech articulation in computer-based repetition therapy in six individuals with chronic post-stroke anomia. Participants received three types of repetition therapy:

i. Repetition of auditory speech in the presence of a picture and articulation (RIPPA)

ii. Repetition of auditory speech in the presence of a picture (RIPP)

iii. Repetition of auditory speech in the presence of articulation but no picture (ARTIC)

Intuitively, providing semantic, auditory and articulatory information may be expected to result in equivalent or greater therapy gains than providing only semantic and auditory cues. Indeed, this expectation guided the construction of the repetition therapy tasks used in our earlier tDCS-plus-therapy studies (Chapters 3 and 4). In the present study we hypothesised that therapy gains following RIPPA may be a) equal to those following RIPP and/or ARTIC, b) the sum of the gains achieved following both RIPP and ARTIC, or c) greater than the sum of the gains achieved following both RIPP and ARTIC, due to simultaneous boosting of the links between both semantics and phonology, and phonology and articulation. Via the case series design, we aimed to confirm which therapy condition would result in the greatest improvement in confrontation noun naming for each of the six patients, and relate patterns of therapeutic response to neuropsychological and lesion profiles. A range of secondary outcome measures examined the impact of the intervention programme on patients' connected speech and self-reported ratings of communicative effectiveness. Participants' feedback regarding the perceived ease, enjoyment and effectiveness of each type of therapy was also collected.

Method

Participants

Six stroke survivors with chronic anomia were recruited from a database of participants held by the Neuroscience and Aphasia Research Unit (NARU) at the University of Manchester, or via referrals from Stroke Association communication support group contacts. All participants were right-handed, native English speakers who had suffered a single left hemisphere stroke at least one year before taking part in the current study. No participants had severe apraxia of speech or dysarthria, or a confirmed or suspected diagnosis of dementia.

AB

AB was a 52 year old male who lived with his wife and young son, and enjoyed gardening. As a result of his stroke in 2008, he had a right hemiplegia predominantly affecting his upper limb, as well as limited vision in his left eye and poor peripheral vision in his right eye. He was consequently unable to return to his previous role as an operations director. He presented with moderate word finding difficulties, but accompanied his spoken language with intonation, facial expressions and gestures to support communication. AB was classified as having anomic aphasia.

DF

DF was a 52 year old ex-post office worker who lived with her two teenage sons. Her mother lived nearby and visited frequently to help with household chores. A care worker took DF shopping each week and she regularly attended three local stroke support groups and associated social events. In addition to her stroke in 2009, DF had also had had a kidney transplant in 2013. She experienced some right-sided hemiparesis, but was able to walk short distances unassisted, with occasional unsteadiness. DF presented with mild word finding difficulties and mild agrammatism in conversation. She was classified as having anomia aphasia.

DM

DM was a 54 year old previous building surveyor who had a stroke in 2007. He lived with his wife and was fully mobile, plus able to drive and ride a bicycle. He had a busy social calendar, including several regular volunteering engagements that involved gardening and restorative work, and was also an active member of a number of stroke support groups. DM presented with moderate-severe word finding difficulties and severe agrammatism, although he was able to facilitate conversation by writing some words he could not produce verbally on a small whiteboard. He was classified as having Broca's aphasia.

PM

PM was a 74 year old retired print buyer. He lived with his wife, and they regularly spent time with their extended families. PM also had a keen interest in gardening and enjoyed watching cricket on television. PM had a stroke in 2006 and his stroke had resulted in a right-sided hemiplegia, which particularly affected his upper limb. He presented with moderate-severe word finding difficulties and mild dysarthria. PM was classified as having Broca's aphasia.

PR

PR was a 73 year old retired clerical worker who had a stroke in 2011, immediately following a lumbar spine disc operation. She lived with her husband and they enjoyed spending time with family based both locally and in New Zealand, as well as attending a nearby aphasia support group. PR was fully independently mobile. She presented with moderate word finding difficulties and mild apraxia of speech in conversational speech tasks, and also had a moderate stammer. She was classified as having transcortical motor aphasia.

RH

RH was a 66 year old music teacher who lived with his wife. He played a variety of instruments and, although his stroke in 2015 had adversely affected his ability to read music, at the time of his participation in the current study, he had begun to offer private music lessons again to friends and family members. He also enjoyed playing golf. Functionally, RH's word finding difficulties were much less pronounced than on formal assessment and he was an animated conversation partner. He was classified as having conduction aphasia.

Behavioural Assessment Battery

All participants had completed a comprehensive range of speech, language and cognitive tests prior to recruitment to the current study. The results of the behavioural test battery are shown in Table 6.1. The speech and language tests included the short form of the Boston Diagnostic Aphasia Examination (BDAE, Goodglass et al., 2001), including the Boston Naming Test (BNT, Kaplan et al., 2001). The BDAE provided the aphasia classification for

each participant. In addition, participants completed a number of phonological subtests from the PALPA (Kay et al., 1992): auditory discrimination of non-word minimal pairs (PALPA 1), and word minimal pairs (PALPA 2), immediate and delayed repetition of non-words (PALPA 8), and immediate and delayed repetition of words (PALPA 9). Four tests from the 64-item Cambridge Semantic Battery (Bozeat et al., 2000) were also included: the picture naming test, spoken and written word to picture matching tests, and the picture version of the Camel and Cactus Test of semantic association. The assessment battery also contained a 96-item synonym judgement task, including words presented in both spoken and written form (Jefferies et al., 2009), and the spoken sentence comprehension task from the Comprehensive Aphasia Test (CAT, Swinburn et al., 2005). The additional cognitive tests comprised forward and backward digit span (Weschler, 1987), the Brixton Spatial Anticipation Test (Burgess & Shallice, 1997), and the Raven's Coloured Progressive Matrices a test of non-verbal reasoning (Raven, 1962).

Table 6.1: Percentage scores for each participant on the behavioural assessment battery. Scores in bold indicate performance outside the normal range.

Name	Boston Naming Test	64-item naming	Minimal pairs (non-words)	Minimal pairs (words)	Non-word repetition (immediate)	Non-word repetition (delayed)	Word repetition (immediate)	Word repetition (delayed)	Spoken word to picture matching	Written word to picture matching	CAT Spoken sentence comprehension	96 synonym judgement	Camel and Cactus Test (pictures)	Forward digit span	Backward digit span	Brixton Spatial Anticipation Test	Raven's Coloured Progressive Matrices*
AB	**41.67**	**76.56**	80.56	87.50	**26.67**	**13.33**	**86.25**	**63.75**	**95.31**	98.44	75.00	**75.00**	**79.69**	**37.50**	**14.29**	88.89	88.89
DF	**50.00**	**87.50**	90.28	95.83	**53.33**	**10.00**	**93.75**	**41.25**	100.00	**96.88**	**62.50**	**78.13**	92.19	**37.50**	**14.29**	**43.64**	88.89
DM	**71.67**	**75.00**	80.56	93.06	**60.00**	**10.00**	**73.75**	**68.75**	98.44	98.44	**56.25**	95.83	98.44	**37.50**	**0.00**	**50.91**	91.67
PM	**51.67**	**59.38**	91.67	93.06	10.00	**13.33**	**65.00**	**55.00**	**92.19**	98.44	**62.50**	**69.79**	**65.63**	**25.00**	**14.29**	30.91	47.22
PR	**38.33**	**60.94**	80.56	94.44	**56.67**	**43.33**	**85.00**	91.25	100.00	100.00	87.50	**83.33**	**84.38**	75.00	**0.00**	**50.91**	80.56
RH	**1.67**	**3.13**	95.83	95.83	3.33	**3.33**	**21.25**	**5.00**	**96.88**	**96.88**	**3.13**	**89.58**	89.06	**25.00**	28.57	61.82	83.33

*Norms were unavailable for this assessment

Neuroimaging

High resolution structural T1-weighted MRI scans (Figure 6.1) had also been previously acquired for each participant on a 3.0 Tesla Philips Achieva scanner (Philips Healthcare, Best, The Netherlands), using an 8-element SENSE head coil. T1-weighted inversion recovery sequences with 3D acquisition were employed with the following parameters: TR (repetition time) = 9.0 ms, TE (echo time) = 3.93 ms, flip angle = 8 °, 150 contiguous slices, slice thickness = 1mm, acquired voxel size 1.0 x 1.0 x 1.0 x1.0 x 1.0 mm^3, matrix size 256 x 256, FOV = 256 mm, T1 (inversion time) = 1150 ms, SENSE acceleration factor 2.5, total scan acquisition time = 575 seconds.

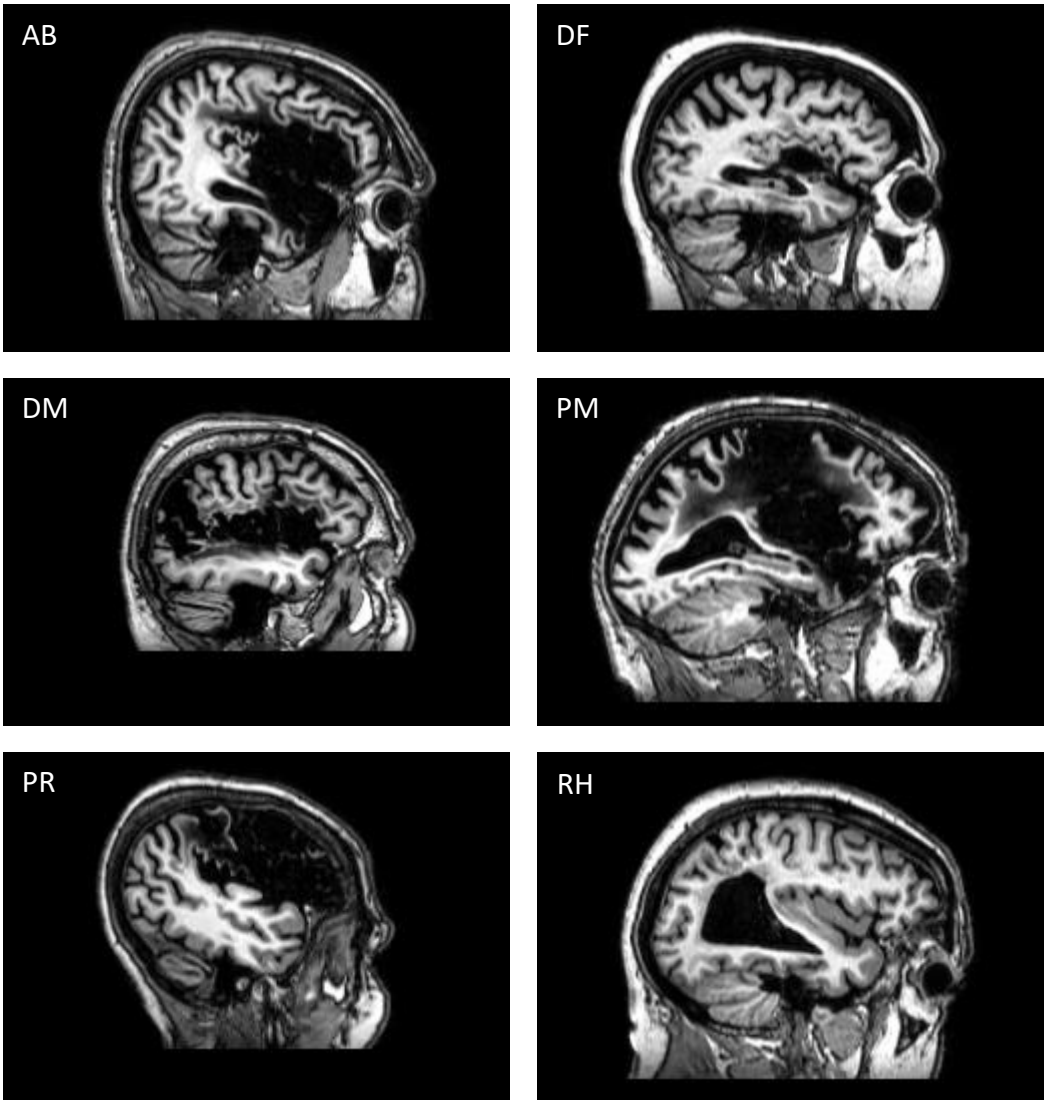


Figure 6.1: MRI images of participants' lesions.

Procedure

The design of the current study is illustrated in Figure 6.2. The study was approved by the Health Research Authority NRES Committee North West (13/NW/0844).

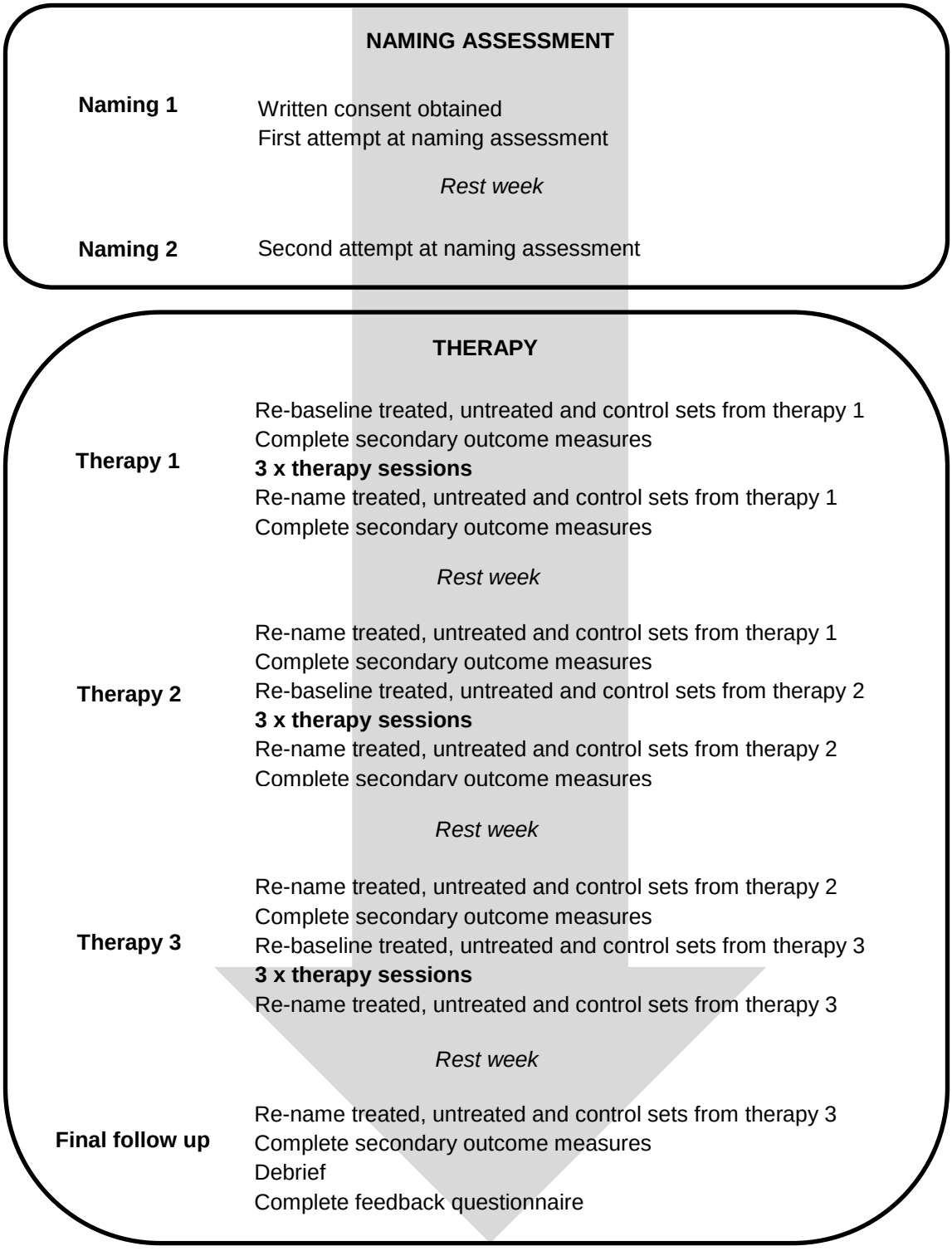


Figure 6.2: Flowchart to show the design of the RIPPA study.

Naming Assessment

All individuals gave written consent to participate in the study. Participants completed an extensive naming assessment on two occasions, with at least a one week interval between sessions. The stimuli were 408 black and white images of nouns taken from the International Picture Naming Project (IPNP, 2000, available at https://crl.ucsd.edu/experiments/ipnp/1stimuli.html), randomly divided into eight blocks of 51 items (Appendix A). Blocks were matched on length in phonemes, number of syllables, frequency, and age of acquisition, using values provided by the IPNP. In each session, items were presented on a laptop computer using E-Prime (Psychology Software Tools Inc., Sharpsberg, Philadephia), with the initial presentation of each image accompanied by a discreet beep sound. Participants were asked to try to produce the name of each item. No cues were provided, although general encouragement was given. Each image was shown for up to 10 seconds, after which time images automatically timed out if they had not yet been named correctly. Participants completed blocks 1-8 in order in the first assessment session and in the reverse order (i.e. from 8-1) in the second session. All sessions were recorded using an Olympus VN-713PC digital voice recorder, placed to the side of the laptop computer. Participants' first naming attempts within the ten second time limit were graded as correct or incorrect. Other verbalisations, including filler words/phrases (e.g. 'er', 'come on, think'), were ignored.

The numbers of items named incorrectly and correctly by each participant during the two assessment sessions are shown in Table 6.2. Naming assessment responses were used to create nine personalised item sets for each participant. For all participants, six sets contained 20 items that they had named incorrectly on at least one occasion, whilst, for five participants (AB, DF, DM, PM and PR), three further, control sets contained 20 items that they had named correctly twice. Due to the severity of RH's naming impairment, he only named seven items correctly across both assessment sessions, meaning that each of his control sets contained a total of 17 items: two named correctly twice, eight named correctly once and seven named incorrectly twice. The control items that had not been named correctly twice had, however, been self-corrected within the ten second item presentation

window when named incorrectly (items incorrectly named once), or during at least one of the assessment sessions (items incorrectly named twice). This was not the case for items in the treated and untreated sets. For each participant, the six incorrect sets were matched on length in phonemes, number of syllables, frequency and name agreement (see Appendix I), as were the three correct control sets (Appendix J). Three of the six incorrect sets were randomly assigned to be treated and the remaining sets were allocated to be untreated. All sets were randomly allocated to the three therapy conditions. Each therapy condition included one treated, one untreated and one correct control set.

Table 6.2: Number of items named incorrectly once, incorrectly twice and correctly twice across both naming assessment sessions by each participant.

Name	Incorrectly named once	Incorrectly named twice	Correctly named twice	Total number of items*
AB	115	162	127	404
DF	100	95	210	405
DM	116	115	172	403
PM	114	132	161	407
PR	137	83	235	406
RH	24	373	7	404

*Although 408 items were available at the start of each assessment session, items were occasionally inadvertently skipped. Therapy sets only included items attempted in both sessions.

Computerised Naming Therapy

Microsoft PowerPoint slides were created for all treated items to be included in each therapy condition (Figure 6.3), and presented on a laptop computer. In the RIPPA condition, slides showed a colour Google image of a single item and an AV clip of a woman's mouth saying the item name, displayed side by side. In the RIPP condition, slides depicted a colour Google image of an item alongside a black star figure in lieu of articulatory information. In the ARTIC condition, slides included an AV clip of a woman's mouth saying the item name, alongside a black star figure in lieu of a Google image. The black star figures in the RIPP and ARTIC conditions served as visual controls. In all conditions, there was an automatic

two second delay after the slide appeared to allow participants to process visual information before the AV (RIPPA and ARTIC) or audio (RIPP) clip began to play. After each clip had finished playing, participants were asked to try to repeat back the item name. Once they had attempted to name the item, the next slide was revealed. Each item was repeated 10 times per therapy session. Two additional practice items were each presented once at the start of each session to familiarise participants with the format of the upcoming therapy slides. In each condition, participants received three therapy sessions within a working week.

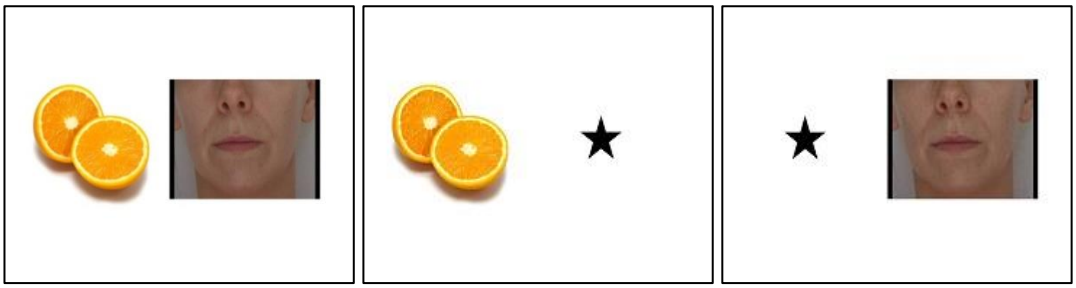


Figure 6.3: Examples of therapy slides used in each condition.

Participants were randomly allocated to receive each form of therapy in a different order: AB: RIPP, ARTIC, RIPPA; DF: RIPPA, RIPP, ARTIC; DM: ARTIC, RIPP, RIPPA; PM: RIPPA, ARTIC, RIPP; PR: RIPP, RIPPA, ARTIC; RH: ARTIC, RIPPA, RIPP. All assessment and therapy for the current study was carried out in participants' own homes by the lead author (a qualified speech and language therapist). Although she was necessarily not blinded to the order in which therapy conditions were offered, the same therapy protocol was strictly followed in every session.

