Spontaneous and Induced Linguistic Change in Chronic Stroke Aphasia

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Abstract

Recent investigations indicate that language abilities in people with chronic stroke aphasia may continue to evolve spontaneously. However, it is not clear to what extent this linguistic change occurs, and how it relates to neural structures. Behavioural speech and language therapy can improve performance of chronic aphasic participants, and it would be clinically useful to understand the neuropsychological and neural predictors of successful outcomes. This thesis, therefore, comprised four longitudinal studies to explore and predict the trajectory of linguistic symptoms in chronic stroke aphasia. The first two studies concentrated on spontaneous change, whilst the two later focused on therapy-induced change. **Chapter 2** demonstrated that an amount of sentence comprehension change, both positive and negative, occurred in 34 chronic (> 12 months) participants over a course of 26 months (mean time interval = 26.18 months, SD = 11.32). Decline in sentence comprehension was mapped using voxel-based correlational methodology (VBCM) to a neural cluster centred in the left posterior superior temporal gyrus. This finding is in line with previous research showing that this area is involved in sentence comprehension processes. **Chapter 3** extended this work by (prospectively) examining chronic change in a detailed neuropsychological battery (n = 11 tests). This project was a progression from my work in Chapter 2, and it included 26 participants (mean time interval = 28.37 months, SD = 12.66). The majority of these individuals (n = 25/26) had previously participated in the study described in Chapter 2. Behavioural analyses indicated a degree of individual variability (recovery as well as decline) in performance. At the group-level, participants significantly declined in sentence comprehension and marginally improved in non-word repetition. VBCM revealed two neural clusters associated with behavioural change: decline in naming abilities was related to the right anterior temporal lobe and frontal cortex (and the uncinate fasciculus connecting them); and recovery in non-word repetition was related to the white matter underlying the right caudate and surrounding tissue. These results are consistent with the current knowledge of the role of anterior temporal lobes/frontal cortex in naming functions, and the caudate in speech motor processes. **Chapter 4** included a therapy study in 26 chronic aphasic participants (> 12 months post-stroke) who underwent a range of repetition-based treatments. The participants were recruited for this study and had not participated in the spontaneous change studies (Chapters 2 and 3). The treatments included an existing one, repetition in the presence of a picture, as well as two novel variants: repetition in the presence of articulation, and repetition in the presence of a picture and articulation. Each therapy cycle lasted two weeks, and patients were assessed at 7-days post treatment (i.e., immediate testing)

and at a 12-day follow-up (i.e., delayed testing). All therapies induced a significant improvement in naming performance. Participants' pre-therapy phonological abilities correlated with the therapeutic gains. The right precentral gyrus and superior parietal lobule were further associated with gains. These results indicated that key neuropsychological functions and right hemisphere structures can be used as predictors of therapeutic outcomes. Finally, **Chapter 5** constitutes an analysis of an additional outcome measure from the study in Chapter 4, namely therapy-induced changes in phonological error-profiles. This final exploratory study examined the evolution of error-profiles as a result of the therapies described in Chapter 4. Importantly, the same individuals participated in the studies reported in Chapters 4 and 5. Post-therapy, there was a reduction in the proportion of errors farthest from the target (i.e., omissions and distant phonological), and an increase in the proportion of errors closer to the target (i.e., eventually correct responses). Overall, these empirical studies advance the current understanding of the trajectory of performance observed amongst people with chronic stroke aphasia. These findings may lead to more targeted interventions for people with aphasia, which may enhance their quality of life.

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The Author

I did a BA in Linguistics at University College, London after which I continued to explore the intersection between language (and other cognitive functions) and neurobiology in a MSc in Neuroscience at King's College, London. For my MSc dissertation, I worked with Professor Marco Catani in a DTI-Tractography project. I virtually reconstructed the arcuate fasciculus in people with primary progressive aphasia and healthy controls. I investigated whether atrophy to the arcuate fasciculus correlated with specific language and working memory deficits. During this time I started to volunteer with a local aphasia support group. I have very much enjoyed doing a PhD that combined my love for cognitive neuroscience with language research.

Chapter 1: Introduction

Thesis overview

This thesis is presented in journal format, meaning that each empirical chapter (Chapters 2-5) is written in a style suitable for publication.