Outcome Measures

Naming

The primary outcome measure was naming accuracy. This was measured before the start of the first therapy session in each condition in order to re-establish baseline accuracy for all of the treated, untreated and correct control items within that cycle. As per Figure 6.2, naming accuracy was assessed again immediately after the third therapy session and at a follow-up session approximately 12 days later (mean = 12.22, SD = 1.36). The follow-up assessment for the first two therapy conditions was carried out immediately prior to the start of the next therapy condition. On each occasion, participants were presented with the same black and white line drawings used in the initial naming assessment (i.e. different to the colour training images) of all 60 (57 for RH) items used in the current therapy condition on a laptop screen. As in the initial naming assessment sessions, participants were asked to try to produce the name of each item without any cues. Items were shown for up to 10 seconds, after which time images automatically timed out if they had not yet been named correctly.

To investigate any effects of treatment on naming speed, the time taken by the participants to correctly name the 20 (17 for RH) correct control items in each condition was measured pre- and post-therapy, and at follow-up. The time from initial item presentation (signified on the recording by the accompanying beep) to the onset of the first naming attempt was calculated manually for each item, in milliseconds, using Audacity 2.0.0 (available at http://audacity.sourceforge.net/).

Secondary Outcome Measures

Participants completed the secondary outcome measures at the same time points that naming ability was assessed. To assess the extent of generalisation of therapy to connected speech, participants completed a picture description task ('Cookie Theft', Goodglass et al., 2001). Verbal responses on each occasion were transcribed and timed. The following measures were calculated: 1) total number of real words or 'tokens' per

sample, which indicated quantity of speech output, 2) mean length of utterance (MLU) in morphemes, which indicated grammatical complexity and speech fluency, and 3) type/token ratio (TTR, calculated by dividing the number of unique words per sample by the total number of tokens), which indicated lexical diversity (as per Borovsky et al., 2007). In addition, the number of silent pauses (of at least one second duration) per response were recorded, and the number of tokens per minute (TPM) was calculated for each sample. Both measures provided further indications of speech fluency. To examine any effects of therapy on participants' self-perceptions of functional communication and quality of life, they completed the validated 20-item Communication Outcome After Stroke (COAST) scale (Long et al., 2008). Total scores on the COAST were converted to percentages, with higher percentages indicating better outcomes.

Participant Feedback

At the end of the final follow-up session, participants were debriefed and, using aphasia-friendly visual materials, asked to rate each type of therapy for ease, enjoyment and effectiveness. Responses to each question were graded from 0-4, with higher scores indicating more positive perceptions.

Results

Behavioural Results

Oral picture naming in people with aphasia is often inconsistent, with individuals successfully naming the same items correctly on one occasion and incorrectly on another (Capitani et al., 2012; Freed et al., 1996; Howard et al., 1985), as also shown in Table 6.2 and in Chapter 5 of this thesis. To minimise the impact of inherent naming response inconsistency on any therapy-induced changes in naming accuracy, naming responses immediately following the third therapy session in each condition and naming responses at follow-up were combined such that, if an individual correctly named an item at either time point, this was rated as correct. Whilst this approach may bias toward an increased therapeutic effect, the same

procedure was adopted across all three conditions. Raw naming accuracy data is provided in Appendix K. For the remaining measures (speed of naming, the connected speech measures in the picture description task, and the COAST), mean responses across the two post-therapy sessions (immediately following the third therapy session in each condition and at follow-up) were calculated, and included in the following analyses.

Naming Accuracy

Treated Items

Figure 6.4 shows the percentage changes in naming accuracy from baseline to post-therapy for all treated items in each therapy condition, for each participant.

Group Level

Paired-samples t-tests were used to compare changes in mean percentage naming accuracy from baseline to post-therapy in each therapy condition. Mean percentage naming accuracy increased significantly in all conditions (RIPPA: 41% - 72%, $t(5)=-4.56$, $p=0.006$; RIPP: 44% - 68%, $t(5)=-3.16$, $p=0.025$; ARTIC: 42% - 71%, $t(5)=-4.85$, $p=0.005$). These findings indicate that, overall, all three types of therapy were effective.

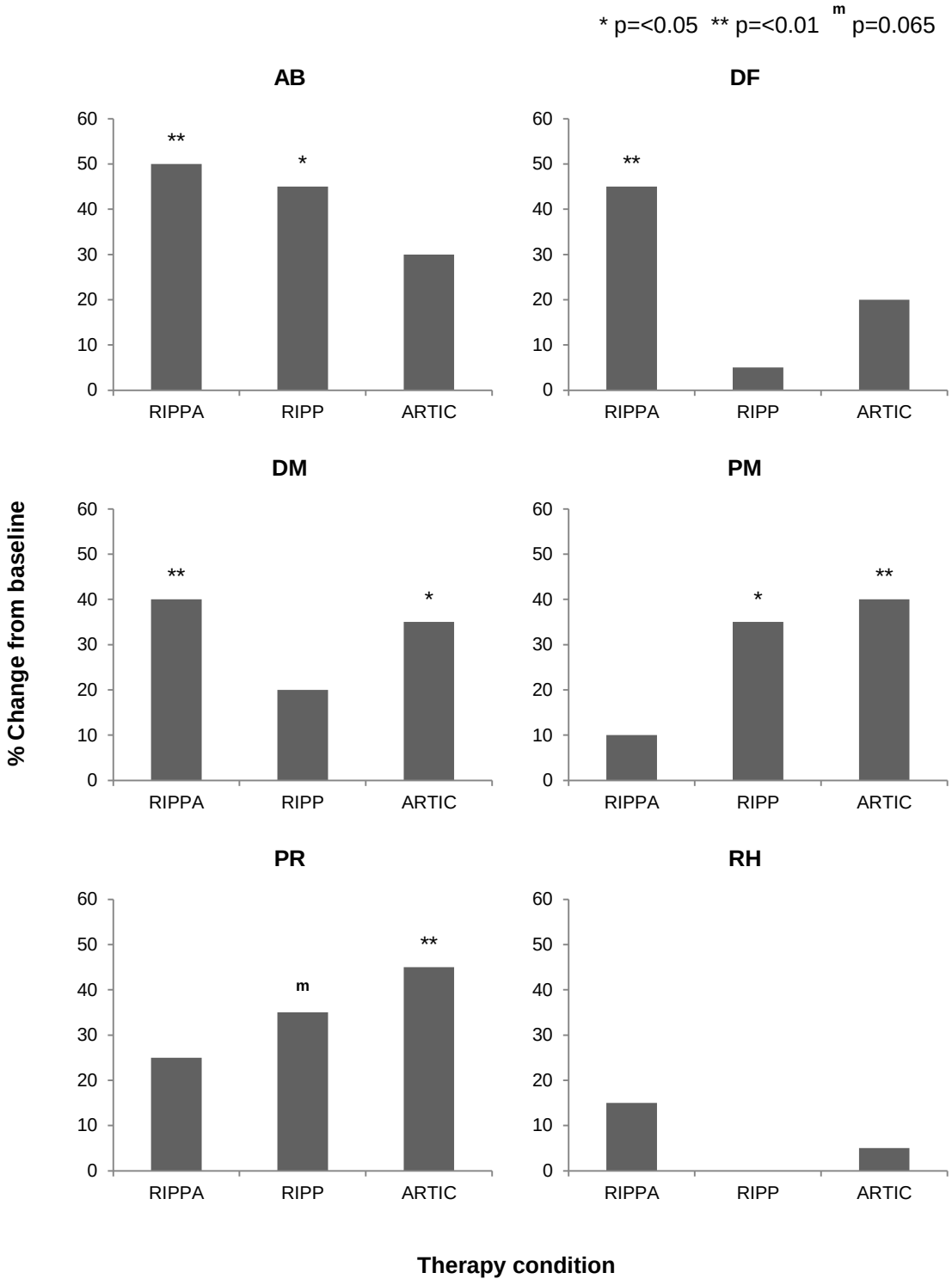


Figure 6.4: Percentage changes in naming accuracy from baseline for all treated items.

Individual Level

McNemar tests were used to determine the statistical significance of any changes in raw naming accuracy scores from baseline to post-therapy in each therapy condition. For 5/6 participants, naming accuracy for the treated items increased numerically from baseline in all three therapy conditions, indicating beneficial therapeutic effects of the short treatment programme. However, no particular type of therapy was optimally effective for all patients. For AB, RIPPA resulted in the greatest percentage increase in naming accuracy (50%), followed by RIPP (45%). Both of these increases were significant (RIPPA χ^2=6.75, p=0.006; RIPP χ^2=5.82, p=0.012). RIPPA also resulted in the greatest increases in naming accuracy for DF and DM. For DF, this increase (45%) was highly significant (χ^2=7.11, p=0.004). In addition, chi square tests (again based on raw naming accuracy scores) indicated that the percentage increase following RIPPA was significantly greater than that following RIPP (χ^2=7.35, p=0.007). For DM, increases in naming accuracy following both RIPPA (40%, χ^2=6.13, p=0.008) and ARTIC therapy (35%, χ^2=4.00, p=0.039) were significant. For PM and PR, ARTIC resulted in the greatest increases in naming accuracy. For PM, therapy gains were significant following ARTIC (40%, χ^2=6.13, p=0.008) and RIPP (35%, χ^2=4.00, p=0.039), with the effect of ARTIC significantly greater than that for RIPPA (χ^2=4.07, p=0.044). Similarly, for PR, although only the gain following ARTIC therapy was significant (45%, χ^2=7.11, p=0.004), this effect was significantly greater than that following either RIPPA (χ^2=4.10, p=0.043) or RIPP. PR also demonstrated a marginal therapy gain following RIPP therapy (35%, χ^2=3.27, p=0.065) (indicated in Figure 6.4 by ^{m}). For the remaining participant, RH, therapy gains were minimal in two conditions (RIPPA 15%; ARTIC 5%). Neither of these percentage changes was significant. His percentage naming accuracy did not change from baseline following RIPP therapy.

Untreated Items

Figure 6.5 shows the percentage changes in naming accuracy from baseline to post-therapy for all untreated items, for each participant.

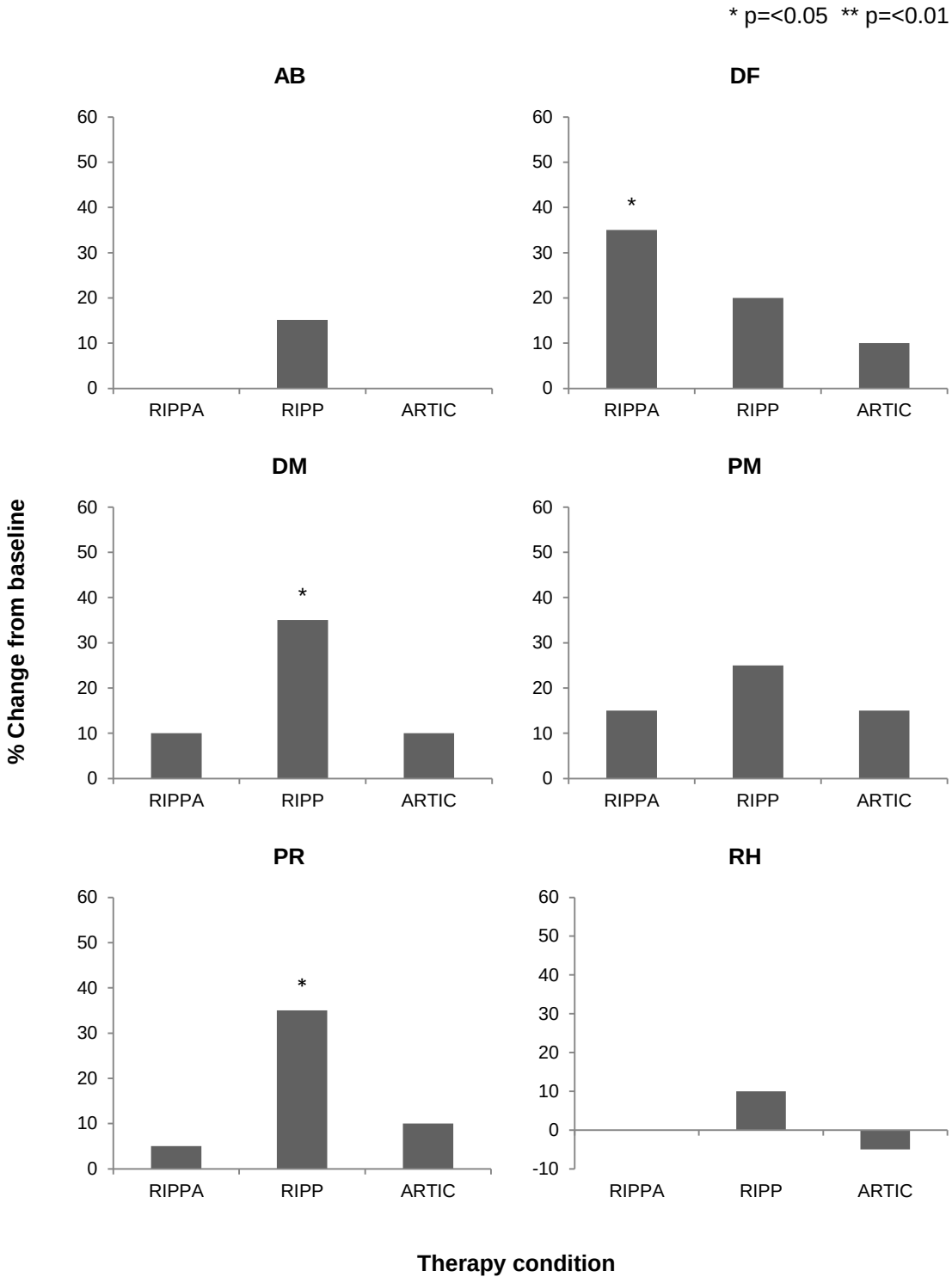


Figure 6.5: Percentage changes in naming accuracy from baseline for all untreated items.

Group Level

Paired-samples t-tests were used to compare changes in mean percentage naming accuracy from baseline to post-therapy in each therapy condition. Mean percentage naming accuracy increased in all conditions, however, only the mean increase in the RIPP condition (43% - 62%) was significant (t(5)=-5.53 p=0.003) (RIPPA: 43% - 54%, t(5)=-2.01, p=0.101; ARTIC: 46% - 53%, t(5)=-2.17, p=0.082).

Individual Level

McNemar tests were used to determine the statistical significance of any changes in raw naming accuracy scores from baseline to post-therapy in each therapy condition. For DF, DM, PM and PR, naming accuracy for the untreated items increased numerically from baseline in all three therapy conditions. None of these increases were significant for PM but, for the remaining three participants, there were significant pre- to post-therapy increases in naming accuracy. For DF, there was a significant increase in naming accuracy following RIPPA therapy (35%, χ^2=4.00, p=0.039), and chi square tests indicated that this increase was significantly greater than that following ARTIC therapy (10%, χ^2=5.05, p=0.025). Similarly, for DM, there was a significant percentage increase following RIPP therapy (35%, χ^2=5.14, p=0.023) that was also significantly greater than that following ARTIC therapy (10%, χ^2=4.44, p=0.035). For PR, RIPP therapy resulted in a significant increase in naming accuracy (35%, χ^2=4.00, p=0.039), although this increase was not significantly greater than those seen following either RIPPA or ARTIC therapy. For the remaining two participants, AB and RH, there were small, non-significant increases in naming accuracy following RIPP therapy (AB 15%; RH 10%), whilst naming accuracy remained the same or decreased relative to baseline following RIPPA and ARTIC therapy.

Speed of Naming

The mean time in seconds taken by each participant to name the 20 (17 for RH) control items in each therapy condition correctly at baseline and post-therapy are shown in Figure 6.6.

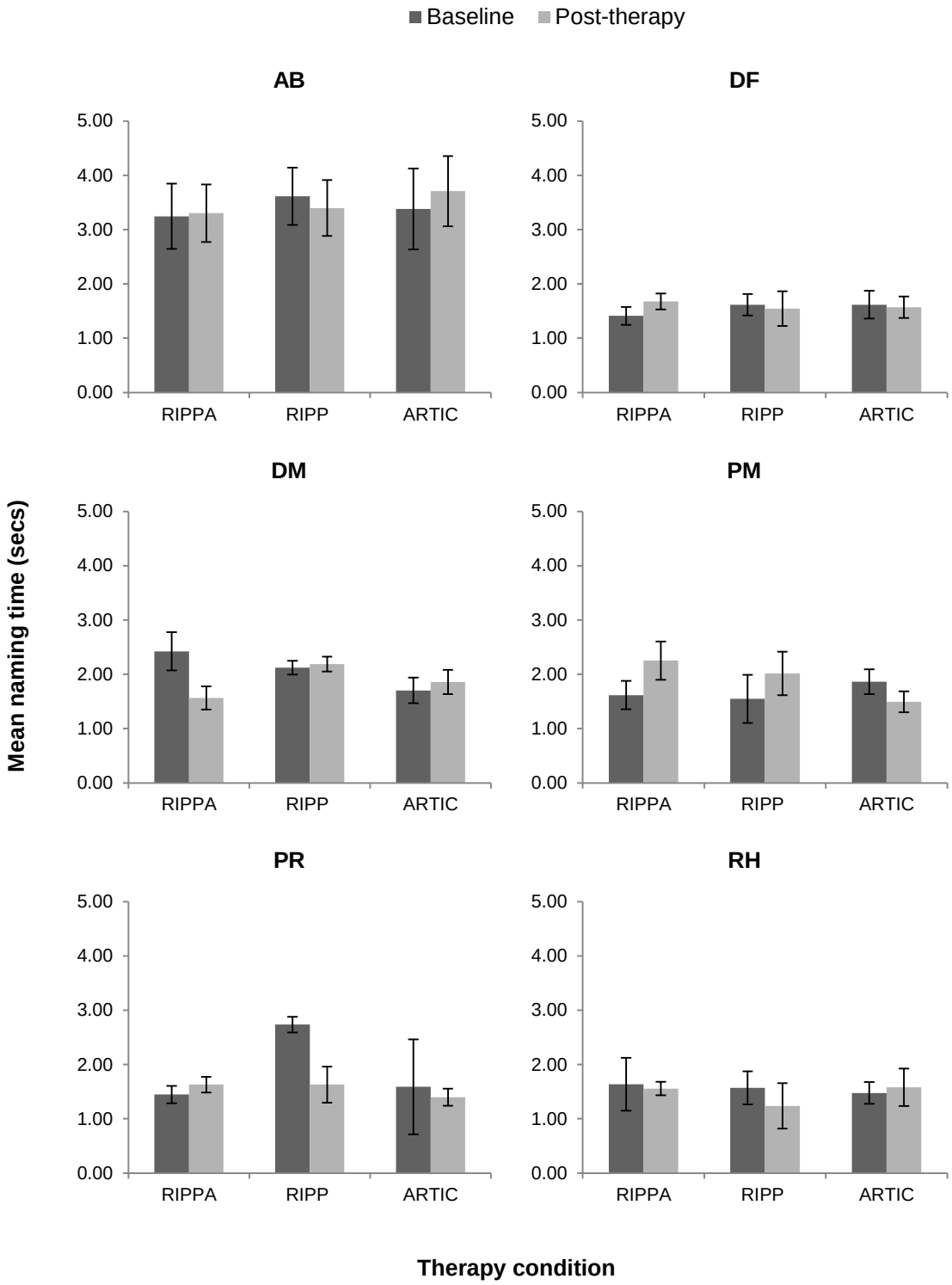


Figure 6.6: Mean time (secs) taken by participants to correctly name control items at baseline and post-therapy. Error bars show +/-1 standard error.

Group Level

Paired-samples t-tests were used to compare changes in the mean time in seconds taken to correctly name the control items from baseline to post-therapy in each therapy condition. None of these changes were significant (RIPPA: 1.93s – 1.95s, t(74)=-0.09, p=0.930; RIPP: 2.19s – 1.99s, t(76)=0.87, p=0.390; ARTIC: 1.84s – 1.78s, t(73)=0.33, p=0.742).

Individual Level

Wilcoxon Signed Ranks tests were used to determine the statistical significance of any changes in naming speed from baseline to post-therapy in each therapy condition. DM named the control items marginally faster following RIPPA therapy than at baseline in the same condition (z=-1.86, p=0.063). There were no significant changes in his naming speed following RIPP and ARTIC. For the remaining participants, none of the observed changes in the length of time taken to correctly name the control items from baseline to post-therapy in any of the three conditions were significant, meaning that they did not name the control items significantly faster or slower after any type of therapy.

Secondary Outcome Measures

Picture Description Task

The total response length (in seconds), number of pauses, total number of tokens, tokens per minute (TPM), total number of morphemes, mean length of utterance (MLU) in morphemes, and type to token ratio (TTR, expressed as a percentage) were calculated when participants were asked to describe the Cookie Theft image at each time point. These values are shown in Table 6.3.

Table 6.3: Total response length (secs), number of pauses, number of tokens, TPM, number of morphemes, MLU, and TTR for the picture description task for each participant.