These self-contained Chapters include an introductory section on the relevant literature, the research aims, methods, results, and discussion. The empirical chapters are preceded by an Introductory Chapter, where three main research themes and (consequent) research questions are presented. The final General Discussion Chapter merges our findings together, and outlines potential directions for future research.

Stroke, language and aphasia

According to the World Health Organisation (WHO) cerebrovascular disease, or stroke, is the second cause of death worldwide, taking the life of a person every five seconds (Murray & Lopez, 1997). The WHO defines stroke as 'a clinical syndrome consisting of rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin' (Aho et al., 1980). Depending on the aetiology of the stroke it is classified as ischaemic or haemorrhagic, where the first refers to the occlusion of a blood vessel, and the latter to the rupture of a vessel (Andersen et al., 2009). Of the two types of stroke one is much more common than the other, with over 80% of all strokes being ischaemic and less than 20% haemorrhagic (Mozaffarian, 2015). Not only does stroke kill 6 million people each year, but it further leaves 5 million patients chronically disabled (Mackay & Mensah, 2014). These disabilities may manifest in multiple forms, as stroke may damage a wide network of cortical and subcortical areas (Phan et al., 2005). One of the most prevalent impairments resulting from stroke is the acquired inability to comprehend and/or produce language, a collection of disorders known as aphasia (Pedersen et al., 2004). Clinicians and researchers distinguish three phases following the stroke: the acute phase, which are the first few days post-stroke, the subacute phase, from ~ 2 weeks to 6/12 months (there is no clear consensus), and the chronic phase, from > 6/12 months (Saur et al., 2006). Due to the multi-dimensional nature of language, stroke aphasic patients may present a heterogeneous range of linguistic deficits. Multiple classification schemes for these disorders exist, including the widely used Boston Diagnostic Aphasia Examination (BDAE;

Goodglass & Kaplan, 1983), which provide a way of summarising co-occurring constellations of deficits (Fig. 1.1).