Name	Condition	Time point	Connected speech measure						
			Length	Pauses	Tokens	TPM	Morphemes	MLU	TTR
AB	RIPPA	Baseline	491.7	66	356	44.4	441	7.7	38.6
		Post-therapy	465.6	53	373	47.0	453	9.9	37.7
	RIPP	Baseline	265.1	33	191	43.2	240	8.9	44.5
		Post-therapy	314.9	46	232	44.3	279	7.1	42.9
	ARTIC	Baseline	314.9	46	232	44.3	279	7.1	42.9
		Post-therapy	491.7	66	356	44.4	441	7.7	38.6
DF	RIPPA	Baseline	87.4	19	56	59.0	103	5.7	66.3
		Post-therapy	160.0	25	166	61.8	204	9.9	47.1
	RIPP	Baseline	160.0	25	166	61.8	204	9.9	47.1
		Post-therapy	222.8	34	237	64.8	288	9.7	45.6
	ARTIC	Baseline	222.8	34	237	64.8	288	9.7	45.6
		Post-therapy	288.8	56	243	50.5	298	6.4	37.1
DM	RIPPA	Baseline	65.5	20	32	29.2	39	2.0	77.2
		Post-therapy	78.3	23	35	26.5	43	2.1	81.2
	RIPP	Baseline	62.3	20	36	34.7	44	2.5	72.6
		Post-therapy	65.5	20	32	29.2	39	2.0	77.2
	ARTIC	Baseline	56.2	14	33	35.2	40	2.7	75.8
		Post-therapy	62.3	20	36	34.7	44	2.5	72.6
PM	RIPPA	Baseline	104.5	21	35	20.1	38	2.5	48.6
		Post-therapy	52.4	10	25	28.4	28	2.6	62.9
	RIPP	Baseline	58.4	8	27	31.8	32	3.6	64.0
		Post-therapy	44.6	8	24	28.4	27	3.4	63.6
	ARTIC	Baseline	52.4	10	25	28.4	28	2.6	62.9
		Post-therapy	58.4	8	27	31.8	32	3.6	64.0
PR	RIPPA	Baseline	54.8	9	35	37.7	41	5.1	50.4
		Post-therapy	38.6	9	30	50.2	38	5.8	54.2
	RIPP	Baseline	80.3	15	35	26.1	43	3.9	51.4
		Post-therapy	54.8	9	35	37.7	41	5.1	50.4
	ARTIC	Baseline	38.6	9	30	50.2	38	5.8	54.2
		Post-therapy	34.6	7	32	55.1	39	6.1	53.0
RH	RIPPA	Baseline	115.7	6	243	126.1	308	44.8	46.8
		Post-therapy	105.9	5	215	121.9	264	59.0	48.2
	RIPP	Baseline	105.9	5	215	121.9	264	59.0	48.2
		Post-therapy	80.1	3	190	143.5	240	126.7	53.1
	ARTIC	Baseline	91.5	4	206	135.1	267	53.4	46.6
		Post-therapy	115.7	6	243	126.1	308	44.8	46.8

Group Level

Paired-samples t-tests were used to compare changes in the mean values for each of the connected speech measures for the picture description task from baseline to post-therapy in each therapy condition. None of these changes were significant (RIPPA: length t(5)=0.18, p=0.864, pauses t(5)=0.85, p=0.433, tokens t(5)=-0.72, p=0.502; TPM t(5)=-1.24, p=0.271, morphemes t(5)=-0.50, p=0.636, MLU t(5)=-1.62, p=0.167, TTR t(5)=-0.13, p=0.904; RIPP: length t(5)=-0.53, p=0.616, pauses t(5)=-0.80, p=0.462, tokens t(5)=-0.92, p=0.400; TPM t(5)=-1.14, p=0.307, morphemes t(5)=-0.89, p=0.414, MLU t(5)=-0.97, p=0.375, TTR t(5)= -0.97, p=0.535; ARTIC: length t(5)=-1.63, p=0.164, pauses t(5)=-1.75, p=0.141, tokens t(5)=-1.47, p=0.203; TPM t(5)=0.84, p=0.441, morphemes t(5)=-1.44, p=0.210, MLU t(5)=-1.12, p=0.313, TTR t(5)=1.85, p=0.123).

Individual Level

As per Table 6.3, scores on all seven measures were highly variable between individuals, in accordance with their differing aphasia classifications and severity of word finding difficulties. For instance, DM and PM, who both had moderate-severe Broca's aphasia, were the least fluent participants (DM: MLU range = 2.0 – 2.7, TPM range = 26.5 – 35.2; PM: MLU range = 2.5 – 3.6, TPM range = 20.1 – 31.8), although DM's brief utterances had high lexical diversity, as indicated by his TTR scores (range = 72.6 – 81.2). In contrast, RH, who was classified as having conduction aphasia, was highly fluent and made few pauses, resulting in correspondingly much greater MLU and TPM scores (MLU range = 44.8 – 126.7, TPM range = 121.9 – 143.5) on all of his attempts at the picture description task.

Within participants, various patterns in scores on the seven connected speech measures emerged both after therapy and over time from the start of their first therapy sessions to post-therapy in their final conditions. The total length of AB's responses increased following RIPP and ARTIC, and the numbers of tokens and morphemes he produced rose post-therapy in all three conditions. At the same points, his TTR decreased, indicating that, although AB produced more words following therapy than at baseline in each condition, he produced more repetitions. There were also more general trends for the numbers of tokens

and morphemes per attempt to increase over the course of AB's involvement in the current study from his first (RIPP) to last (RIPPA) therapy cycles, likely reflecting repeated retrieval practice for the same lexical items. The length of DF's responses increased after all three types of therapy, as did her number of tokens, morphemes and pauses, whilst her TTR decreased. The same pattern was observed from the start of her first (RIPPA) condition to following her final (ARTIC) condition. These results indicate that repeated attempts at the picture description task increased the quantity of DF's speech output, but her attempts became less fluent and more repetitive over time. Decreased fluency associated with repeated attempts was similarly noted for DM, whose total response length and number of pauses tended to increase throughout the study from the ARTIC to RIPPA therapy conditions, whilst his TPM decreased.

In contrast, PR's picture description performance became more fluent over the course of her participation in the study from her first (RIPP) to her third (ARTIC) therapy condition. Over time, there were trends for the total length of her responses and her number of pauses to decrease, alongside increases in MLU and TPM. The number of tokens and morphemes she produced were very similar at each time point. These observations suggest that, with increased practice, PR took less time and fewer pauses to produce a similar quantity of speech output. PM's first picture description attempt (immediately prior to his first RIPPA therapy session) was longer and more hesitant than all subsequent attempts, with the greatest values for total length, and numbers of tokens, morphemes, and pauses. However, there were no consistent patterns of improvement or reduction in performance on any of the measures across his involvement in the study. Similarly, for RH, there were no clear trends over time or within therapy conditions relating to any of the connected speech measures, although immediately after RIPP (his final therapy condition), his response length, number of tokens and morphemes dropped. Across the two post-therapy sessions, he made an average of only three pauses, resulting in a very large MLU score (126.7) relative to his other attempts.

COAST

Table 6.4 shows the total percentage scores for each participant on the COAST at each time point, in each of the three therapy conditions.

Group Level

Paired-samples t-tests were used to compare changes in the mean percentage scores on the COAST from baseline to post-therapy in each therapy condition. Mean percentage scores increased significantly within all three conditions (RIPPA: 65.5% - 68.5%, $t(118)=-2.84$, $p=0.005$; RIPP: 63.3% - 68.8%, $t(119)=-3.70$, $p<0.001$; ARTIC: 67.3% - 71.0%, $t(118)=-3.56$, $p=0.001$).

Table 6.4: Total percentage scores on the COAST for each participant.

Participant	Condition	Time point	
		Baseline	Post-therapy
AB	RIPPA	70.9	74.7
	RIPP	55.0	68.1
	ARTIC	68.1	70.9
DF	RIPPA	71.9	71.3
	RIPP	71.3	80.0
	ARTIC	80.0	85.6
DM	RIPPA	58.8	60.0
	RIPP	61.3	58.8
	ARTIC	56.3	61.3
PM	RIPPA	66.3	74.4
	RIPP	74.4	73.8
	ARTIC	74.4	74.4
PR	RIPPA	63.5	67.1
	RIPP	53.8	63.5
	ARTIC	67.1	71.7
RH	RIPPA	61.6	63.1
	RIPP	63.1	68.1
	ARTIC	57.5	61.6

Individual Level

Table 6.4 shows that participants' percentage scores on the COAST varied both within and between therapy conditions (total range = 53.8% - 85.6%). Wilcoxon Signed Ranks tests showed the increase in DM's percentage score from baseline before his first (ARTIC) therapy session to post-therapy was significant (z=2.00, p=0.046), although this condition had the lowest baseline value. The same pattern was observed for two further participants: PM, who received RIPPA therapy first (z=2.16, p=0.030) and PR, who received RIPP therapy first (z=2.07, p=0.038). Similarly, DF's second therapy cycle (RIPP) had the lowest baseline value, and the increase in percentage score from this time point to follow-up was also significant (z=3.13, p=0.002). In contrast, percentage scores throughout RH's final therapy cycle (also RIPP) rose significantly from pre- to post-therapy (z=2.87, p=0.004), despite this condition having the highest baseline value. There were no significant within-condition changes in total percentage scores on the COAST for AB.

Four participants (AB, DF, PR, and RH) displayed an overall trend to score more highly on the COAST over time as they continued to participate in the study. Wilcoxon Signed Ranks tests were used to determine the significance of these trends. For AB, DF, PR, and RH, average percentage scores within their final conditions were significantly greater than average percentage scores within their first conditions: AB: RIPP = 61.6% to RIPPA = 72.8%, z=3.07, p=0.002; DF: RIPPA = 71.6% to ARTIC = 82.8%, z=3.45, p=0.001; PR: RIPP = 58.6% to ARTIC = 69.4%, z=3.19, p=0.001; RH: ARTIC = 59.5% to RIPP = 65.6%, z=2.30, p=0.021. There was no similar trend observed for DM (ARTIC = 58.8% to RIPPA = 59.4%, z=0.18, p=0.859). For the remaining participant, PM, there was a significant increase in average percentage score from his first (RIPPA = 66.3%) therapy condition to his third (RIPP = 74.1%) (z=2.27, p=0.023). However, his average percentage scores across both the second (ARTIC = 74.4%) and third therapy conditions were not significantly different (z=-0.30, p=0.763), indicating that his scores increased following the first therapy condition and stayed high for the remainder of his involvement in the study rather than increasing throughout his participation.

Participant Feedback

Figure 6.7 shows participants' ratings of ease, enjoyment and effectiveness for each therapy type.

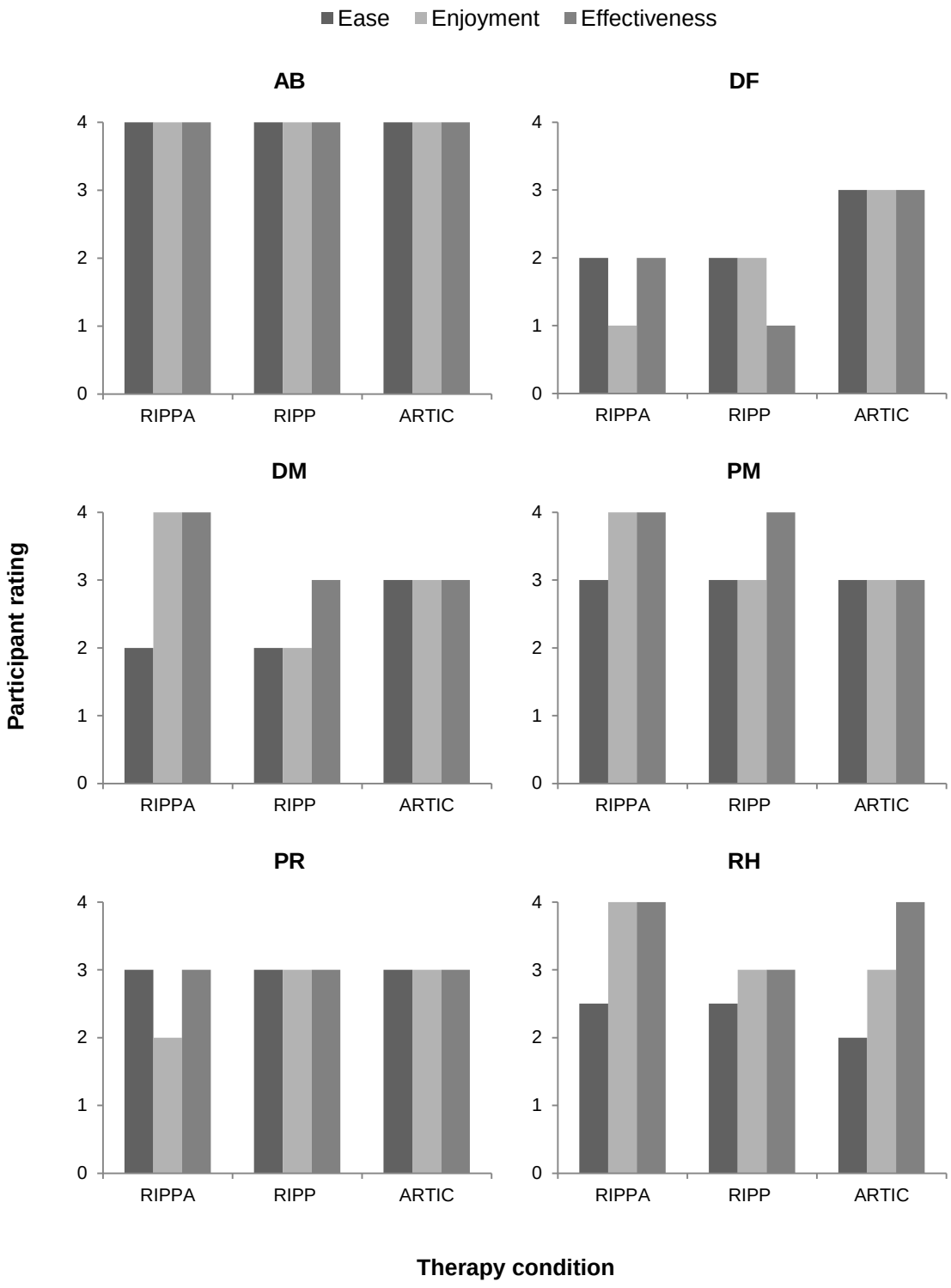


Figure 6.7: Participant's ratings of ease, enjoyment and effectiveness for each therapy type.

Group Level

The mean (SD) ratings of ease, enjoyment and effectiveness for each therapy were as follows: RIPPA: ease = 2.75 (0.76), enjoyment = 3.17 (1.33), effectiveness = 3.50 (0.84); RIPP: ease = 2.75 (0.76), enjoyment = 2.83 (0.75), effectiveness = 3.00 (1.10); ARTIC: ease = 3.00 (0.63) enjoyment = 3.17 (0.41), effectiveness = 3.33 (0.52). A one-way ANOVA was conducted to compare ratings on each of the subscales between the three therapy conditions. None of the subscale ratings differed significantly between conditions (ease: $F(2,15)=0.11$, $p=0.901$; enjoyment: $F(2,15)=0.07$, $p=0.937$; effectiveness: $F(2,15)=0.31$, $p=0.741$).

Individual Level

Figure 6.7 reveals that no particular therapy type unanimously received high or low ratings of ease, enjoyment or effectiveness. Instead, aside from AB, who gave maximum scores on all three dimensions for RIPPA, RIPP and ARTIC, participants' perceptions of each therapy type differed both within and between individuals. PR graded all three therapies equally in terms of ease and effectiveness, but rated RIPPA as less enjoyable than RIPP and ARTIC. DF also rated RIPPA as the least enjoyable therapy type, in addition to reporting RIPP to be the least effective. She was the only participant who ranked ARTIC therapy above both RIPPA and RIPP on all three aspects. Conversely, the remaining three participants (DM, PM and RH) rated RIPPA as the most enjoyable type of therapy, even though DM felt that ARTIC therapy was easier than RIPPA. Furthermore, DM, PM and RH awarded RIPPA a maximum score of 4 for effectiveness, although PM considered RIPP, and RH considered ARTIC, to be as effective as RIPPA.

Neuroimaging Results

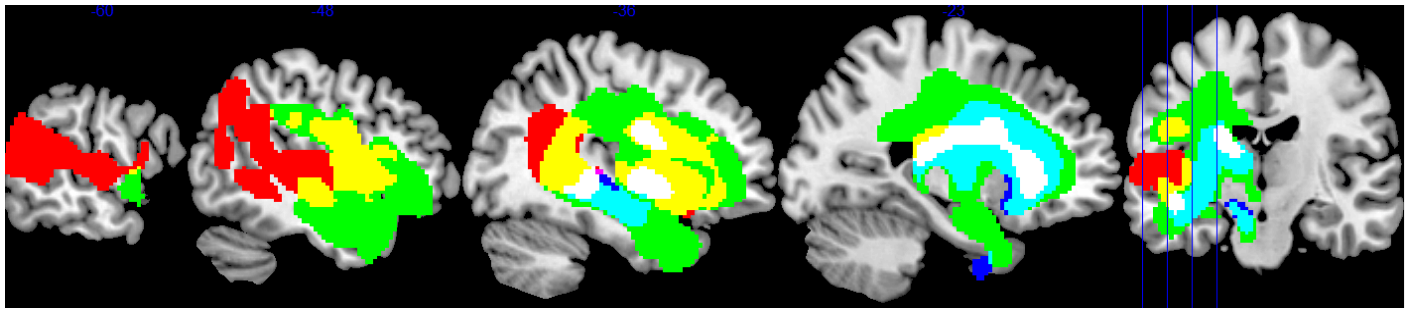
For each patient, their T1 scan was normalised using the Seghier et al. algorithm (Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008) to provide an abnormality map. This was binarised for each patient and then, following the 'all or none' overlap approach of Meteyard, Price, Woollams and Aydelott (2013), these were overlaid to provide lesion overlap maps for

those participants who named significantly more treated items correctly following treatment than at baseline (responders) and those who did not (non-responders). Figure 6.8 shows lesion overlaps for the three participants who responded to RIPPA therapy (AB, DF and DM) and the three non-responders (PM, PR and RH). PR's therapy gain (35%) following RIPP was marginally significant (p=0.065), and equal percentage increases in treated item naming accuracy were significant for DM in the ARTIC condition and for PM in the RIPP condition. Therefore, for lesion comparison purposes, PR was considered a RIPP responder. Lesion overlaps for the three responders (AB, PM and PR) and three non-responders (DF, DM and RH) to RIPP therapy are shown in Figure 6.9. Finally, Figure 6.10 shows lesion overlaps for the three responders (DM, PM and PR) and non-responders (AB, DF and RH) to ARTIC therapy.

RIPPA

As per Figure 6.8, the three RIPPA responders' lesions all spared the left premotor cortex (BA6). In addition to roles in auditory and visual speech processing, this region is believed to act as a multimodal integration area (e.g. Weisberg, Hubbard, & Emmorey, 2017). Therefore, having this area intact may have allowed AB, DF and DM to effectively process concurrent semantic, auditory and articulatory cues, and benefit from RIPPA. In contrast, PM and PR shared damage to BA6, corresponding with a failure to demonstrate any significant improvements in naming ability following RIPPA. The final RIPPA non-responder, RH, had a medial left hemisphere lesion that severed the posterior portions of the arcuate and inferior longitudinal fasciculi. The arcuate fasciculus, a dorsal stream tract running between language regions in the left temporal and frontal lobes, is believed to play critical roles in repetition as well as oral picture naming, whilst damage to the left inferior longitudinal fasciculus, which follows the ventral stream and connects the occipital lobe with the inferior frontal lobe, has been linked to impaired object naming (Baldo et al., 2013; Breier, Hasan, Zhang, Men, & Papanicolaou, 2008; Marchina et al., 2011; Shinoura et al., 2010). Therefore, it is likely that RH's lesion prevented auditory input from progressing along either pathway, weakening his ability to repeat back item names during all three types of therapy, as well as impairing his confrontation naming ability.

RIPPA Responders (DM=red; DF=blue; AB=green)



RIPPA Non-Responders (PR=red; PM=blue; RH=green)

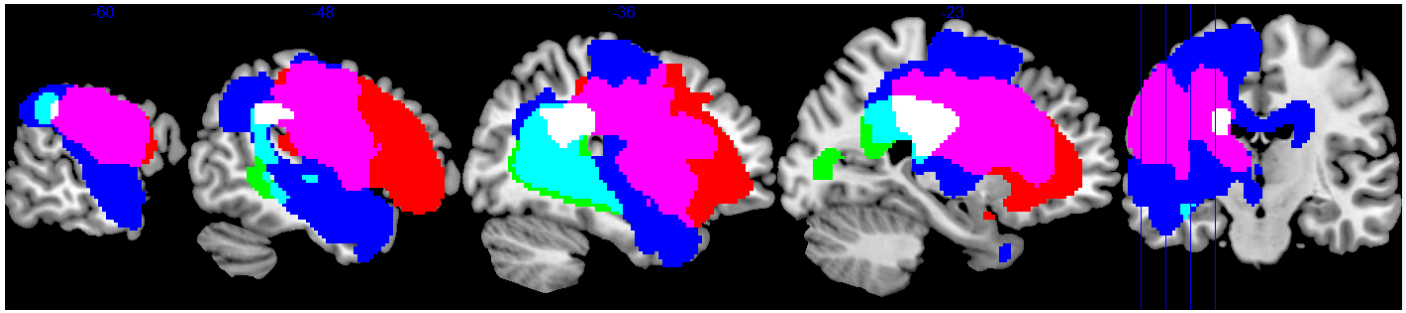
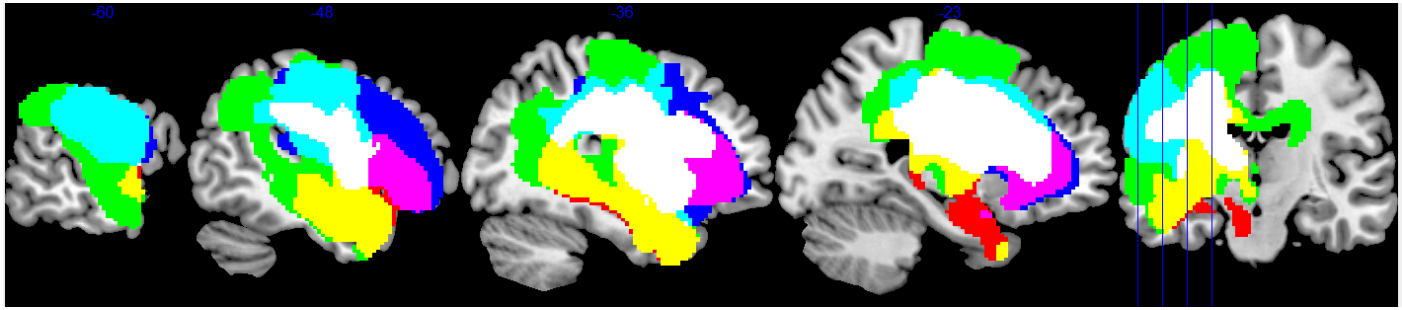


*Figure 6.8: Lesion overlap models showing voxels lesioned in responders and non-responders to **RIPPA** therapy.*

RIPP Responders (AB=red; PR=blue; PM=green)



RIPP Non-Responders (DM=red; DF=blue; RH=green)

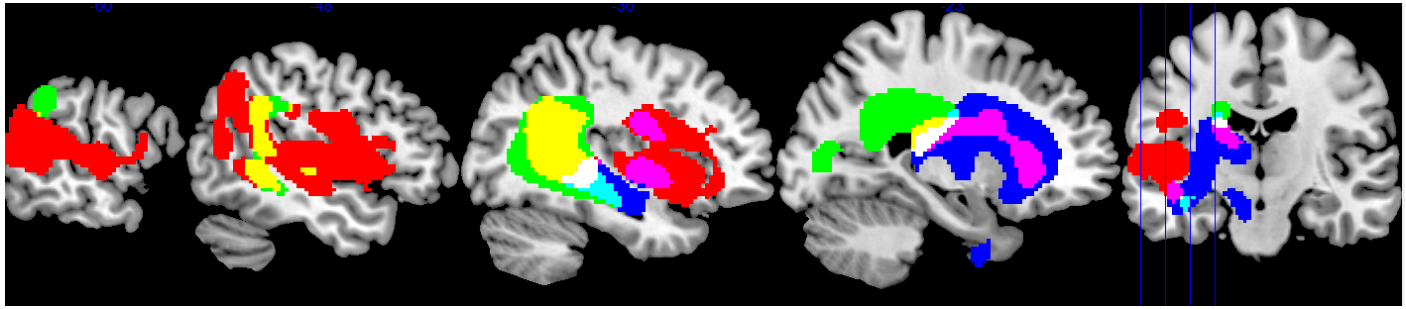
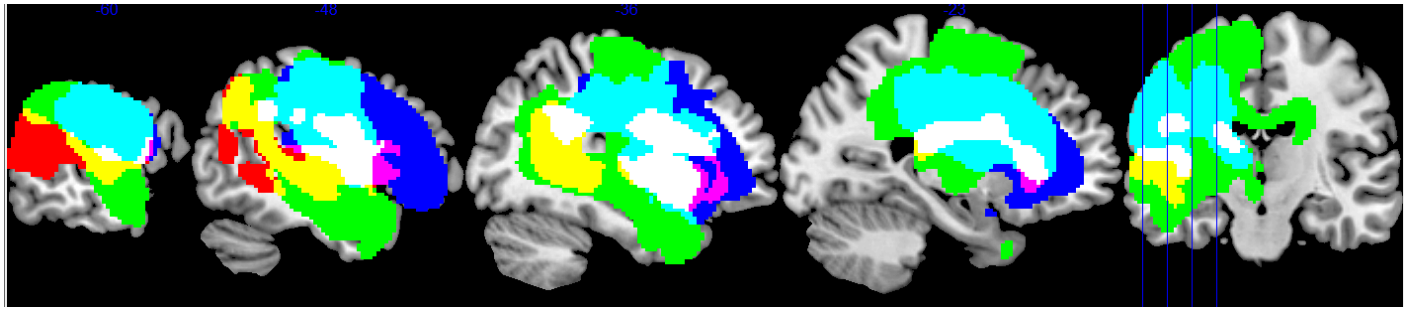


*Figure 6.9: Lesion overlap models showing voxels lesioned in responders and non-responders to **RIPP** therapy.*

AV Responders (DM=red; PR=blue; PM=green)



AV Non-Responders (DF=red; AB=blue; RH=green)

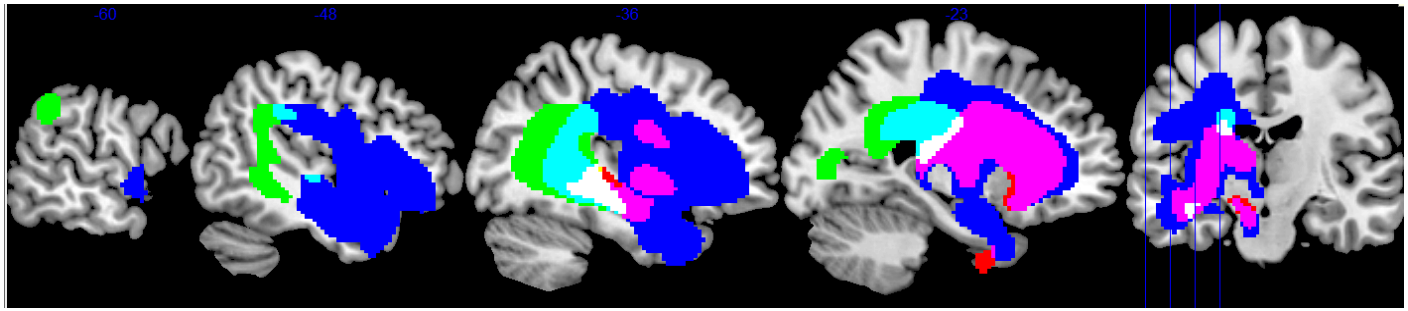


*Figure 6.10: Lesion overlap models showing voxels lesioned in responders and non-responders to **ARTIC** therapy*.

RIPP

Figure 6.9 shows that the three RIPP responders, AB, PM and PR, had larger lesions than the three non-responders. However, all of the responders had largely intact left inferior temporal, and particularly, fusiform gyri. The fusiform gyrus has been consistently implicated in semantic processing in the semantic dementia literature (e.g. Mion et al., 2010), and has also been linked to semantic tasks including comprehension of spoken language in stroke survivors (Spitsyna, Warren, Scott, Turkheimer, & Wise, 2006). This region may also have facilitated therapeutic gains following RIPP for AB, PM and PR. In comparison, DM had a lesion in the left posterior MTG, a region shown to be important for semantic access (Thompson, Robson, Lambon Ralph, & Jefferies, 2015), whilst DF's lesion encompassed the inferior fronto-occipital fasciculus (IFOF), a tract known to be involved in picture naming, as demonstrated by the neurosurgical work of Duffau and colleagues (Duffau, Moritz-Gasser, & Mandonnet, 2014). Both of these areas were intact in the RIPP responders. Considered together, the poor responders' lesions illustrate that disruption to multiple different parts of the semantic naming network can undermine anomia therapies that have a semantic component. Thus, a lesion to either the left posterior MTG or IFOF may result in non-response to RIPP. DF's lesion profile, like RH's, also underlines the critical role of white matter in mediating treatment success.

ARTIC

Figure 6.10 illustrates that the ARTIC responders also had larger lesions than the non-responders. However, all three responders to ARTIC treatment had either the left lateral anterior and posterior insula (DM), medial posterior insula (PR) or medial anterior insula (PM) intact. Conversely, AB and DF, who responded poorly to ARTIC therapy, shared damage to both the medial anterior and posterior insula. Therefore, it is possible that intactness of at least one part of the medial anterior insula is key for success of ARTIC. In support of this suggestion, the anterior insula has been shown to be involved in both visual speech perception and articulation - two tasks integral to ARTIC therapy (Ackermann & Riecker, 2010; Ardila, Bernal, & Rosselli, 2014; Oh, Duerden, & Pang, 2014). AB and DF's results highlight the potential situation that benefitting from the presentation of articulatory

information in the absence of a concurrent item image requires the combination of two medial insula regions and, consequently, that a lesion to both may undermine therapy effectiveness.

Discussion

The primary aim of the current case series was to determine the relative importance of visual speech articulation in computer-based repetition therapy for increasing confrontation picture naming ability in six individuals with chronic post-stroke anomia. Participants received three types of therapy, RIPPA, RIPP and ARTIC, which varied the semantic and articulatory input components provided for immediate repetition. The group level results showed that all three therapies led to significant improvements in treated item naming accuracy. However, the individual level findings revealed that no one type of therapy was most effective in increasing naming ability for all participants, nor did any of the six participants benefit most from RIPP, a therapy technique commonly used to treat anomia in clinical settings (Nickels, 2002b). Instead, RIPPA led to the greatest significant increases in treated item naming accuracy for AB, DF and DM, whilst ARTIC led to the greatest significant improvements in picture naming accuracy for PM and PR. These findings indicate that, for all five patients who responded positively to the intervention programme, providing a visual speech articulation component was necessary for optimal treatment success. In contrast, only two individuals required the concurrent presence of a picture to realise significant gains in naming accuracy. Contrary to expectations, two further participants benefitted only from RIPP and ARTIC, implying that providing semantic, auditory and articulatory cues during RIPPA therapy adversely affected their naming performance.

To our knowledge, the current study is the first to manipulate semantic, auditory and articulatory components when patients complete language production tasks aimed at alleviating their word finding difficulties, meaning that it is not possible to directly compare our results to previous work. However, the current group level finding that therapy involving AV speech did not lead to significantly greater increases in treated naming accuracy than

therapy including audio-only speech does not support the work of Fridriksson, Baker, Whiteside et al. (2009) although, as similarly noted by Fridriksson and colleagues, the individual level results highlighted considerable between-participant variability in response to the types of therapy provided in the present study. In addition, RH, who had the most severe baseline naming deficits, did not demonstrate any significant gains in naming performance following any type of therapy.

One factor that could potentially account for such variability in response to the three types of therapy in the current case series is differing aphasia classifications. Both individuals (PM and PR) who showed the greatest therapy gains following ARTIC therapy were non-fluent: PM had Broca's aphasia and PR had transcortical motor aphasia. In contrast, of the three participants who showed the largest gains in confrontation noun naming accuracy following RIPPA therapy, two (AB and DF) were classified as having fluent, anomic aphasia, whilst the third (DM) was classified as having Broca's aphasia. Taking into account responses to other conditions, DM also demonstrated significant increases in naming accuracy after receiving ARTIC therapy, with his post-treatment gains in this condition almost as great as following RIPPA. Thus, all three non-fluent participants responded to ARTIC therapy, but none of the fluent ones did. Moreover, for two of the non-fluent participants (PM and PR), RIPPA resulted in non-significant, relatively small gains compared to either RIPP or ARTIC. This pattern of results indicates that presenting an item image during therapy was required by the two participants with fluent aphasia who benefitted from the treatment provided in the current study, whilst for those with non-fluent aphasia, a picture was not only unnecessary but, in two cases, was disadvantageous.

There were less straightforward relationships between aphasia classification and treatment gains following RIPP, the only therapy condition that did not include speech articulation as part of the stimulus. Including PR, the three RIPP responders showed larger increases in naming accuracy following either RIPPA (AB) or ARTIC (PM and PR) therapy. All had contrasting aphasia diagnoses and clinical presentations. In comparison, DF, who had a similar language profile to AB, demonstrated only minimal naming improvements following

RIPP. These findings suggest that, for AB, semantic cues were critical for therapy success, whilst DF required both semantic and articulatory cues. In summary, the above observations indicate that aphasia classification alone cannot predict which of the three types of therapy offered in the current study will result in the greater therapeutic gains for individuals with anomia, and which will not prove beneficial. The exception to this is RH, who, as well as not responding to any of the three types of therapy, was the only participant who struggled to complete the repetition therapy task, commensurate with his diagnosis of conduction aphasia.

A related behavioural factor that could have influenced responses to the three types of therapy is apraxia of speech. Apraxia of speech commonly co-occurs in stroke survivors with non-fluent aphasia and affects speech planning and sequencing, resulting in inconsistent, distorted phoneme production and characteristic 'groping' articulatory gestures (Ballard et al., 2000; Fridriksson, Hubbard, et al., 2012; McNeil et al., 1997). Although apraxia of speech was not formally assessed here, the lead author (a qualified speech and language therapist) used clinical judgement to exclude potential participants with moderate to severe apraxia of speech. Of the six individuals who completed the study, PR had mild apraxia of speech. The SWORD computer software programme was specifically designed for, and has been shown to be effective with, patients with apraxia of speech (Varley et al., 2016; Whiteside et al., 2012). This programme includes a repetition task with very similar multimodal input to RIPPA. Consequently, one may have expected PR to benefit from RIPPA. However, this was not the case, and apraxia of speech is unlikely to have affected any participants' therapeutic responses in the present study.

An alternative explanation why participant responses to the three types of therapy varied in the current study is their differing lesion profiles. RH's lesion severed the posterior portions of the arcuate and inferior longitudinal fasciculi, preventing the transmission of auditory input provided in all three therapy conditions, culminating in minimal treatment gains following RIPPA and ARTIC, and no changes in treated item naming accuracy following RIPP. The remaining five participants responded to at least one type of therapy and failed to respond to

at least one other type. This finding suggests that therapy gains in each of the three conditions were mediated by different brain regions. All lesion analysis findings are necessarily exploratory in nature due to the small sample size in the current study. Nevertheless, lesion overlaps for each type of therapy revealed intact cortical areas and white matter pathways common to all responders that were damaged in all non-responders. The most striking finding was that responders to RIPPA (AB, DF and DM) had lesions that spared BA6, a multimodal integration hub in the left frontal lobe, which may have allowed them to successfully process semantic, auditory and articulatory information provided simultaneously during therapy. Conversely, damage to this region (PM and PR) was associated with failure to respond to RIPPA. Both PM and PR responded to RIPP and ARTIC therapy, demonstrating that they were able to make use of both semantic and articulatory cues when offered separately alongside auditory speech. However, they did not benefit when all three types of cues were given at the same time, implying that RIPPA resulted in undesirable information overload.

The lesion overlaps were less clear-cut for responders and non-responders to RIPP and ARTIC. Results suggest that responsiveness to RIPP therapy may rely on the intactness of the inferior temporal and fusiform gyri, whilst damage to two parts of the medial anterior insula appears to be related to lack of responsiveness to ARTIC treatment. However, despite damage to semantic areas, and poor responses to RIPP, both DF and DM responded positively to RIPPA, which also involved the presentation of item images to provide semantic cues. One plausible explanation is that the concurrent articulatory cues provided by RIPPA enabled these individuals to compensate for semantic damage, although the potential underlying mechanisms responsible for this are not yet known. Similarly, the presence of a picture during RIPPA therapy may have supported AB and DF in overriding damage to insular regions implicated in visual speech perception and speech production that hindered their responsiveness to ARTIC. A further, prominent neuroimaging finding was that RIPP and ARTIC responders had larger left hemisphere lesions than non-responders. It is wholly possible that regions in the contralesional right hemisphere mediated treatment effects for these individuals, in accordance with the work of Heath et al. (2013) and Nardo et

al. (2017). These regions could have remained engaged in long-term recovery for those with larger lesions but not those with smaller lesions.

All of these suggestions cannot be substantiated without functional imaging work, with participants scanned as they complete each type of therapy. It remains possible that different regions and mechanisms may mediate similar treatment effects for different patients, due to varying patterns of neural reorganisation following a stroke (Jarso et al., 2013). Such individual variation could be revealed by scanning patients before, during and after each type of therapy, and comparing these results to activations observed in matched healthy control participants. Repeat structural imaging, including DTI, could also be used to better understand relationships between neural changes and treatment outcomes, given evidence of structural changes in connectivity in response to therapy (e.g. Schlaug, Marchina, & Norton, 2009). In order to increase the reliability of any findings, it would be advisable to carry out all of the above suggested imaging work with larger groups of participants than the six included in the present study. Overall, the current neuroimaging findings provide some interesting foundations for future study to elucidate the brain regions responsible for improving confrontation naming ability following different forms of repetition therapy in individuals with chronic post-stroke anomia, and clearly suggest a central role for multimodal processing in mediating gains from RIPPA.

Discussion of the results thus far has focused on treated items. There were also varying effects of each type of therapy on untreated naming accuracy. All participants (except RH) demonstrated numerical increases in naming accuracy relative to baseline following at least one type of treatment, although absolute gains were smaller than for treated items. At the group level, the percentage of untreated items named correctly rose significantly from baseline only following RIPP, and there were no significant effects of treatment on control item naming speed in any of the three conditions. The equivalent response patterns were not dissimilar at the individual level. DM and PR demonstrated significant gains in untreated item naming accuracy following RIPP, whilst DF demonstrated significant gains following RIPPA. These findings may provide some promising evidence of generalisation, with DF's

result consistent with Fridriksson, Baker, Whiteside et al. (2009), who noted generalisation to untreated nouns when speech articulation was provided during therapy. However, although DF and PR named significantly more untreated items correctly post-therapy in conditions in which they had also named significantly more (marginally so in the case of PR) treated items correctly, DM named significantly more untreated items in the only condition in which he did not show any treated item gains. In contrast, DM correctly named the control items marginally faster following RIPPA, which was also the condition that led to his greatest gains in naming accuracy for treated items. For the remaining participants, there were no significant effects of therapy on naming ability with respect to the untreated or control items. Taken together, these results show that therapy gains for the untreated and control items were inconsistent, and provide only modest support for the beneficial effects of including articulatory cues in repetition therapy for stroke survivors with chronic anomia on these measures.

The secondary aim of the current study was to investigate the effects of the intervention programme on participants' connected speech and self-reported ratings of communicative effectiveness. The results showed that specific effects of each therapy on the secondary outcome measures were limited. There were no significant group level changes from baseline to post-therapy on any of the connected speech measures elicited by the picture description task. Examining individual results indicates that, when asked to describe the Cookie Theft image, the length of AB's responses increased following RIPP and ARTIC and the numbers of words and morphemes he produced increased following all three types of therapy. Similarly, the length of DF's responses, and the number of words and morphemes produced also increased after each form of therapy. These findings indicate that therapy transiently increased the quantity of AB's and DF's speech, possibly because successful completion of the errorless repetition therapy tasks led to general increases in confidence and/or word finding abilities. However, these effects were not restricted to particular therapy conditions. Aside from PM and RH, all participants showed more general trends across the picture description measures from the start of their first therapy conditions to post-therapy in their final conditions. Two fluent participants, AB and DF, produced more words and

morphemes over time, although DF also made increasing numbers of pauses, making her output less fluent. With regards to the non-fluent participants, PR became more fluent over time, DM became less fluent, whilst PM's fluency remained constant after his first attempt at the task. Since these observed changes in speech production were also unrelated to any specific type of therapy, it is possible that they reflect cumulative effects of retrieval practice for the same lexical items across multiple attempts or, for DF and DM, reduced interest in the task as it became more familiar.

With respect to the COAST, the group of participants rated their communicative effectiveness significantly higher post-therapy than pre-therapy in all three conditions. At the individual level, however, significant increases in percentage scores on the COAST from baseline to post-therapy corresponded with conditions that had the lowest baselines (or the final therapy condition in RH's case) rather than conditions associated with maximal gains on any of the naming measures. Similarly, four patients (AB, DM, PR and RH) tended to score more highly as they continued to participate in the study, from their first cycle to the last. However, each patient completed the therapy conditions in a different order and, again, there were no direct relationships between COAST scores and any measures of naming ability for these four individuals. A plausible explanation for this latter pattern of results is that participants' self-perceived communicative skills increased over time as a by-product of taking part in the study. Participants had received little speech and language therapy since their discharge from hospital following their strokes, which had occurred many years previously in some cases. During the therapy phase of the present investigation, the lead author visited patients regularly at home over a six-week period. Anecdotally, all six participants reported that they enjoyed these visits and the opportunities to not only receive therapy but also engage in conversation with a new partner, and take part in research that may benefit other stroke survivors with similar language difficulties. All of these factors may have led to increasingly positive states of mind for AB, DM, PR and RH as they progressed through the study.

Whilst it is disappointing that enhanced confrontation naming ability did not directly correspond to improvements on the picture description task, this finding is not entirely unexpected as it is unusual for item gains following impairment-based anomia therapy to translate to connected speech contexts, especially if the required vocabulary is not directly targeted in therapy (Conroy et al., 2009b; Conroy et al., 2018). Another possible reason why no relationships were found for any participants between particular types of therapy and improvements on either the picture description task or the COAST is that these measures were not sensitive enough to detect more subtle changes in functional communication. Including untreated and control items as well as a range of secondary outcome measures in future studies should facilitate further exploration of the potential generalisation of treatment effects beyond single treated nouns in this patient population.