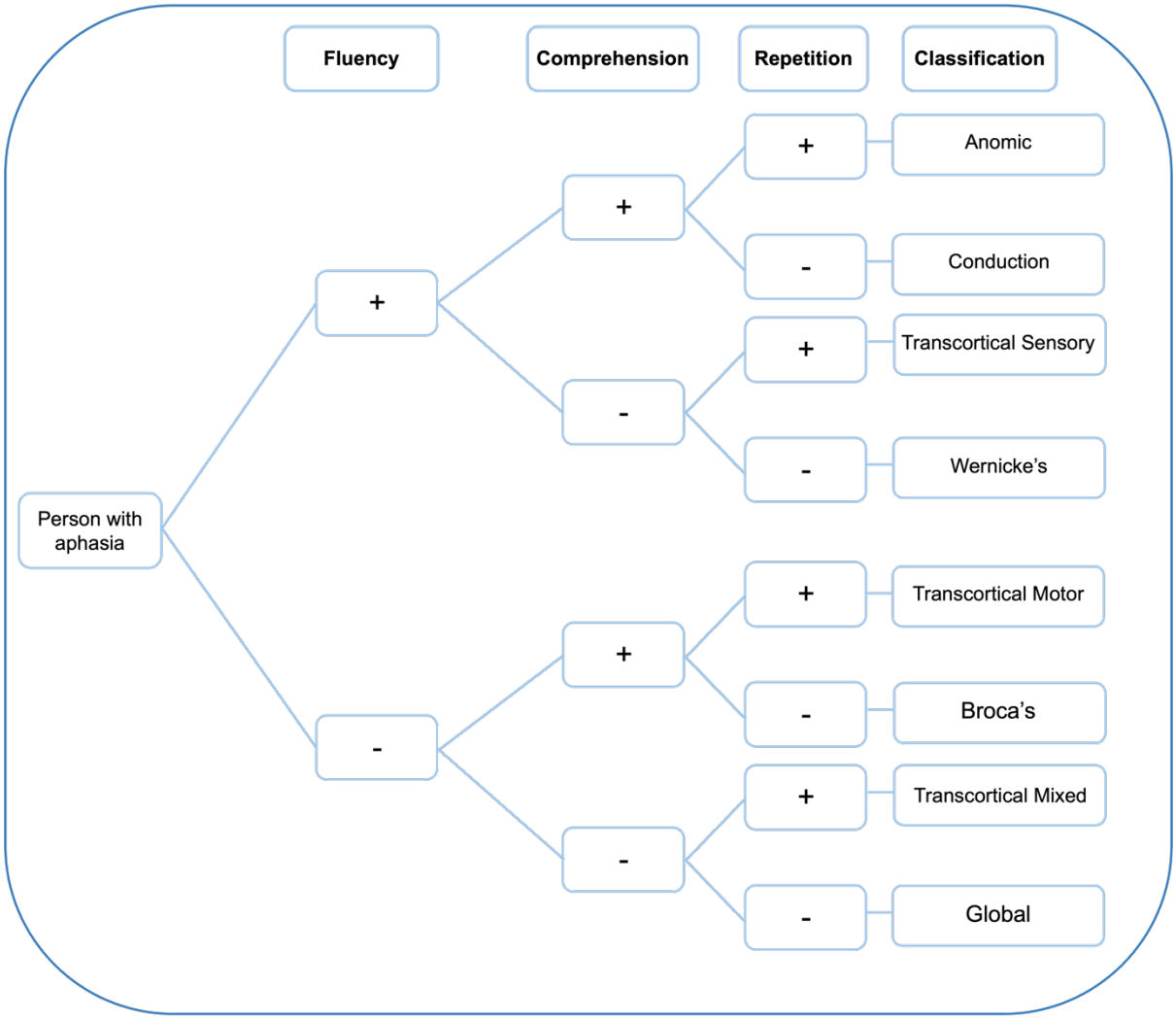


Figure 1. 1 Schematic representation of aphasic subtypes according to Boston Diagnostic Aphasia Examination (modified from Goodglass et al., 2001).

According to the BDAE there are eight aphasic subtypes, including four fluent and four non-fluent. The most severe subtypes are non-fluent, and consist of: global, transcortical mixed, Broca's and transcortical motor. Non-fluent language is characterised by effortful speech, frequent pauses, brief sentences (consisting mainly of nouns), syntactically simple constructions, and difficulties with prosody (Goodglass et al., 2001). Some individuals with non-fluent aphasia present with *agrammatism*, which is an impairment specific to syntax.

Agrammatism manifests in both production (e.g., difficulties with inflectional morphemes, auxiliaries and prepositions; Damasio, 1992; Goodglass, 1993), and comprehension, particularly in the context of (semantically reversible) sentences with a non-canonical word-order (e.g., in passives; Caramazza & Zurif, 1976). In contrast, individuals with Wernicke's, transcortical sensory, conduction, and anomia have fluent aphasia. Fluent aphasia is characterised by relatively effortless speech, syntactically more complex and longer sentences, preserved prosody, but with paraphasic errors (Goodglass et al., 2001). The main symptom in stroke-aphasic individuals, affecting all subtypes, is anomia, or difficulties with naming. Although aphasia is predominantly a language disorder, motor articulation difficulties, known as apraxia of speech, are often found in people with stroke aphasia (Wade et al., 1986). Moreover, other non-linguistic cognitive domains, such as vision (Siegel et al., 2016), attention (Murray et al., 1997), working memory (Salis et al., 2017), and executive functions (Fridriksson et al., 2006; Schumacher et al., 2019) are often impaired in people with aphasia.

The BDAE (and other neuropsychological batteries) are useful in terms of broadly conceptualising linguistic deficits but they are not necessarily sensitive to graded (symptom) variations within each aphasic category. Given that the intention of clinical test batteries is to sample a relatively broad set of domains, due to time constraints, they do so using a shallow testing set. This limits the dynamic range or ability to grade patients along a continuum. In fact, people classified with the same aphasic subtype will present different symptoms, and there are 'fuzzy boundaries' between categories. Furthermore, there is no clear consensus over what constitutes 'mixed' aphasia. All of the issues above has meant that a substantial percentage of aphasic individuals (~ 30 - 80%) are unclassifiable with the BDAE alone (Benson, 1979; Wertz et al., 1984). A statistical decomposition technique that can help overcome these issues is principal component analysis (PCA). PCA is a data reduction method that can be applied to large datasets (including neuropsychological batteries) to capture graded (cognitive-linguistic) variations in a multi-dimensional continuous space (Jain & Shandliya, 2013). Applying varimax rotation to the PCA can aid cognitive interpretability of the extracted components, as it simplifies the sub-space generated by the PCA. This rotation has the benefit of transforming the component-coordinate system to make the components orthogonal (i.e., independent), whilst at the same time illustrating the extent to which individual tests load onto these components (Kaiser, 1958). PCA has been successfully used to explain linguistic variance in stroke aphasia (Butler et al., 2014; Halai et al., 2017; Kummerer et al., 2013; Lacey et al., 2017; Mirman et al., 2015). This work has shown that neuropsychological abilities can be distilled as