The feedback ratings provided by all six participants revealed some surprising findings. As a group, participants rated all three types of therapy equally on all three subscales. However, excluding AB, who gave all three therapies maximum ratings of ease, enjoyment and effectiveness, all individuals reported perceived differences between RIPPA, RIPP and ARTIC on at least one subscale. In some cases, ratings tallied with improved naming ability. For example, PR rated RIPPA the least enjoyable type of therapy and this condition also led to her smallest therapy gains. Similarly, DM ranked RIPPA over ARTIC and ARTIC over RIPP in terms of enjoyment and effectiveness. This order of preference between therapy conditions mirrored the pattern of percentage increases in treated item naming accuracy, suggesting that DM had good awareness of his own abilities and limitations. In contrast, for DF and PM, feedback ratings did not correspond with gains in confrontation naming accuracy across the three therapy conditions. DF was the only participant to score ARTIC more highly than both RIPPA and RIPP on all three dimensions, yet she failed to demonstrate any significant gains in this treatment condition. Conversely, she ranked RIPPA as less enjoyable than either ARTIC or RIPP, but this was the one type of therapy that resulted in significant increases in both her treated and untreated naming accuracy. Likewise, although ARTIC led to the greatest therapy gains for PM, he rated this form of treatment as less effective than either RIPPA or RIPP, and less enjoyable than RIPPA.

During RIPPA and RIPP therapy, PM had a tendency to try to name each item image as soon as it was presented. These attempts were occasionally inaccurate, meaning that he needed frequent reminding in therapy sessions for these two conditions to wait for the AV or audio clip to finish playing before repeating the correct item name. It is conceivable that providing item images led to difficulties with attention control for PM. Consequently, he experienced greater therapeutic benefits when he was able to repeat back AV speech in the ARTIC condition without being distracted by detailed noun images, yet he was unaware that this was the case. This suggestion is strengthened by his poor performance on neuropsychological tests of executive functioning relative to other participants (Table 6.1).

The above observations demonstrate that stroke survivors with anomia do not always have insight into which types of therapy are optimally effective, nor does enjoyment necessarily correlate with effectiveness. These findings have a number of important clinical implications. For instance, patients who enjoy therapy tasks may be more likely to complete them, in turn facilitating treatment success, whilst other individuals may not wish to continue treatment that they find difficult or boring. Alternatively, patients could be more motivated to complete exercises even if they do not enjoy them if they are advised that the therapy approach is likely to be effective. The implications may be especially pertinent when individuals are carrying out exercises independently in their own homes, as is increasingly the case in order to maximise the efficiency of sparse clinical resources (e.g. Palmer, Enderby, & Paterson, 2013). Further work could explore the relationships between patient perceptions of therapy effectiveness, enjoyment, motivation and therapy success in greater detail, in a variety of treatment contexts.

A key finding from the current study is that providing speech articulation during computer-based repetition therapy was necessary for optimal treatment success for all of the participants who responded to therapy. This observation indicates that the ongoing provision of RIPP in lieu of repetition therapy that includes an articulatory component warrants careful consideration. At the same time, although it may be intuitively appealing to present as much information as possible during therapy by providing semantic, auditory and

articulatory cues, this approach may be counterproductive for certain patients who have difficulties integrating simultaneous, multimodal input. This finding has implications for traditional face to face therapy, plus treatment supplemented via commercially available language software applications such as StepbyStep and SWORD in that, before using such programmes, it may be prudent to trial a number of different input options in order to confirm which is most appropriate for each individual patient. In future, greater understanding of the brain regions associated with success following particular forms of treatment may assist with predicting therapeutic responses from clinical scans.

Conclusions

By adopting a case series design that enabled us to explore the effects of treatment for individual patients, we have clearly shown that providing a visual speech articulation component was necessary for optimising treated item naming accuracy for all five participants who responded positively to a brief, focused computer-based repetition therapy programme for chronic stroke-induced anomia. In contrast, semantic cues, in the form of a concurrently presented noun picture, were not critical for naming success for three of these individuals, two of whom markedly did not benefit from the provision of concurrent semantic, auditory and articulatory cues. Participants demonstrated significant increases in naming ability following just three, 20-minute therapy sessions with only 10 repetitions of each item per session in each condition, indicating the efficiency of the treatment provided. Going forward, research could replicate the protocol with larger numbers of participants representing a range of neuropsychological and lesion profiles, as well as incorporating longer follow-up periods, in order to confirm the current findings and explore the potential longevity of treatment effects. Future findings would be enhanced by carrying out detailed functioning neuroimaging before, during and after treatment to determine the brain regions and mechanisms responsible for mediating the effects of repetition therapy in individual patients. Such work should ultimately facilitate greater personalisation of repetition-based treatment programmes for stroke survivors with chronic anomia.

Chapter 7

General Discussion

Overview

The overarching purpose of this thesis was to enhance current understanding regarding the nature and treatment of anomia in people with chronic post-stroke aphasia. These topics were explored over a series of self-contained chapters. In contrast to much previous work that has focused on group results, case study or case series designs were utilised in all of the empirical chapters, in order to focus on variability at individual patient level. Chapter 2 comprised a comprehensive literature review that evaluated existing research pertaining to the use of tDCS to improve confrontation naming in this patient population, identified outstanding gaps in the literature, and made specific recommendations for future research. Further to this review, the primary aim of Chapters 3 and 4 was to examine the therapeutic effects of systematically varying the laterality and polarity of stimulation in stroke survivors with chronic anomia, something which has not previously been attempted. The investigation described in Chapter 5 followed directly from observed inconsistencies in performance on an extensive pre-therapy confrontation naming assessment completed twice by potential participants in Chapters 3 and 4. The goal of this work was to describe and explain patterns of response inconsistency in noun picture naming in a group of individuals with chronic post-stroke anomia, as this is a key issue when evaluating therapeutic effectiveness.

Chapters 3 and 4 paired tDCS with a computer-based repetition therapy task. Individualised slides were created for each word to be repeated, consisting of an AV clip of a mouth saying the item name accompanied by a colour item image. Evidence suggests that providing both auditory and articulatory cues in behavioural treatment for stroke survivors with chronic anomia may be beneficial, although previous research has not directly compared the effects of manipulating semantic, auditory and articulatory components in repetition therapy in this target population. Consequently, the main aims of the final study included in this thesis, detailed in Chapter 6, were to determine the relative importance of visual speech articulation in computer-based repetition therapy for increasing naming ability in stroke survivors with chronic anomia, and relate patterns of therapeutic response to neuropsychological and lesion profiles.

This final chapter will begin by summarising the key issues raised in Chapter 2 and reviewing the main results of empirical Chapters 3 – 6. Following this, the broader theoretical and clinical implications of these findings will be discussed. The limitations of the thesis will also be considered. Finally, potential directions for future research suggested by the current work will be explored.

Summary of Thesis Findings

Chapter 2

Chapter 2 critically evaluated previous research available at the time of acceptance for publication (August 2015) relating to the use of tDCS to improve confrontation naming of noun and verb pictures in chronic post-stroke anomia. Overall, such research indicates that administering tDCS alongside concurrent behavioural speech and language therapy can lead to greater therapeutic gains than those achieved following behavioural therapy alone. In particular, combining anodal stimulation applied to the damaged left hemisphere and/or cathodal stimulation applied to the intact right hemisphere has been linked to increased naming accuracy and speed in diverse groups of individuals with chronic anomia following a left hemisphere stroke (e.g. Baker et al., 2010; Fiori et al., 2013; Flöel et al., 2011; Fridriksson et al., 2011; Kang et al., 2011; Marangolo et al., 2013; Vestito et al., 2014). These observations are in line with neuroimaging findings highlighting the importance of neural activation in left perilesional regions for language recovery in the chronic stage following a stroke, with the exception of patients with very large or extensive left hemisphere lesions (e.g. Fridriksson, Richardson, et al., 2012; Heiss & Thiel, 2006; Marcotte et al., 2012; Meinzer et al., 2008). However, support for the use of tDCS as an adjunct to behavioural therapy in this patient population has been limited by the highly varied protocols used in different studies, many of which did not use scanning data to individualise electrode placement or examine the effects of tDCS-plus-therapy on outcome measures other than increased ability to name single treated items. Moreover, existing studies have included no more than two active electrode montages that varied either the polarity or site of stimulation, making it impossible to determine the optimal stimulation parameters to treat chronic anomia in stroke survivors. The studies presented in Chapters 3 and 4 were specifically designed to address these concerns.

Since producing Chapter 2, a number of additional studies have compared the effects of anodal and sham tDCS applied to the left motor cortex (Meinzer et al., 2016), or have

included single trials of multiple different electrode montages at a preliminary stage (Lifshitz Ben Basat et al., 2016; Norise et al., 2017; Shah-Basak et al., 2015). Further details on these more recent studies are provided, where relevant, in the introductory and discussion sections of Chapters 3 and 4. However, in all of these investigations, participants still only received one form of active stimulation alongside concurrent behavioural therapy, meaning that the optimal parameters to combine with therapy for individual patients remain unclear on the basis of their results.

Chapter 3

Chapter 3 focused on the effects of combining tDCS with concurrent, personalised, noun repetition therapy in an individual (JSc) with chronic Broca's aphasia arising from a left frontal lesion. JSc completed a comprehensive intervention programme involving six, four week-long cycles of computer-based picture naming therapy, each paired with a different tDCS electrode montage. Stimulation targeted either the left IFG, or its contralateral homologue, in four active (perilesional anodal, perilesional cathodal, contralesional anodal and contralesional cathodal) and two sham (perilesional and contralesional) conditions. Three, 20-minute treatment sessions were provided in the first week of each therapy cycle. On the basis of previous research, combining therapy with perilesional anodal and/or contralesional cathodal stimulation was predicted to be most beneficial for this particular individual. Ipsilateral active and sham stimulation conditions were directly compared in order to confirm the effectiveness of tDCS-plus-therapy relative to the effectiveness of therapy alone, within each hemisphere.

The research hypothesis was partly confirmed. Increases in JSc's confrontation naming accuracy of treated items were significantly greater immediately and three weeks following perilesional anodal than perilesional sham stimulation. These observations are in accordance with previous group-level findings supporting the use of left hemisphere anodal stimulation to enhance oral picture naming in individuals with relatively circumscribed left hemisphere lesions, as well as research linking increased activation in perilesional regions

with post-stroke language recovery (e.g. Baker et al., 2010; Fridriksson, 2010; Meinzer et al., 2016; Shah-Basak et al., 2015). Contrary to expectations, cathodal stimulation did not significantly enhance JSc's naming accuracy. Consequently, the results from this individual patient do not support previous research involving cathodal stimulation to the right Broca's homologue (Kang et al., 2011; Rosso et al., 2014) or the notion of transcallosal disinhibition (Geranmayeh et al., 2014; Karbe et al., 1998; Martin et al., 2009). In addition, the effects of active stimulation on JSc's confrontation naming accuracy of untreated items, speed of naming control items, and scores on a range of secondary outcome measures were inconsistent.

The findings from the case study are important as they confirm, for the first time, the feasibility of completing a relatively long-term, multiple outcome measure intervention programme that systematically varies the laterality and polarity of stimulation with individuals with chronic stroke-induced anomia. tDCS was well-tolerated by JSc throughout his involvement in the study and he was unable to reliably distinguish active from sham tDCS sessions, indicating that 1mA tDCS was appropriate to ensure comfort and blinding in this participant. His results demonstrate that naming accuracy can be significantly increased and maintained for three weeks in an individual almost a decade post-stroke via just three 20-minute sessions of perilesional anodal stimulation combined with computer-based repetition therapy. Previous studies have obtained similarly significant results following between five and 16 therapy sessions in each treatment condition. Thus, JSc's results also indicate that it may be possible to decrease the typical dosage of tDCS plus behavioural therapy without compromising effectiveness, potentially making such treatment more efficient and therefore less demanding for both patients and clinicians.

Chapter 4

Following the case study investigation reported in Chapter 3, three additional participants repeated the same tDCS-plus-therapy programme completed by JSc: GH, who had severe mixed non-fluent aphasia associated with extensive damage to the left frontal, temporal and

parietal lobes, and EBe and JSo who had mild-moderate anomic aphasia as a result of more focal, posterior lesions affecting the left supramarginal gyrus, and the left STG and occipital gyrus, respectively. Chapter 4 comprised a case series including all four patients. In line with both the hierarchical model (Heiss & Thiel, 2006) and previous research showing significant language improvements linked to increased activation in the intact right hemisphere in patients with similarly large lesions, GH was anticipated to benefit most from supplementing therapy with perilesional cathodal and/or contralesional anodal stimulation. Due to the paucity of evidence regarding combining behavioural therapy with more posterior regions, the optimal stimulation parameters for the two non-fluent participants were more difficult to predict. However, their speed of naming correct control items was predicted to be significantly faster following perilesional anodal than perilesional sham stimulation, in accordance with Fridriksson et al. (2011).

The longitudinal treatment protocol continued to be well-tolerated by participants, none of whom reported perceived differences between active and sham stimulation conditions, further indicating the viability of adopting similar study designs with groups of stroke survivors in the future. However, the results provided only limited support for any of the hypotheses. Instead, the main finding from the case series was that, in contrast to the results previously obtained with JSc, there was no clear benefit of one particular form of active tDCS compared to sham for any of the three further participants. Although EBe's treated item naming accuracy was significantly greater three weeks following contralesional cathodal than following contralesional sham stimulation, there was also a significantly greater increase in her naming accuracy at the same time point after contralesional anodal than contralesional sham stimulation. Similarly, whilst JSo named the correct control items significantly faster immediately post-therapy than at baseline in the perilesional anodal condition, the difference in her naming response time in this condition was not significantly different to that observed in the perilesional sham condition. JSo also named control items significantly faster at various time points from baseline in a number of other stimulation conditions. For GH and JSo, improvements in naming accuracy were not significantly greater following any type of active stimulation than following sham, at any time post-

treatment. Furthermore, neither untreated item naming accuracy nor scores on the secondary outcome measures differed consistently as a result of any form of active tDCS, for any of the four participants. Taken together, the results of the case series study do not support previous research showing superior therapeutic gains for patients with more severe anomia, or group studies showing significantly greater improvements in confrontation picture naming or word production elicited via picture description following active versus sham stimulation (e.g. Baker et al., 2010; Meinzer et al., 2016; Norise et al., 2017; Shah-Basak et al., 2015; Volpato et al., 2013).

Whilst it is disappointing from a clinical perspective that two participants did not demonstrate significantly greater improvements on any of the outcome measures following any form of active stimulation than following sham stimulation, the case series' findings bring the key issue of variability in response to tDCS-plus-therapy intervention programmes to the fore. Such variability was typically also present in earlier studies, but masked by group level analysis (e.g. Baker et al., 2010; Fiori et al., 2013; Kang et al., 2011). EBe's and JSo's results also confirm that similar stimulation parameters may have different effects on language abilities even in individuals with relatively comparable behavioural and lesion profiles. As a whole, Chapter 4 provides evidence that only a subset of individuals benefit from the addition of tDCS alongside behavioural treatment for their word finding difficulties.

Chapter 5

Chapter 5 presented an investigation that aimed to describe and explain patterns of inconsistent confrontation picture naming accuracy across multiple assessment sessions in a diverse group of 15 individuals with chronic post-stroke anomia. Previous work has noted that patients may correctly name certain items correctly on a first attempt but not a second, and vice versa (e.g. Capitani et al., 2012; Freed et al., 1996), yet such inconsistency has not been systematically studied until now. Participants attempted to name 408 noun pictures, without cues, on two separate occasions, at least one week apart.

All participants demonstrated considerable naming response inconsistency: the mean percentage of items named correctly on one occasion and incorrectly on the other was 25.98% (range = 16.54% - 34.15%). These results clearly demonstrate that confrontation noun naming accuracy of stroke survivors with chronic anomia may be inherently highly variable across trials, and that degree of inconsistency differs between individuals. In line with prior observations, each patient named items incorrectly-then-correctly and correctly-then-incorrectly. There were no relationships between degree of response inconsistency and an extensive range of demographic and behavioural variables, including lesion size, aphasia subtype, overall anomia severity, or scores on specific linguistic or cognitive subtests, although there was limited evidence for an association between mild apraxia of speech and above average response inconsistency scores, and for a role of repetition priming (as per Nickels, 2002a) in producing incorrect then correct naming for five participants.

Psycholinguistic properties of item names known to influence naming performance in individuals with chronic post-stroke anomia, such as length in phonemes, number of syllables, and item frequency, were found to be important predictors of consistently correct or incorrect naming, as in previous studies. In contrast, the same variables played much weaker roles in predicting inconsistent correct-then-incorrect naming for only five participants and incorrect-then-correct naming for just seven individuals. Consequently, it is likely that alternative factors other than psycholinguistic variables are responsible for inconsistent naming for the majority of patients. Moreover, correct-then-incorrect and incorrect-then-correct naming patterns were not influenced in the same way by the included psycholinguistic variables, suggesting different mechanisms underpin the two different patterns of response inconsistency. Overall, the investigation is the first to comprehensively document patterns of response inconsistency in oral picture naming in stroke survivors with chronic anomia and to rule out a number of potentially plausible explanations for this phenomenon.

Chapter 6

The final empirical chapter presented an original case series in which six individuals with chronic stroke-induced anomia (three non-fluent and three fluent) received three different types of computer-based behavioural therapy, each of which manipulated the semantic, auditory and articulatory components of input presented for immediate repetition. Auditory noun names were provided in all three conditions. In the RIPPA condition, participants were also given both semantic and articulatory cues, in the RIPP condition, participants additionally received only semantic cues, and in the ARTIC condition, only articulatory cues accompanied the auditory item names. In each condition, patients completed three, 20-minute therapy sessions within a working week.

Whilst all three therapy conditions led to significant gains in treated item naming accuracy for the group as a whole, the individual level analysis showed that different types of therapy resulted in significant gains for different participants. Five participants responded to at least one type of therapy and did not respond to at least one further type of therapy. More specifically, three individuals benefitted most from RIPPA and two benefitted most from ARTIC. This finding indicates that the inclusion of a speech articulation component was necessary for optimising the success of repetition therapy for all five participants who responded to the intervention programme. The final participant, RH, demonstrated only minimal gains following all three therapies, consistent with his diagnosis of conduction aphasia arising from critical damage to the left arcuate and longitudinal fasciculi. Relationships were found between aphasia classifications and the most effective therapy type for each participant. Thus, aside from RH, the remaining two patients with fluent aphasia required the presence of a noun picture to respond to therapy, and providing both articulation and a picture led to the largest increases in naming accuracy. Conversely, all three non-fluent participants benefitted from ARTIC and, contrary to expectations, two of these individuals did not respond to RIPPA, implying that providing auditory, articulatory and semantic cues was unhelpful.

The behavioural results were complemented by tentative neuroimaging findings, which revealed specific left hemisphere regions that were commonly intact in good responders and lesioned in non-responders. In particular, damage to BA6 appeared to account for the pattern of non-response to RIPPA, such that individuals with lesions to this region appeared to be unable to process multimodal therapy input and thereby benefit from RIPPA. In addition to significant benefits of the intervention programme on treated item naming accuracy, at both group and individual levels, there was limited evidence of treatment generalisation to untreated and control items. In contrast, changes in scores on the secondary outcome measures were unrelated to specific types of therapy.

The RIPPA case series study is valuable for a number of reasons. Firstly, the findings highlight the interplay between therapy components and patient neuropsychological and lesion characteristics for maximal treatment success following repetition therapy for chronic anomia. The results clearly demonstrate the importance of including articulatory cues during treatment, whilst cautioning against providing articulatory and semantic cues for a subset of patients who have difficulties integrating multimodal input. In addition, collating participants' feedback revealed non-straightforward relationships between naming outcomes and patient perceptions of ease, enjoyment and effectiveness of therapy, with associated inferences for clinical practice.

Theoretical Implications

The results of Chapters 3 and 4 raise a number of issues regarding how non-invasive neurostimulation is believed to influence activity in the post-stroke brain and how changes in neural activation in both the left and right hemispheres correspond to improvements in language abilities. The majority of previous studies investigating the effects of tDCS-plus-therapy have delivered anodal tDCS to damaged regions in the left hemisphere or to intact perilesional areas, based on evidence indicating that relateralisation of language abilities is advantageous for language recovery in the chronic stage post-stroke. For JSc, combining repetition therapy with perilesional anodal stimulation targeting the left IFG led to

significantly greater gains in treated item naming accuracy immediately and three weeks post-therapy than sham stimulation, and was more effective than alternative forms of active stimulation delivered to either the left or right frontal lobes. Consequently, JSc's results support the notion that applying 1mA anodal tDCS directly to left, frontal perilesional areas increased activation in this region, and that such activation improved his anomia. At the same time, the observed dip in JSc's naming performance at one week post-therapy demonstrates that the relationship between increased activation in left perilesional areas and behaviour change is not necessarily straightforward. Instead, this pattern of results is consistent with the belief that different mechanisms underpin the effects of anodal tDCS at varying time points (Nitsche, Fricke, et al., 2003; Stagg & Nitsche, 2011) and/or that a consolidation period may be required to realise lasting, stable improvements in naming performance following stimulation (Reis et al., 2009).

Relative to research investigating the effects of perilesional anodal stimulation, a more limited number of previous studies have shown that administering cathodal tDCS to the undamaged right hemisphere can enhance naming ability. The primary rationale of this approach is resolving transcallosal disinhibition, such that inhibiting supposed dysfunctional hyperactivity in the contralesional hemisphere may indirectly facilitate advantageous activation in the left hemisphere (e.g. Geranmayeh et al., 2014; Martin et al., 2009), yet there were no discernible effects of cathodal stimulation applied to JSc's contralateral IFG. A plausible explanation for this finding is that, contrary to the transcallosal disinhibition hypothesis, his right hemisphere was not overactive during picture naming and, therefore, reducing activation in this region via cathodal stimulation did not influence activation in left perilesional areas, and subsequently improve language performance. For some stroke survivors, increased activation in right homologous areas in the chronic stage may represent adaptive reorganisation, particularly for patients with extensive damage to left hemisphere language regions (Heiss & Thiel, 2006). In line with Hickok and Poeppel's (2004, 2007) dual stream model, beneficial recruitment of contralesional areas in patients with chronic anomia may also be more likely when completing semantically-mediated tasks that typically involve ventral stream structures in the bilateral temporal lobes of healthy individuals than when

carrying out purely phonological tasks that rely on the predominantly left-lateralised dorsal route (Crinion & Price, 2005; Geranmayeh, Leech, & Wise, 2015). Chapters 3 and 4 show that attempts to directly increase activation in JSc's contralesional hemisphere via anodal stimulation applied to the right IFG or indirectly via perilesional cathodal stimulation had no significant effects on his naming ability. Taken together, the lack of behavioural outcomes noted following perilesional cathodal, contralesional anodal and contralesional cathodal stimulation imply that, although the involvement of more posterior right hemisphere sites cannot be confirmed or ruled out, JSc's right frontal lobe was not involved in picture naming in either an adaptive or maladaptive capacity. This suggestion runs counter to his belief that therapy cycles targeting the contralesional hemisphere had been more beneficial than those targeting the left, but could provide further evidence that patients' perceptions of therapeutic effectiveness are not always accurate, as detailed in Chapter 6.

A further participant in Chapter 4, EBe, demonstrated an unexpected pattern of improvements in treated item naming accuracy three weeks post-stimulation, which suggests that she benefitted from increased *and* decreased activation in her contralesional parietal lobe. At first glance, these findings appear difficult to reconcile with theories regarding the roles of the right and left hemispheres in language recovery in the chronic stage post-stroke. However, it is possible that interactions between tDCS and the SSRI fluoxetine could have reversed either the inhibitory effects of contralesional cathodal stimulation or the excitatory effects of contralesional anodal stimulation through the actions of the drug on serotonin levels. As a result, therapy gains may have essentially been linked to *either* increased or decreased activation in the right hemisphere, in line with research positing a beneficial role for recruitment of posterior right hemisphere regions when completing semantically-mediated tasks, or the notion of transcallosal disinhibition, respectively (e.g. Geranmayeh et al., 2014; Mohr, Difrancesco, Harrington, Evans, & Pulvermüller, 2014).

Alternatively, EBe's naming accuracy improvements may have been significantly greater in the contralesional anodal and contralesional cathodal conditions than in the contralesional

sham condition at the three week follow-up due to her uncharacteristically poor naming performance in the contralesional sham condition at this time point. In addition to the tDCS case series study presented in Chapter 4, both EBe and JSc participated in the naming response inconsistency study reported in Chapter 5. Across the two naming assessment sessions, both patients named around 30% of items incorrectly on one occasion and correctly on another. Thus, for either participant, apparent increases in treated item naming accuracy of up to 30% following tDCS may reflect inherent naming response inconsistency rather than true treatment gains. Three weeks post-therapy, EBe's naming accuracy was 21% higher than at baseline in the contralesional anodal condition and 37% higher in the contralesional cathodal condition. These observations suggest that, were it not for her naming accuracy decreasing by 5% from baseline at the same time point in the contralesional sham condition, the effect of contralesional anodal stimulation may not have been significant, and the effects of contralesional cathodal stimulation may have been only marginally so. In comparison, JSc's naming accuracy immediately following perilesional anodal stimulation was 55% greater than at baseline and 50% greater than at baseline at the three week follow-up, indicating a more convincing effect of tDCS-plus-therapy. It is possible that EBe's significant gains immediately (53%) and one week (42%) following perilesional anodal stimulation could similarly have been significantly greater than her gains following sham treatment had her naming accuracy been lower in the perilesional sham condition at both time points, when intrinsic naming inconsistency could account for her non-significant increases in correct item naming (immediate 26%, one week 16%). Taking all of the above observations into account, it is conceivable that, in line with previous research supporting the use of tDCS to increase beneficial activation in the damaged left hemisphere, EBe's naming was influenced more substantially by perilesional anodal and contralesional cathodal stimulation than by sham but such effects were concealed by her inherent response inconsistency.

In contrast to the results obtained with JSc and EBe, Chapter 4 revealed that the remaining two participants, GH and JSo, did not demonstrate significant gains in treated item naming accuracy following any form of active stimulation than following sham. Repetition therapy

proved particularly effective for JSo, whose naming accuracy was significantly improved from baseline in all six conditions on at least one occasion following treatment. As such, her naming performance could have already been at or approaching ceiling as a product of the behavioural treatment, leaving little opportunity for 1mA stimulation to influence her results. This observation implies that supplementing therapy with tDCS may not be worthwhile for individuals who, irrespective of baseline anomia severity, are able to glean substantial benefits from behavioural treatment alone. Alternatively, it is conceivable that some patients with chronic stroke-induced anomia require a higher current intensity than 1mA to induce short- and/or long-term alterations in neural activation and exhibit any corresponding behavioural changes in response to active stimulation. Current flow modelling studies have shown that, compared to healthy brains, the presence of stroke-induced lesions and associated enlarged CSF-filled ventricles in stroke-damaged brains can reduce the average electrical field strength generated by tDCS across the cortex, as well as influence which neural regions receive the greatest current concentrations (Datta et al., 2011; Minjoli et al., 2017). Furthermore, differing lesion profiles between individuals mean that applying the same current to the scalp may lead to substantial differences in measured currents throughout the brain (Esmaeilpour et al., 2018). In turn, these factors may cause areas involved in picture naming to receive insufficient current following 1mA tDCS to mediate significant increases in naming ability in certain participants.

The effects of 1mA tDCS on activity in underlying tissue cannot be examined or correlated with therapeutic gains without functional imaging of neural activation before, during and after stimulation. Similarly, within-participant study designs are required to investigate the consequences of varying the intensity of tDCS on language outcomes. However, closer inspection of the findings of prior work that has incorporated higher current intensities (typically 2mA) indicates that a proportion of participants still failed to demonstrate significant improvements in language abilities following stimulation (e.g. Volpato et al., 2013; Shah-Basak et al., 2015). Moreover, scrutinising the individual level results of all previous tDCS-plus-therapy studies that aimed to enhance word finding in stroke survivors with chronic anomia reveals considerable variability in response to the treatment programmes provided,

regardless of the polarity, location or intensity of stimulation. Between-participant variability in response to tDCS has also been noted outside of the field of post-stroke language recovery, in both healthy and clinical populations (e.g. Ferrucci et al., 2014; Li, Uehara, & Hanakawa, 2015; Westwood, Olson, Miall, Nappo, & Romani, 2017). In accordance with the above findings, GH and JSo may be additional tDCS non-responders.

It is unclear why some individuals respond positively to tDCS whilst others apparently do not. For certain participants, the possibility exists that suitable electrode montages have yet to be identified. For example, bilateral montages that simultaneously deliver perilesional anodal and contralesional cathodal stimulation may be more effective for some patients than either type of stimulation delivered unilaterally in focusing current in left perilesional areas, resulting in more consistent language gains (Galletta et al., 2015). For other individuals, unique physiological features could make them less sensitive to external attempts to modify neuronal excitability (Horvath, Carter, & Forte, 2014; Labruna et al., 2016). Until the reasons for variability in response to stimulation are better understood, unreliable effects are likely to undermine the impact of evidence supporting the use of tDCS alongside behavioural speech and language therapy.

The results of Chapter 6 have additional implications for our understanding of post-stroke language reorganisation in individuals with chronic anomia and the subsequent effects of such reorganisation on response to treatments aimed at improving word finding abilities. In line with Chapter 5, all significant treatment gains in Chapter 6 were associated with increases in treated item naming accuracy of at least 35%, indicating that such improvements were more likely to be directly related to the treatment provided rather than due to inherent naming response inconsistency. Five participants responded to at least one form of repetition therapy and did not respond to another. This observation implies that successful processing of semantic, articulatory, or semantic and articulatory cues provided during repetition therapy involves different parts of the language network, and that stroke-induced damage to specific regions can selectively impair individuals' ability to benefit from particular types of treatment. Accordingly, the structural neuroimaging findings revealed a

potential role for BA6 in mediating therapeutic gains following RIPPA, such that individuals with damage to this region were unable to integrate simultaneous semantic and auditory cues, and so were unable to benefit from this type of therapy.

Less straightforward neuroimaging findings suggest that lesions affecting the left inferior and fusiform gyri are associated with non-response to RIPP, and those involving parts of the left medial anterior insula are associated with non-response to ARTIC. However, the larger left hemisphere lesions of the RIPP and ARTIC responders relative to non-responders suggest that treatment success in these two conditions may be mediated by the contralesional hemisphere, either independently or in conjunction with the left. Thus, the results of the RIPPA study may implicate adaptive recruitment of the right hemisphere in language recovery, which was not found in the tDCS work. The sixth participant, RH, whose lesion severed the posterior portions of the arcuate and inferior longitudinal fasciculi, did not respond to any type of repetition therapy. Whilst this finding was not surprising as RH was largely unable to complete the therapy tasks, his neuroimaging results highlight the importance of white matter tracts for success on picture naming tasks.

Including PR's marginally significant response to RIPP, four participants responded to at least two types of treatment. However, all five responders demonstrated the greatest improvements in naming accuracy following either RIPPA or ARTIC therapy, indicating that the inclusion of articulatory information was the key element for optimal treatment success. Why this should be the case is uncertain. It is possible that the results of the study provide some support for controversial 'mirror neuron' theories of speech perception. Based on studies with animal subjects, these theories maintain that certain cells are activated both when an individual performs a particular action and when s/he observes another performing the same action (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). In humans, these neurons may be located in regions shown to be involved in both speech production and visual speech perception in healthy adults, including Broca's area and the left inferior premotor cortex (Fridriksson, Moser, et al., 2009; Skipper et al., 2005; Skipper, van Wassenhove, Nusbaum, & Small, 2007), although other authors argue that such cells do not play an

important role in human speech perception (Lotto, Hickok, & Holt, 2009). In Chapter 6, mirror neurons may have been activated by providing articulatory cues during repetition therapy, resulting in more favourable language outcomes, but this hypothesis is impossible to verify without neuroimaging. Overall, whilst the brain regions linked in Chapter 6 to response and non-response to repetition therapy are plausible on the basis of previous research, they cannot be confirmed without structural imaging of grey and white matter, and functional imaging as participants complete each type of treatment to elucidate the areas involved on a patient-by-patient basis.

Clinical Implications

In addition to theoretical implications, the thesis findings have practical implications for clinicians working with stroke survivors with chronic anomia. All of the empirical studies presented here emphasise within- and between-patient variability in terms of lesion profiles, behavioural characteristics and response to treatment. People with aphasia are known to be a highly heterogenous group of individuals. However, this thesis has revealed some novel observations that could be utilised to help guide assessment and treatment, potentially resulting in improved language skills in this patient population. For instance, the results of the response inconsistency investigation indicate the need to carry out baseline naming assessments at least twice to determine which items patients have repeated difficulty in naming and which they are able to name correctly on certain occasions but not others, in order to establish a more sensible baseline against which to assess therapeutic gains. The two types of items may also require different treatments. In addition, it is important to recognise that seemingly substantial increases in naming accuracy following therapy may reflect inherent inconsistency rather than the effects of intervention, even if such effect sizes prove statistically significant.

In considering treatment options, the results of the RIPPA investigation highlight the importance of including a speech articulation component when delivering computer-based repetition therapy, whilst also clearly illustrating that it may be counterproductive to provide

too much information to individuals who have difficulties in processing multimodal input sources. As further findings become available, neuroimaging tools could be used to predict which therapy components are likely to benefit participants. In the interim, or when detailed scanning information is not available, it may be judicious to provide short trials of different types of repetition therapy to confirm effectiveness.

In contrast with research indicating the need for intensive therapy schedules that incorporate many hours of input over a short period of time (Brady et al., 2016), Chapters 3, 4 and 6 all demonstrate that significant gains in treated item naming accuracy can be efficiently achieved following just three, 20-minute treatment sessions. Consequently, even when clinical resources are very limited, it may be possible to successfully treat a number of items that an individual patient has difficulty retrieving via a brief, targeted intervention programme. When increased amounts of therapy input are desired, perhaps to ensure maintenance of treatment effects, all three therapy conditions included in the RIPPA study could be readily adopted into increasingly popular home-based programmes. Doing so would allow patients to carry out multiple, self-guided practice sessions in their own time, thus reducing demands on limited clinical resources. In offering treatment, clinicians should be mindful that patients' perceptions of therapeutic effectiveness may not match with reality, particularly if they have executive function deficits, meaning that some individuals may require additional encouragement to carry out appropriate exercises if they perceive them to be boring or ineffectual. Based on the current findings, consistent and predictable generalisation from treated items to untreated items and alternative communication measures should not necessarily be anticipated.

The results of the tDCS studies imply that stimulation may be a useful adjunct to behavioural therapy for the right candidates. Like computer-based treatments, tDCS may further enhance therapeutic efficiency when delivered in domestic settings. Despite potential concerns, including those relating to manual dexterity and cognitive ability, tDCS has been self-administered successfully and safely by stroke survivors, as well as patients with multiple sclerosis and Parkinson's disease (two additional neurological disorders also

associated with physical and cognitive limitations), in their own homes (Crinion, 2015; Shaw et al., 2017). Nevertheless, the thesis findings suggest that ongoing use of tDCS be accompanied by the caveat that combining behavioural therapy with stimulation should not be expected to enhance the effects of behavioural therapy alone for a considerable number of eligible patients. Practical difficulties and inconsistent results may deter the adoption of tDCS into mainstream speech and language therapy practice. Consequently, neurostimulation may ultimately prove to be best suited to research contexts as a tool for investigating neuroplasticity and neural connectivity rather than a practical treatment option alongside behavioural therapy in everyday clinical settings.

Limitations of the Thesis

It is acknowledged that certain methodological limitations of the research presented in this thesis could have influenced the results obtained and the conclusions that may be drawn on the basis of these findings. Firstly, only four participants completed the tDCS-plus-therapy protocol (Chapters 3 and 4). Although this small, manageable sample permitted in-depth study of each participant, it is difficult to make generalisations or support or challenge hypotheses, such as the notion of transcallosal disinhibition, from so few individuals. The original intention was to complete the intervention programme with 12 participants (six non-fluent and six fluent). Many more individuals than this were keen to participate. However, there was a necessarily high exclusion rate based on contraindications to stimulation on safety grounds, such as a history of seizures or the presence of metal within the body. Initially, potential participants were also excluded over concerns that interactions between SSRIs and tDCS would confound results, yet an unexpectedly high proportion of individuals were found to be taking such medication. Despite relaxing the recruitment criteria to include patients taking one SSRI (including EBe) in order to more accurately reflect real-life clinical practice, several would-be participants remained ineligible due to their use of multiple drugs that affect the central nervous system. For instance, some individuals had been prescribed citalopram for anxiety and amitriptyline for chronic neuropathic pain. The issue of low participant numbers in the tDCS case series was compounded by the need to exclude a fifth

individual (MD) after he suffered an unrelated seizure after completing his first (perilesional sham) therapy cycle. Overall, a sizeable number of people who wanted to take part in the study were unable to do so for medical reasons. A key implication of this observation is that it is likely many patients in real-life clinical settings would be similarly unsuited to receiving tDCS, further hindering the translation of stimulation-based interventions to mainstream practice.

Three additional stroke survivors who were willing and medically eligible to participate were excluded because they did not name enough items incorrectly on their first and/or second attempts during the pre-therapy naming assessment. In order to produce six personalised treated and six untreated 20-item sets, individuals were required to have difficulty producing at least 240 of the 408 available items. There was a degree of flexibility with regards to this target, however, DM, EBo and MaD (see Chapter 5) named only 123, 124 and 136 nouns incorrectly at least once, respectively, meaning that each of their 12 item sets would have contained far fewer than 20 items had they been admitted to the tDCS study. A similar linguistic criterion applied to the RIPPA investigation presented in Chapter 6 but was a lesser concern as only 120 incorrect items were needed to create six item sets for the three therapy cycles. Providing fewer than six cycles of tDCS-plus-therapy would have precluded investigating the effects of varying both polarity and laterality of stimulation, and treating 20 items per therapy cycle was considered necessary to detect any significant effects (e.g. Snell, Sage, & Lambon Ralph, 2010). Nevertheless, a remaining option may have been to offer more than 408 items at baseline. In particular, in line with known relationships between correct naming and psycholinguistic item properties, potential participants may have been more likely to struggle with naming larger numbers of long, infrequent, abstract, unfamiliar, atypical items (e.g. Kittredge et al., 2008; Nickels & Howard, 1995). Although such items may have been more challenging to depict via black and white images, their inclusion could have resulted in greater numbers of available items for treatment for some individuals with less severe anomia, thereby facilitating the recruitment of additional participants to the study.

Whilst the number of therapy sessions per stimulation condition was considerably lower than in previous research, some prospective participants may still have felt that the protocol was too demanding and, consequently, they were dissuaded from entering the study. This may have been especially true for individuals with limited physical mobility and/or those who lived a considerable distance from the therapy site, given that they were required to travel to hospital to complete all sessions involving the application of tDCS. Including regular home visits for baseline and follow-up testing, participants were involved in the study for at least seven months. Thus, participation required a level of commitment that some individuals may not have been willing or able to sustain. Whilst no recruited participant voluntarily left the study, all remarked that they would have preferred to have received therapy in their own homes. The decision was made to carry out all stimulation sessions in a hospital setting to ensure prompt medical assistance in the highly unlikely event that a participant suffered a serious adverse reaction to tDCS. Nevertheless, taking into account the increasing body of evidence confirming the safety of tDCS in this patient population, administering tDCS in a hospital setting may have been overly cautious.

Irrespective of participant recruitment issues, the findings obtained for the four individuals who completed the tDCS case series and their resulting implications may have been restricted by certain aspects of the chosen methodology. As already discussed, it is plausible that the number of therapy sessions and/or current intensity was insufficient to produce significantly greater changes in naming accuracy following active rather than sham stimulation for at least two of the participants. Furthermore, for the participants who did demonstrate significantly greater gains in treated naming accuracy following particular active stimulation montages rather than sham, there were no similar treatment effects on measures other than increased accuracy of confrontation noun naming at single word level. It was hoped that including a range of secondary outcome measures would extend the results of previous studies, which have typically only examined the effects of tDCS-based therapy programmes on picture naming. Instead, it is possible that the selected measures in the tDCS studies were not sensitive enough to capture any differences in behaviours as a result of active relative to sham stimulation. The same issue may have influenced outcomes in the

exploratory RIPPA study, which also failed to find consistent results of individual therapy conditions on outcomes other than treated item naming accuracy.

Patient's scores on the COAST in the tDCS and RIPPA studies (as well as the bespoke mood questionnaire and Carer COAST) appeared to correspond to either random fluctuations or generally increasing trends in self-perceived communicative effectiveness and mood over the course of participation. The broad questions and simple response scales contained in these aphasia-friendly measures may have been insensitive to any subtle changes induced by specific treatment conditions. Similarly, whilst the Cookie Theft image was chosen as a means to elicit connected speech in the tDCS and RIPPA investigations as it is readily available, has been tested extensively with this particular patient population, and was specifically designed to facilitate generation of multiple single words within a coherent narrative, this measure may not have been the most appropriate stimulus to elicit production of the treated items. Generalisation from unrelated treated items to the connected speech generated by this task would likely require simultaneous cross-task and cross-item transfer. Expecting both forms of transfer to occur may have been unrealistic. Consequently, it is perhaps unsurprising that no direct effects of specific treatment conditions were found with respect to any of the connected speech measures analysed in Chapters 3, 4 and 6. Asking participants to describe alternative composite images that included items targeted in therapy may have led to more consistent patterns of generalisation, as per Conroy et al. (2018). In addition, each participant completed the same picture description task 18 times in the tDCS studies and seven times in the RIPPA study. Cumulative practice effects, such as increased fluency or boredom, may have overridden more minor changes resulting from any particular type of stimulation or therapy. Thus, amending the study designs to include a variety of different composite images may also have reduced any such effects.

Recommendations for Future Research

The tDCS studies detailed in Chapters 3 and 4 addressed the majority of recommendations for future work identified by the literature review presented in Chapter 2 by using

neuroimaging data to ensure perilesional electrode placement, systematically varying the polarity and laterality of stimulation within participants and considering potential generalisation to untreated items and scores on a range of secondary outcome measures. Nevertheless, several issues pertaining to the use of tDCS as an adjunct to therapy in individuals with individuals with chronic post-stroke anomia remain outstanding. Thus, further studies could vary the length, number and frequency of therapy-plus-tDCS sessions, plus current strength, to establish whether non-responders to three, 20-minute sessions involving 1mA stimulation may benefit from increased input. Determining optimal treatment dosages may subsequently improve the reliability of stimulation effects, although researchers must be mindful of the potential trade-off between therapeutic effectiveness and greater likelihood that participants will be able to distinguish active from sham stimulation, thereby undermining both blinding and patient comfort. Individuals taking SSRIs are typically excluded from tDCS studies. However, relatively high proportions of potential participants for the tDCS case series study were found to be taking these medications and EBe, who was taking fluoxetine, exhibited an unexpected pattern of results following tDCS-plus-therapy. These observations suggest that future research to investigate how SSRIs may affect expected responses to stimulation is warranted if tDCS is to be incorporated into everyday clinical practice.