reflecting core phonological, semantic, speech fluency, and cognitive-executive functions. However, not much is known about applying PCA to examine therapy-data, or (PCA-derived) neuropsychological predictors of therapy-outcomes. I therefore conducted these analyses in Chapter 4. Before we delve into lingustic recovery in aphasia, one must first consider (briefly) what is language and how it is represented in the brain.

The hitchhiker's guide to the language network

The traditional view of the language network postulates that there are two primary language areas in the brain, namely Broca's area in the left inferior frontal gyrus (IFG) involved in language production (Broca, 1861), and Wernicke's area in the left posterior superior temporal gyrus (STG) related to language comprehension (Wernicke, 1874). Broca's and Wernicke's areas are directly linked by a dorsal connection (Lichtheim, 1885). The advent of neuroimaging, however, has shown that this model is in need of re-evaluation (Tremblay & Dick, 2016; Ueno et al., 2011). The current neurolinguistic consensus is that language is processed along two parallel streams, a dorsal and a ventral one (Fig. 1.2) (Cloutman, 2013; Fridriksson et al., 2018; Hickok & Poeppel, 2000, 2004; Lopez-Barroso & de Diego-Balaguer, 2017; Poeppel et al., 2012). These language streams are both functionally and anatomically segregated, and are involved in complementary linguistic functions. The dorsal, parieto-frontal, stream maps sensory inputs to motor outputs, processing phonology and speech repetition (Saur et al., 2008; Saur et al., 2010). Cortical regions in the dorsal pathway, which is predominantly left-lateralised, include posterior inferior frontal gyrus, premotor cortex and anterior insula. In terms of white matter tracts, the most important are the three segments of the arcuate fasciculus (AF; Catani et al., 2005), although current evidence suggests that there may be others (e.g., the frontal aslant tract; Catani et al., 2013). Damage to the dorsal network has been linked to speech repetition and phonological difficulties, as well as difficulties in language production (Kummerer et al., 2013). The ventral, temporo-parietal, component fuses semantic information, giving humans the semantic ability to comprehend and produce language (Saur et al., 2008, 2010). Key grey matter regions from the ventral route are the (bilateral) anterior middle and inferior temporal gyri, extending into posterior temporal cortices. There is no clear-cut consensus on the tracts that constitute the ventral network, but studies often include the uncinate fasciculus, the inferior fronto-occipital fasciculus and the inferior longitudinal

fasciculus (Bajada et al., 2015). Damage to the ventral network often leads to comprehension impairments in stroke patients (Kummerer et al., 2013).

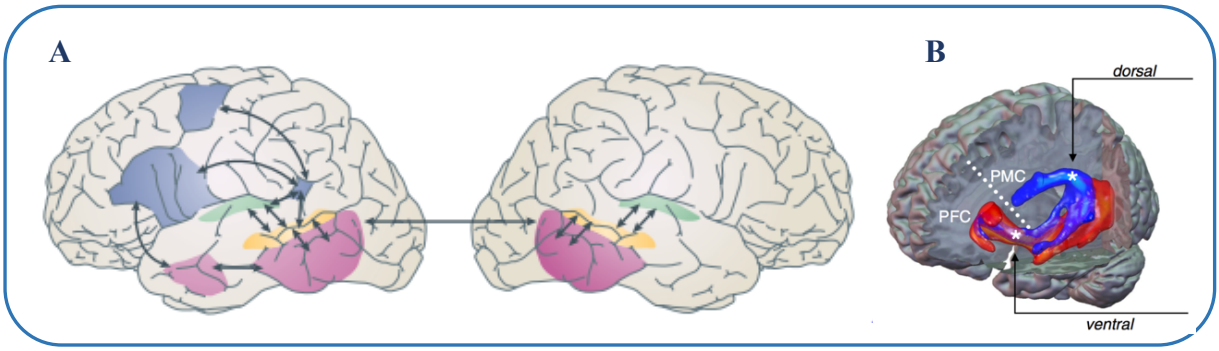


Figure 1. 2 The dual stream model of language. Pink/red regions = ventral route (semantic). Blue regions = dorsal route (mapping phonology to articulators). Figures taken from A) Hickok and Poeppel (2007) and B) Saur et al. (2008).