The RIPPA case series study demonstrated significant improvements in naming ability in five of the six participants. To confirm findings and increase the generalisability of the findings to the wider population of stroke survivors with chronic anomia, a similar protocol could be repeated with a larger number of individuals. Although the tDCS and RIPPA studies included a variety of secondary outcome measures, as mentioned previously, these may not have been appropriate for detecting small changes in response to particular therapy conditions. In future, alternative measures could be adopted to continue to explore the range of potential benefits of treatment on patients' connected speech, emotional well-being and self-perceived communicative effectiveness. For instance, participants could be asked to describe composite pictures requiring vocabulary targeted during therapy or, more functionally, to generate sentences using treated (and untreated) items. Fewer repetitions of

such measures by use of alternative equivalent versions may also reduce the likelihood of more general, cumulative practice effects. Future work could also incorporate longer follow-ups to confirm the longevity of effects on any primary or secondary outcome measures following both tDCS combined with repetition therapy and repetition therapy alone.

Despite incorporating the above methodological adaptations into future studies, it is probable that some individuals with chronic post-stroke anomia will continue to respond poorly to tDCS. Going forward, there is a clear need to clarify who is likely to benefit from treatment and who is not. An appropriate starting point may be a meta-analysis of all tDCS-plus-therapy studies that have included scans in order to identify any potential common brain regions spared and lesioned in responders and non-responders. Future research could also extend existing current flow modelling findings by carrying out functional neuroimaging during stimulation in participants representing a wide range of lesion profiles. Such work may enhance our understanding of which regions are directly and indirectly influenced by tDCS applied to different cranial sites and how activation changes in these areas relate to therapy gains. Additional imaging pre- and post-therapy may also elucidate the potential mechanisms mediating longer lasting changes in activation and connectivity as a result of tDCS-plus-therapy treatment. Similarly, scanning participants before, during and after different types of repetition therapy may further identify the neural substrates underpinning responsiveness and non-responsiveness to each form of treatment. A key aim of these neuroimaging studies would be to predict, from scans, which individuals are anticipated to improve as a result of which form of treatments, enabling therapy resources to be directed accordingly. Notwithstanding the importance of neuroimaging work, for many patients, detailed scans are not routinely available in everyday clinical settings. Consequently, complementary future studies could investigate the possible existence of behavioural markers that can predict whether or not an individual is likely to be a good candidate for tDCS and/or which type/s of repetition therapy are expected to result in the greatest therapy gains. If such markers are found, this knowledge could help to guide clinical decision making in the absence of brain imaging.

The naming response inconsistency findings reported in Chapter 5 indicate several additional avenues for subsequent research. Firstly, studies could investigate further explanations why some people with chronic stroke-induced anomia are more inconsistent than others, including psychological variables like mood, motivation and attention. This line of inquiry is likely to also involve neuroimaging to discover whether specific lesion sites are shared by highly consistent and by highly inconsistent individuals. Alternatively, once patients' optimal repetition therapy parameters have been identified, the effects of these treatments could be compared between items named consistently incorrectly, incorrectly-then-correctly or correctly-then-incorrectly. To broaden this research, types of naming errors associated with different response patterns could also be analysed, and related to cognitive neuropsychological models of lexical access. For instance, different underlying processing errors are likely to underpin consistent errors of omission and situations where a patient names an item correctly on one occasion and produces a formal phonological error on another.

Finally, Chapter 6 revealed that participants' ratings of ease, enjoyment and effectiveness of therapy do not necessarily correspond to measured therapy outcomes. This may be especially true for individuals with executive function deficits. These observations could be studied in greater depth, leading to an increased understanding of the links between patient perceptions and treatment success, and how these relationships may be influenced in order to maximise therapeutic effectiveness. Such work may be facilitated by increasingly popular self-directed home treatment programmes that enable clinicians to automatically log the amount of independent practice that patients complete.

Conclusions

Chronic aphasia has wide-ranging, adverse consequences for stroke survivors and those around them. The number of individuals affected rises year on year, leading to ever-increasing personal and societal costs. Persisting anomia is a common symptom across all types of aphasia, yet typical behavioural speech and language treatments for word finding

difficulties are not always effective and, if effective, are not necessarily efficient. Drawing upon existing models of word production, plus neurostimulation and neuroimaging findings, this thesis aimed to advance current knowledge regarding the nature and treatment of chronic stroke-induced anomia.

Based on the limitations of previous work identified in Chapter 2, a thorough, long-term intervention programme that systematically varied the polarity and laterality of tDCS was devised in order to investigate the effects of combining this non-invasive neurostimulation technique and behavioural therapy on a range of language measures. The case series design facilitated in-depth exploration of the effects of all six tDCS montages. Chapter 3 showed that pairing just three, 20-minute sessions of computer-based repetition therapy with 1mA excitatory anodal tDCS delivered to the left IFG of an individual with chronic Broca's aphasia led to significantly greater improvements in treated item naming accuracy than those achieved following therapy alone, and that the effects of treatment were maintained for three weeks. This result is in line with neuroimaging findings linking increased activation in regions perilesional to damaged parts of the left hemisphere language network to post-stroke language recovery, and supports a growing body of evidence showing that tDCS can enhance the effectiveness and efficiency of anomia therapy.

Chapter 4 aimed to obtain similar results with three further individuals with differing lesion profiles and aphasia diagnoses. Although behavioural therapy led to significant gains in naming accuracy, there were no additional benefits of any particular form of active stimulation for two of these three individuals and the results for the remaining patient were inconsistent. As such, the results of Chapter 4 clearly highlight substantial between-participant variability in response to tDCS. Further research may clarify crucial differences between responders and non-responders, as well as elucidate the mechanisms by which stimulation leads to improved word finding. However, at present, despite some promising findings, unreliable results and frequently-occurring contraindications mean that tDCS is far from a "panacea for all neurological ills", including chronic post-stroke anomia (Li et al., 2015, p.1).

Both within- and between-participant variability were key themes throughout Chapter 5. This exploratory investigation revealed that, on average, a diverse group of 15 stroke survivors named over a quarter of object pictures inconsistently across two naming attempts. Furthermore, all individuals named some items correctly only on the first occasion and others correctly only on the second. None of the included demographic, behavioural and psycholinguistic variables were able to fully account for either degree of naming response inconsistency or explain patterns of correct then incorrect or incorrect then correct naming, although these novel findings provide important foundations for future study.

Finally, Chapter 6 comprised a behavioural investigation that aimed to determine the relative importance of visual speech articulation in computer-based repetition therapy. This case series directly compared the effects of three types of repetition therapy, which varied the semantic, auditory and articulatory cues provided for immediate repetition. As in Chapters 3 and 4, participants received three, 20-minutes therapy sessions in each condition. Despite the limited amount of therapy input, five of the six participants experienced significant gains in naming ability following at least one type of treatment. In accordance with previous research suggesting that common neural substrates underlie both speech production and speech articulation, all five required the presence of articulatory cues for optimal treatment gains. For two individuals, however, the presence of all three types of cues was detrimental, suggesting that they had difficulties integrating multimodal input. Links between aphasia classifications and patterns of therapeutic response were complemented by exploratory structural neuroimaging findings indicating that different neural regions may mediate the effects of each type of therapy. Participants' feedback regarding the perceived ease, enjoyment and effectiveness of each type of therapy was also collected, yet only two individuals' ratings matched their behavioural results.

All of the thesis findings have considerable practical applications for assessment and therapy provision both in research settings and mainstream clinical practice. Nevertheless, the current findings could benefit from ongoing work to try to identify brain regions and behavioural markers that may predict patterns of naming response inconsistency, as well as

response or non-response to tDCS and varying types of repetition therapy. There is a need to continue to utilise case series designs that consider the characteristics of anomia and responses to therapy on a patient-by-patient basis, which was a fundamental premise of the thesis. Such work may facilitate the delivery of the most appropriate treatments to those anticipated to benefit most from them, with the ultimate goal of improving everyday lives of those living with chronic post-stroke anomia.

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Appendices

Appendix A

Word lists for the 408-item picture naming assessment.

Block 1	Block 2	Block 3	Block 4
moon	car	cat	duck
clock	drum	lips	beard
pipe	eskimo	kangaroo	rainbow
safetypin	gorilla	camel	dolphin
tree	dustpan	chimney	sink
desk	thumb	belt	skirt
chain	stocking	nest	castle
leopard	sword	corkscrew	bowl
horse	glass	table	hoe
ear	celery	witch	clamp
bench	cloud	tank	rug
fork	fishtank	bridge	walrus
paintbrush	antlers	hanger	donkey
mountain	lobster	plug	octopus
bell	peanut	telescope	balcony
sandwich	bow	handcuffs	dragon
rocket	door	neck	screwdriver
foot	grave	banana	man
shoulder	ostrich	crackers	eagle
rockingchair	porcupine	whistle	pitchfork
arrow	flag	canoe	frog
microscope	lightbulb	bus	drill
soldier	crown	spatula	butterfly
cheese	plate	waiter	doll
barrel	rollingpin	tear	can
turkey	hammer	map	bear
raccoon	needle	rake	worm
skis	lizard	fountain	peas
stethoscope	thread	skeleton	yoyo
flower	anchor	knight	dog
lightswitch	tweezers	glasses	pelican
screw	chicken	towel	cactus
fox	tyre	asparagus	wolf
heart	box	slide	bomb
axe	heel	priest	violin
unicycle	palmtree	piggybank	bicycle
bee	ladle	pencil	submarine
wheelbarrow	church	skunk	pliers
dentist	net	wheel	windmill

nose	button	sun	robot
basket	seesaw	chest	typewriter
onion	tiger	deer	shower
ashtray	cowboy	wood	scarf
jar	helmet	magnet	barbecue
ring	harp	orange	ruler
bed	skateboard	well	saxophone
camera	pillow	glove	lemon
branch	highchair	match	tail
mouse	ant	shark	iron
bottle	drawer	mask	eye
hand	gun	panda	sheep
Block 5	**Block 6**	**Block 7**	**Block 8**
boat	fish	chair	pen
kite	shirt	knife	bone
toilet	penguin	grasshopper	hippo
llama	cannon	trophy	necklace
potato	piano	cherry	pumpkin
cigarette	cow	girl	mop
broom	present	king	shovel
hoof	queen	leg	cork
bucket	brush	stool	zebra
parrot	elephant	wheat	razor
boy	suitcase	moose	egg
volcano	cross	radio	pencilsharpener
dress	log	tie	bride
carousel	fireman	recordplayer	watch
fence	bat	unicorn	cup
anvil	ironingboard	hair	tomato
squirrel	thimble	peacock	lightning
hammock	genie	rose	leaf
pinecone	hay	paper	seahorse
train	grapes	carrot	boot
feather	tent	shell	butter
wheelchair	dinosaur	wateringcan	swing
arm	nut	letter	acorn
peach	funnel	helicopter	igloo
pot	scorpion	beaver	comb
accordion	toaster	music	candle
hook	tennisracket	mirror	tv
teeth	fire	pillar	strawberry
owl	trumpet	jacket	balloon
scissors	book	vase	binoculars
medal	pig	safe	sailor
fly	parachute	woman	goat
spider	window	lawnmower	watermelon

rock	house	finger	key
monkey	picture	fan	mosquito
teapot	microphone	pyramid	bird
wing	lion	shoe	paperclip
spaghetti	steeringwheel	banjo	toe
bra	paw	cage	roof
hose	rabbit	baby	pineapple
whale	tripod	sewingmachine	saw
hamburger	mushroom	ghost	mousetrap
clown	crab	umbrella	cake
smoke	pizza	pirate	knot
spoon	lighthouse	envelope	lettuce
lipstick	guitar	giraffe	snowman
toothbrush	swan	nail	globe
lamp	statue	road	rope
sock	saddle	flute	hinge
wig	ball	hat	ladder
pear	apple	salt	snail

Appendix B

Mean length in phonemes, number of syllables, frequency, and name agreement for JSc's treated and untreated therapy sets (figures shown for all items and for single and double incorrect items).

Set		Variable			
		Phonemes	**Syllables**	**Frequency**	**Name agreement**
1	**All**	4.85	1.90	2.30	0.53
	Single	4.30	1.70	2.97	0.31
	Double	5.40	2.10	1.63	0.74
2	**All**	4.60	1.85	2.59	0.67
	Single	3.64	1.27	2.90	0.45
	Double	5.78	2.56	2.21	0.95
3	**All**	4.40	1.65	2.98	0.47
	Single	4.10	1.60	3.00	0.47
	Double	4.70	1.70	2.96	0.46
4	**All**	4.90	1.90	2.49	0.78
	Single	5.33	2.00	2.16	0.74
	Double	4.55	1.82	2.76	0.82
5	**All**	4.65	1.70	2.43	0.47
	Single	4.40	1.60	2.58	0.60
	Double	4.90	1.80	2.28	0.82
6	**All**	4.80	1.80	2.29	0.45
	Single	4.55	1.82	2.32	0.18
	Double	5.11	1.78	2.24	0.79
7	**All**	5.10	1.90	2.60	0.33
	Single	4.50	1.70	2.80	0.12
	Double	5.70	2.10	2.40	0.53
8	**All**	4.95	1.80	1.77	0.80
	Single	5.63	2.00	1.33	0.72
	Double	4.11	1.56	2.30	0.89
9	**All**	4.75	1.80	2.53	0.73
	Single	5.20	1.90	1.33	0.64
	Double	4.30	1.70	2.47	0.82

Set		Variable			
		Phonemes	**Syllables**	**Frequency**	**Name agreement**
10	**All**	4.85	1.90	2.43	0.57
	Single	4.73	1.82	2.80	0.58
	Double	5.00	2.00	1.99	0.57
11	**All**	4.75	1.75	2.29	0.61
	Single	4.10	1.40	3.20	0.38
	Double	5.40	2.10	1.38	0.84
12	**All**	4.80	1.95	2.13	0.70
	Single	4.73	1.91	2.01	0.64
	Double	4.89	2.00	2.26	0.78
Total	**All**	**4.78**	**1.83**	**2.40**	**0.60**
	Single	**4.60**	**1.73**	**2.55**	**0.48**
	Double	**4.98**	**1.93**	**2.25**	**0.71**

Appendix C

Mean length in phonemes, number of syllables, frequency, and name agreement for JSc's correct control sets.

Set number	Variable			
	Phonemes	**Syllables**	**Frequency**	**Name agreement**
1	4.35	1.60	2.93	0.51
2	4.10	1.50	2.51	0.55
3	4.20	1.65	3.05	0.47
4	4.40	1.70	2.51	0.58
5	4.30	1.70	2.66	0.53
6	4.20	1.55	2.95	0.50
Total	**4.26**	**1.62**	**2.77**	**0.52**

Appendix D

Bespoke mood questionnaire.

Aphasia can affect how you feel. Do any of these pictures show how you have felt in the last week?					
So this week have you felt:	**0**	**1**	**2**	**3**	**4**
1. Angry?*					
2. Frustrated?*					
3. Determined?					
4. Ok?					
5. Under confident?*					
6. A lack of control?*					
7. Able?					
8. Lonely?*					
9. Embarrassed?*					
10. When you look to the future, how do things look?					

*Item scores were reversed when analysed such that higher scores represented the most positive emotional states e.g. not at all angry.

Appendix E

Raw naming accuracy data for JSc for all treated and untreated items in each stimulation condition, at each time point. The table shows the total number of items named correctly (percentage naming accuracy).

Item type	Stimulation condition	Time point			
		Pre	**Immediate**	**1 week**	**3 weeks**
Treated	P Anodal	5 (25%)	16 (80%)	9 (45%)	15 (75%)
	P Cathodal	7 (35%)	14 (70%)	14 (70%)	13 (65%)
	P Sham	10 (50%)	13 (65%)	14 (70%)	11 (58%)*
	C Anodal	8 (40%)	14 (70%)	14 (70%)	14 (70%)
	C Cathodal	10 (50%)	15 (75%)	16 (80%)	12 (60%)
	C Sham	10 (50%)	18 (90%)	16 (80%)	12 (60%)
Untreated	P Anodal	7 (35%)	4 (20%)	7 (35%)	8 (42%)*
	P Cathodal	7 (35%)	10 (50%)	11 (55%)	12 (60%)
	P Sham	11 (55%)	8 (40%)	10 (50%)	11 (55%)
	C Anodal	10 (50%)	10 (50%)	10 (50%)	11 (55%)
	C Cathodal	9 (45%)	10 (50%)	9 (45%)	7 (35%)
	C Sham	16 (80%)	11 (55%)	13 (65%)	20 (100%)

* On two occasions, one item was inadvertently skipped, meaning that JSc attempted to name 19 items rather than 20.

Appendix F

Mean (SD) length in phonemes, number of syllables, frequency, and name agreement for the treated and untreated therapy sets for each participant in the tDCS case series, plus the results of the matching analyses.

Participant	Set	Variable			
		Phonemes	**Syllables**	**Frequency**	**Name agreement**
JSc	1	4.85 (2.08)	1.90 (0.85)	2.30 (1.61)	0.53 (0.50)
	2	4.60 (2.21)	1.85 (1.09)	2.59 (1.55)	0.68 (0.63)
	3	4.40 (1.60)	1.65 (0.75)	2.98 (1.87)	0.47 (0.40)
	4	4.90 (1.41)	1.90 (0.55)	2.49 (1.33)	0.78 (0.74)
	5	4.65 (1.90)	1.70 (0.86)	2.43 (1.20)	0.47 (0.49)
	6	4.80 (2.02)	1.80 (0.77)	2.29 (1.38)	0.45 (0.58)
	7	5.10 (1.94)	1.90 (0.79)	2.60 (1.03)	0.33 (0.48)
	8	4.95 (2.39)	1.80 (1.01)	1.77 (1.41)	0.80 (0.60)
	9	4.75 (1.68)	1.80 (0.83)	2.53 (1.63)	0.73 (0.53)
	10	4.85 (1.98)	1.90 (0.91)	2.43 (1.46)	0.57 (0.50)
	11	4.75 (2.10)	1.75 (1.02)	2.29 (1.85)	0.61 (0.53)
	12	4.80 (1.51)	1.95 (0.76)	2.13 (1.94)	0.70 (0.51)
		F(11,228)=0.173, p=0.999	F(11,228)=0.227, p=0.996	F(11,228)=0.718, p=0.721	F(11,228)=1.470, p=0.144
GH	1	4.40 (1.47)	1.60 (0.68)	2.96 (1.44)	0.48 (0.67)
	2	4.60 (1.31)	1.75 (0.44)	2.36 (1.69)	0.58 (0.57)
	3	4.65 (1.84)	1.65 (0.75)	2.71 (1.60)	0.42 (0.46)
	4	4.50 (1.73)	1.70 (0.73)	1.78 (1.37)	0.70 (0.47)
	5	4.55 (1.90)	1.65 (0.75)	2.60 (1.61)	0.48 (0.45)
	6	4.45 (1.50)	1.65 (0.67)	2.57 (1.30)	0.38 (0.38)
	7	4.60 (1.64)	1.75 (0.72)	2.57 (1.57)	0.68 (0.68)
	8	4.85 (1.31)	1.85 (0.75)	2.02 (1.39)	0.54 (0.51)
	9	4.55 (1.82)	1.70 (1.03)	2.12 (1.39)	0.71 (0.61)
	10	4.40 (1.93)	1.85 (0.99)	2.94 (1.30)	0.61 (0.50)
	11	4.55 (1.57)	1.80 (0.83)	2.72 (1.61)	0.72 (0.69)
	12	4.70 (2.13)	1.85 (1.04)	2.71 (2.15)	0.40 (0.38)
		F(11,228)=0.115, p=1.000	F(11,228)=0.247, p=0.994	F(11,228)=1.116, p=0.350	F(11,228)=1.067, p=0.389

Participant	Set	Variable			
		Phonemes	**Syllables**	**Frequency**	**Name agreement**
EBe	1	5.00 (1.60)	1.95 (0.62)	2.01 (1.28)	0.67 (0.68)
	2	4.95 (1.81)	1.89 (0.66)	1.97 (1.35)	0.56 (0.63)
	3	5.26 (1.73)	2.05 (0.97)	1.54 (1.44)	0.60 (0.58)
	4	5.32 (1.92)	2.21 (0.86)	1.76 (0.90)	0.76 (0.61)
	5	5.11 (1.82)	1.84 (0.90)	1.81 (1.430	0.66 (0.73)
	6	5.42 (1.81)	2.11 (0.88)	2.35 (1.37)	0.65 (0.51)
	7	5.32 (2.08)	2.05 (1.03)	1.75 (1.28)	0.87 (0.63)
	8	4.95 (2.42)	1.74 (0.93)	2.43 (0.98)	0.62 (0.55)
	9	4.95 (1.81)	1.79 (0.86)	2.31 (1.57)	0.77 (0.50)
	10	5.42 (2.09)	1.95 (0.97)	2.16 (1.19)	0.76 (0.61)
	11	4.58 (2.04)	1.89 (0.81)	1.63 (1.51)	0.72 (0.47)
	12	5.32 (1.67)	2.21 (0.79)	1.87 (1.39)	0.75 (0.59)
		F(11,216)=0.337, p=0.997	F(11,216)=0.610, p=0.819	F(11,216)=0.928, p=0.514	F(11,216)=0.409, p=0.951
JSo	1	4.85 (2.43)	2.00 (1.12)	2.15 (1.53)	0.65 (0.66)
	2	4.80 (1.47)	1.75 (0.64)	2.54 (1.31)	0.51 (0.54)
	3	4.80 (2.04)	1.90 (0.91)	2.04 (1.39)	0.79 (0.65)
	4	5.05 (2.19)	1.85 (0.93)	2.70 (1.53)	0.35 (0.39)
	5	5.05 (1.70)	2.05 (0.83)	1.66 (0.90)	0.60 (0.57)
	6	4.85 (2.13)	1.75 (0.91)	2.22 (1.45)	0.66 (0.52)
	7	4.85 (1.87)	1.85 (0.86)	2.54 (1.20)	0.73 (0.62)
	8	4.55 (1.70)	1.70 (0.57)	2.15 (1.81)	0.97 (0.58)
	9	5.50 (1.91)	1.90 (0.85)	1.88 (1.44)	0.69 (0.59)
	10	5.00 (1.52)	1.80 (0.70)	1.76 (1.42)	0.81 (0.62)
	11	5.30 (1.75)	1.95 (0.83)	2.17 (1.22)	0.74 (0.63)
	12	4.80 (1.91)	1.75 (0.79)	2.30 (1.29)	0.60 (0.60)
		F(11,228)=0.198, p=0.998	F(11,228)=0.340, p=0.976	F(11,228)=1.035, p=0.416	F(11,228)=1.445, p=0.154

Appendix G

Mean (SD) length in phonemes, number of syllables, frequency, and name agreement for the control sets for each participant in the tDCS case series, plus the results of the matching analyses.

Participant	Set	Variable			
		Phonemes	**Syllables**	**Frequency**	**Name agreement**
JSc	1	4.35 (1.35)	1.60 (0.68)	2.93 (1.75)	0.51 (0.54)
	2	4.10 (1.48)	1.50 (0.51)	2.51 (1.56)	0.55 (0.51)
	3	4.20 (1.77)	1.65 (0.75)	3.05 (1.48)	0.47 (0.53)
	4	4.40 (1.98)	1.70 (0.86)	2.51 (1.50)	0.58 (0.71)
	5	4.30 (1.87)	1.70 (0.73)	2.66 (1.82)	0.53 (0.59)
	6	4.20 (1.44)	1.55 (0.94)	2.95 (1.36)	0.50 (0.59)
		F(5,114)=0.090, p=0.994	F(5,114)=0.231, p=0.948	F(5,114)=0.452, p=0.811	F(5,114)=0.083, p=0.995
GH	1	3.70 (0.95)	1.30 (0.48)	3.16 (1.72)	0.45 (0.45)
	2	3.80 (1.62)	1.30 (0.48)	2.99 (0.99)	0.43 (0.34)
	3	4.00 (1.83)	1.60 (0.84)	3.18 (1.09)	0.42 (0.49)
	4	3.60 (1.17)	1.40 (0.52)	3.58 (1.01)	0.37 (0.54)
	5	3.90 (2.42)	1.70 (0.95)	3.41 (2.18)	0.34 (0.45)
	6	3.56 (1.59)	1.44 (0.53)	3.63 (1.66)	0.41 (0.60)
		F(5,53)=0.105, p=00.991	F(5,53)=0.601, p=0.699	F(5,53)=0.283, p=0.921	F(5,53)=0.064, p=0.997
EBe	1	3.50 (1.14)	1.30 (0.47)	3.51 (1.28)	0.28 (0.42)
	2	3.85 (1.18)	1.40 (0.50)	3.55 (1.52)	0.32 (0.43)
	3	3.60 (0.88)	1.25 (0.44)	3.74 (1.20)	0.44 (0.46)
	4	4.10 (1.41)	1.70 (0.73)	3.06 (1.68)	0.40 (0.47)
	5	4.10 (1.48)	1.45 (0.69)	3.19 (1.58)	0.51 (0.55)
	6	3.85 (1.50)	1.25 (0.44)	3.25 (1.45)	0.36 (0.36)
		F(5,114)=0.746, p=0.591	F(5,114)=1.881, p=0.103	F(5,114)=0.619, p=0.685	F(5,114)=0.696, p=0.628
JSo	1	4.20 (1.32)	1.60 (0.60)	3.32 (1.41)	0.40 (0.60)
	2	4.25 (1.48)	1.65 (0.81)	3.46 (1.60)	0.46 (0.50)
	3	3.80 (1.32)	1.50 (0.61)	3.18 (2.00)	0.38 (0.41)
	4	4.25 (1.48)	1.55 (0.76)	2.90 (1.46)	0.33 (0.37)
	5	3.70 (1.08)	1.40 (0.60)	3.30 (1.30)	0.31 (0.36)
	6	3.90 (1.97)	1.60 (0.82)	3.26 (1.45)	0.36 (0.49)
		F(5,114)=0.563, p=0.729	F(5,114)=0.321, p=0.900	F(5,114)=0.301, p=0.911	F(5,114)=0.243, p=0.942

Appendix H

Raw naming accuracy data for each participant in the tDCS case series for all treated and untreated items in each stimulation condition, at each time point. The table shows the total number of items named correctly (percentage naming accuracy).

Participant	Item type	Stimulation condition	Time point			
			Pre	Immediate	1 week	3 weeks
JSc	Treated	P Anodal	5 (25%)	16 (80%)	9 (45%)	15 (75%)
		P Cathodal	7 (35%)	14 (70%)	14 (70%)	13 (65%)
		P Sham	10 (50%)	13 (65%)	14 (70%)	11 (58%)*
		C Anodal	8 (40%)	14 (70%)	14 (70%)	14 (70%)
		C Cathodal	10 (50%)	15 (75%)	16 (80%)	12 (60%)
		C Sham	10 (50%)	18 (90%)	16 (80%)	12 (60%)
	Untreated	P Anodal	7 (35%)	4 (20%)	7 (35%)	8 (42%)*
		P Cathodal	7 (35%)	10 (50%)	11 (55%)	12 (60%)
		P Sham	11 (55%)	8 (40%)	10 (50%)	11 (55%)
		C Anodal	10 (50%)	10 (50%)	10 (50%)	11 (55%)
		C Cathodal	9 (45%)	10 (50%)	9 (45%)	7 (35%)
		C Sham	16 (80%)	11 (55%)	13 (65%)	20 (100%)
GH	Treated	P Anodal	7 (35%)	11 (55%)	8 (40%)	5 (25%)
		P Cathodal	5 (25%)	11 (55%)	6 (30%)	7 (35%)
		P Sham	4 (20%)	11 (55%)	3 (15%)	5 (25%)
		C Anodal	4 (20%)	12 (60%)	6 (30%)	10 (50%)
		C Cathodal	2 (10%)	11 (55%)	11 (55%)	7 (35%)
		C Sham	4 (20%)	13 (65%)	9 (45%)	7 (35%)
	Untreated	P Anodal	3 (15%)	1 (5%)	4 (20%)	4 (20%)
		P Cathodal	5 (25%)	6 (30%)	4 (21%)*	3 (15%)
		P Sham	6 (30%)	2 (10%)	3 (15%)	3 (15%)
		C Anodal	2 (10%)	2 (10%)	4 (20%)	7 (35%)
		C Cathodal	5 (25%)	3 (15%)	6 (30%)	3 (15%)
		C Sham	3 (15%)	2 (10%)	4 (20%)	1 (5%)

Participant	Item type	Stimulation condition	Time point			
			Pre	Immediate	1 week	3 weeks
EBe	Treated	P Anodal	8 (42%)	18 (95%)	16 (84%)	11 (58%)
		P Cathodal	11 (58%)	17 (89%)	15 (79%)	14 (74%)
		P Sham	11 (58%)	16 (84%)	14 (74%)	13 (68%)
		C Anodal	10 (53%)	17 (89%)	15 (79%)	14 (74%)
		C Cathodal	7 (37%)	14 (74%)	11 (58%)	14 (74%)
		C Sham	11 (58%)	17 (89%)	12 (63%)	10 (53%)
	Untreated	P Anodal	11 (58%)	11 (58%)	10 (53%)	11 (58%)
		P Cathodal	7 (37%)	7 (37%)	11 (58%)	11 (58%)
		P Sham	9 (47%)	11 (58%)	9 (47%)	15 (79%)
		C Anodal	10 (53%)	12 (63%)	12 (63%)	11 (58%)
		C Cathodal	10 (53%)	12 (63%)	8 (42%)	11 (58%)
		C Sham	7 (37%)	10 (53%)	12 (63%)	11 (58%)
JSo	Treated	P Anodal	10 (50%)	19 (95%)	14 (70%)	14 (70%)
		P Cathodal	8 (40%)	19 (95%)	17 (85%)	16 (80%)
		P Sham	11 (55%)	19 (95%)	15 (75%)	14 (70%)
		C Anodal	6 (30%)	17 (85%)	15 (75%)	12 (60%)
		C Cathodal	5 (25%)	15 (75%)	15 (75%)	12 (60%)
		C Sham	6 (30%)	18 (90%)	17 (85%)	15 (75%)
	Untreated	P Anodal	6 (30%)	10 (50%)	8 (40%)	10 (50%)
		P Cathodal	6 (30%)	11 (55%)	12 (60%)	10 (50%)
		P Sham	8 (40%)	8 (40%)	11 (55%)	8 (40%)
		C Anodal	9 (45%)	11 (55%)	8 (40%)	12 (60%)
		C Cathodal	6 (30%)	9 (45%)	10 (50%)	7 (35%)
		C Sham	5 (25%)	9 (45%)	6 (30%)	10 (50%)

* On three occasions, one item was inadvertently skipped, meaning that participants attempted to name 19 items rather than 20.

Appendix I

Mean (SD) length in phonemes, number of syllables, frequency, and name agreement for the treated and untreated therapy sets for each participant in the RIPPA case series, plus the results of the matching analyses.

Participant	Set	Variable			
		Phonemes	**Syllables**	**Frequency**	**Name agreement**
AB	1	4.60 (1.85)	1.70 (0.86)	2.22 (2.06)	0.56 (0.52)
	2	4.90 (2.13)	1.65 (0.75)	2.30 (1.22)	0.83 (0.71)
	3	4.85 (2.13)	1.85 (0.81)	2.27 (1.57)	0.63 (0.60)
	4	4.40 (1.90)	1.90 (0.91)	3.00 (1.54)	0.69 (0.69)
	5	4.15 (1.50)	1.65 (0.59)	2.03 (1.47)	0.62 (0.61)
	6	4.60 (1.76)	1.70 (0.73)	2.71 (1.72)	0.53 (0.44)
		F(5,114)=0.476, p=0.786	F(5,114)=0.373, p=0.867	F(5,114)=0.998, p=0.422	F(5,114)=0.660, p=0.655
DF	1	5.20 (1.88)	2.00 (0.92)	2.27 (1.33)	0.80 (0.77)
	2	4.80 (1.64)	1.80 (0.70)	1.90 (1.22)	0.71 (0.66)
	3	5.15 (2.25)	2.05 (1.10)	2.06 (1.44)	0.50 (0.49)
	4	5.05 (1.96)	1.90 (0.97)	2.24 (1.27)	0.67 (0.59)
	5	4.45 (1.54)	1.70 (0.73)	2.18 (1.17)	0.57 (0.49)
	6	5.10 (1.86)	1.95 (1.00)	2.04 (1.06)	0.60 (0.54)
		F(5,114)=0.466, p=0.801	F(5,114)=0.408, p=0.843	F(5,114)=0.253, p=0.937	F(5,114)=0.637, p=0.672
DM	1	5.20 (2.24)	2.25 (1.02)	1.95 (1.45)	0.73 (0.55)
	2	5.70 (2.00)	2.15 (0.93)	2.02 (1.78)	0.63 (0.56)
	3	5.10 (1.97)	1.95 (0.89)	2.08 (1.55)	0.67 (0.80)
	4	5.40 (1.93)	2.15 (0.93)	2.33 (1.66)	0.59 (0.65)
	5	6.15 (1.84)	2.35 (0.86)	1.67 (1.04)	0.80 (0.62)
	6	5.65 (2.32)	2.05 (0.94)	1.86 (1.26)	0.69 (0.60)
		F(5,114)=0.697, p=0.627	F(5,114)=0.459, p=0.806	F(5,114)=0.444, p=0.817	F(5,114)=0.257, p=0.936
PM	1	4.90 (1.80)	1.90(0.85)	2.12 (1.51)	0.70 (0.61)
	2	4.70 (1.49)	1.65 (0.67)	2.06 (1.23)	0.62 (0.44)
	3	4.90 (1.59)	1.85 (0.81)	2.40 (1.42)	0.65 (0.58)
	4	4.20 (1.51)	1.60 (0.75)	2.34 (1.65)	0.65 (0.44)
	5	4.40 (1.64)	1.55 (0.51)	2.73 (1.36)	0.65 (0.48)
	6	4.95 (1.96)	1.90 (0.85)	2.10 (1.56)	0.76 (0.73)
		F(5,114)=0.685, p=0.636	F(5,114)=0.899, p=0.484	F(5,114)=0.609, p=0.693	F(5,114)=0.159, p=0.977

Participant	Set	Variable			
		Phonemes	**Syllables**	**Frequency**	**Name agreement**
PR	1	5.30 (2.08)	2.00 (0.79)	1.99 (1.29)	0.64 (0.48)
	2	4.85 (1.90)	1.70 (0.80)	1.90 (1.32)	0.58 (0.43)
	3	5.20 (1.85)	2.10 (1.07)	1.85 (1.63)	0.77 (0.58)
	4	4.80 (2.07)	1.90 (0.97)	1.80 (1.27)	0.72 (0.56)
	5	4.50 (1.54)	1.65 (0.59)	2.53 (1.83)	0.72 (0.59)
	6	5.00 (1.78)	1.95 (0.89)	2.22 (1.88)	0.72 (0.58)
		F(5,114)=0.429, p=0.792	F(5,114)=0.820, p=0.538	F(5,114)=0.635, p=0.674	F(5,114)=0.341, p=0.887
RH	1	4.50 (2.01)	1.70 (0.98)	2.82 (1.54)	0.51 (0.60)
	2	4.25 (1.52)	1.75 (0.72)	2.35 (1.54)	0.46 (0.53)
	3	4.25 (1.48)	1.55 (0.60)	2.28 (1.52)	0.37 (0.35)
	4	4.60 (1.47)	1.75 (0.85)	2.60 (1.36)	0.41 (0.47)
	5	4.65 (1.76)	1.90 (0.85)	2.47 (1.92)	0.56 (0.65)
	6	4.50 (1.85)	1.75 (0.85)	2.77 (1.67)	050 (0.50)
		F(5,114)=0.205, p=0.960	F(5,114)=0.379, p=0.862	F(5,114)=0.383, p=0.860	F(5,114)=0.362, p=0.874

Appendix J

Mean (SD) length in phonemes, number of syllables, frequency, and name agreement for the control sets for each participant in the RIPPA case series, plus the results of the matching analyses.

Participant	Set	Variable			
		Phonemes	**Syllables**	**Frequency**	**Name agreement**
AB	1	4.10 (1.33)	1.60 (0.82)	2.97 (1.15)	0.56 (0.57)
	2	4.15 (1.46)	1.55 (0.60)	3.35 (1.44)	0.46 (0.38)
	3	4.45 (1.57)	1.65 (0.75)	2.85 (1.88)	0.44 (0.36)
		F(2,57)=0.337, p=0.715	F(2,57)=0.094, p=0.910	F(2,57)=0.587), p=0.559	F(2,57)=0.375, p=0.689
DF	1	3.85 (1.14)	1.40 (0.60)	2.80 (1.51)	0.49 (0.46)
	2	3.85 (1.39)	1.55 (0.69)	3.38 (1.53)	0.50 (0.54)
	3	3.80 (1.36)	1.45 (0.60)	3.33 (1.72)	0.42 (0.32)
		F(2,57)=0.010, p=0.990	F(2,57)=0.293, p=0.747	F(2,57)=0.795, p=0.456	F(2,57)=0.455, p=0.637
DM	1	4.05 (1.05)	1.60 (0.68)	2.89 (1.77)	0.45 (0.48)
	2	4.00 (1.34)	1.55 (0.76)	2.92 (1.73)	0.38 (0.52)
	3	4.25 (1.97)	1.60 (0.94)	2.79 (1.50)	0.48 (0.55)
		F(2,57)=0.155, p=0.857	F(2,57)=0.026, p=0.974	F(2,57)=0.033, p=0.968	F(2,57)=0.191, p=0.827
PM	1	3.85 (1.39)	1.60 (0.75)	3.30 (1.46)	0.33 (0.30)
	2	3.95 (1.19)	1.35 (0.59)	2.89 (1.75)	0.37 (0.62)
	3	4.25 (1.65)	1.55 (0.69)	2.98 (1.42)	0.30 (0.48)
		F(2,57)-0.429, p=0.653	F(2,57)=0.759, p=0.473	F(2,57)=0.378, p=0.687	F(2,57)=0.103, p=0.902
PR	1	3.90 (1.12)	1.55 (0.69)	3.31 (1.69)	0.45 (0.38)
	2	3.95 (1.50)	1.50 (0.69)	2.96 (1.54)	0.41 (0.45)
	3	4.00 (1.56)	1.50 (0.76)	3.07 (1.52)	0.31 (0.46)
		F(2,57)=0.025, p=0.975	F(2,57)=0.033, p=0.968	F(2,57)=0.253, p=0.777	F(2,57)=0.575, p=0.566
RH	1	3.71 (1.45)	1.41 (0.71)	3.77 (1.87)	0.40 (0.48)
	2	3.47 (1.33)	1.35 (0.49)	3.92 (1.71)	0.38 (0.46)
	3	3.41 (1.17)	1.12 (0.33)	4.02 (1.32)	0.38 (0.64)
		F(2,48)=0.236, p=0.791	F(2,48)=1.436, p=0.248	F(2,48)=0.100, p=0.905	F(2,48)=0.006, p=0.994

Appendix K

Raw naming accuracy data for each participant in the RIPPA case series for all treated and untreated items in each stimulation condition, at each time point. The table shows the total number of items named correctly (percentage naming accuracy).

Participant	Item type	Therapy condition	Time point			
			Baseline	Immediate	Follow-up	Combined post-therapy
AB	Treated	RIPPA	6 (30%)	12 (60%)	13 (65%)	16 (80%)
		RIPP	9 (45%)	16 (80%)	14 (70%)	18 (90%)
		ARTIC	9 (45%)	10 (50%)	11 (55%)	15 (75%)
	Untreated	RIPPA	8 (40%)	5 (25%)	7 (35%)	8 (40%)
		RIPP	13 (65%)	8 (40%)	13 (65%)	16 (80%)
		ARTIC	9 (45%)	7 (35%)	6 (30%)	9 (45%)
DF	Treated	RIPPA	10 (50%)	17 (85%)	15 (75%)	19 (95%)
		RIPP	15 (75%)	12 (60%)	11 (55%)	16 (80%)
		ARTIC	12 (60%)	16 (80%)	11 (55%)	16 (80%)
	Untreated	RIPPA	10 (50%)	14 (70%)	15 (75%)	17 (85%)
		RIPP	11 (55%)	11 (55%)	15 (75%)	15 (75%)
		ARTIC	10 (50%)	9 (45%)	10 (50%)	12 (60%)
DM	Treated	RIPPA	10 (50%)	14 (70%)	15 (75%)	18 (90%)
		RIPP	14 (70%)	16 (80%)	15 (75%)	18 (90%)
		ARTIC	10 (50%)	13 (65%)	15 (75%)	17 (85%)
	Untreated	RIPPA	8 (40%)	9 (45%)	8 (40%)	10 (50%)
		RIPP	8 (40%)	15 (75%)	11 (55%)	15 (75%)
		ARTIC	12 (60%)	9 (45%)	13 (65%)	14 (70%)
PM	Treated	RIPPA	11 (55%)	13 (65%)	9 (45%)	13 (65%)
		RIPP	6 (30%)	10 (50%)	8 (40%)	13 (65%)
		ARTIC	8 (40%)	12 (60%)	9 (45%)	16 (80%)
	Untreated	RIPPA	10 (50%)	11 (55%)	8 (40%)	13 (65%)
		RIPP	5 (25%)	8 (40%)	8 (40%)	10 (50%)
		ARTIC	9 (45%)	9 (45%)	8 (40%)	12 (60%)

Participant	Item type	Therapy condition	Time point			
			Baseline	Immediate	Follow-up	Combined post-therapy
PR	Treated	RIPPA	12 (60%)	13 (65%)	13 (65%)	17 (85%)
		RIPP	9 (45%)	14 (70%)	11 (55%)	16 (80%)
		ARTIC	11 (55%)	16 (80%)	18 (90%)	20 (100%)
	Untreated	RIPPA	15 (75%)	13 (65%)	13 (65%)	16 (80%)
		RIPP	9 (45%)	10 (50%)	13 (65%)	16 (80%)
		ARTIC	14 (70%)	12 (60%)	13 (65%)	16 (80%)
RH	Treated	RIPPA	0 (0%)	1 (5%)	2 (10%)	3 (15%)
		RIPP	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		ARTIC	0 (0%)	1 (5%)	0 (0%)	1 (5%)
	Untreated	RIPPA	1 (5%)	1 (5%)	0 (0%)	1 (5%)
		RIPP	0 (0%)	2 (10%)	1 (5%)	2 (10%)
		ARTIC	1 (5%)	0 (0%)	0 (0%)	0 (0%)