Research themes

This thesis investigates neuropsychological and linguistic abilities in chronic stroke aphasia, and it explores this in four empirical Chapters. A major goal of this work was to collect and analyse chronic longitudinal behavioural data, and to relate it to neural structures. The three, interconnected, research themes in this thesis are: neuroimaging of aphasia; natural (spontaneous) linguistic change; and therapy-induced recovery. The first theme describes the main neuroimaging methods used in neuropsychological research, with a specific focus on lesion-symptom approaches. In this section, I additionally included a brief history of aphasia, from post-mortem studies to modern neuroimaging. The first theme is found in Chapters 2-5. The second theme concentrates on the main, sometimes contradictory, views on linguistic recovery. There are multiple hypotheses that I have reviewed throughout this Thesis. In brief, one theory focuses on the positive role of the spared left-hemisphere neural language network ('the perilesional hypothesis'), the second on the positive function of the right hemisphere ('the laterality shift hypothesis'), the third on the maladaptive role of the right hemisphere ('the disinhibition hypothesis'), and the fourth on the effect of other cognitive (non-linguistic) networks ('the cognitive compensation hypothesis') and the last hypothesis relates to the expression of timing in linguistic recovery ('the role of timing in hemispheric differences in

recovery'). There might be some 'aspects' of each theory that are correct, as evidenced by neuroimaging studies (that used methods described in Theme 1). Importantly, most of the literature discussed in this section relates to changes in the subacute phase, as traditional models of recovery tended to assume a stabilisation of linguistic abilities in the chronic phase. In Theme 3, I discuss an influential study by Hope et al. (2017) which showed longitudinal behavioural changes in a chronic (> 12 months post-stroke) aphasic cohort, associated with structural adaptations. This study motivated our research in Chapters 2 and 3 to continue exploring the potential for 'chronic' (> 12 months) linguistic change. In this section, I also dived into the field of induced-recovery in chronic aphasia, including some of the interventions that can improve naming (as it is the most common symptom in aphasia). I then discuss Dell et al. (1997)'s dual-route interactive two-step model, which like most cognitive models of naming, is based on a dysruption of the phonological and semantic systems. The focus of the final section is on the therapy-study by Sandars et al. (2018b) that used different phonological and semantic cues to elicit naming gains in chronic aphasia. This study inspired our research in Chapters 4 and 5.

First theme: Neuroimaging of aphasia

Anatomists and researchers have been interested in disentangling the brain regions associated with behaviour since the 19th century. Some of the first clinicians to infer (linguistic) brain-behaviour relationships using post-mortem examinations were Paul Broca (1861) and Carl Wernicke (1874). Lesion studies, including post-mortem, indicate what neural regions or connections between these regions are necessary (not merely sufficient) for a specific function. Advances in neuroimaging in the 20th and 21st centuries have allowed for the exploration and visualisation of brain architecture *in vivo* (Catani et al., 2002). Modern neuroimaging techniques used to study language include Positron Emission Tomography (PET), Electroencephalography (EEG), Transcranial Magnetic Stimulation (TMS)/ transcranial Direct Current Stimulation (tDCS), and Magnetic Resonance Imaging (MRI). PET is a functional method which is used to create neural images by injecting a radio-isotope (i.e., a tracer such as fluorodeoxyglucose (^{18}F); Silverman et al., 2008) into a person's blood flow. Naturally, this tracer will be transported to the brain regions most metabolically involved in a (cognitive) function. This isotope emits gamma rays that are detected by gamma cameras, and this can be mathematically used to derive their neural location. EEG records the electrical activity of the

brain through electrodes placed on the head. Changes in the electrical signal (voltage), as a reflection of a new stimulus, correlate with neural processing. EEG has good temporal resolution compared to spatial, and thus is particularly suited for examining the timing or spatiotemporal dynamics of linguistic processes (Brennan & Pylkkanen, 2017; Maess et al., 2007; Pylkkanen, 2019). TMS and tDCS can change the magnetic or electrical field in the brain (Horvath et al., 2011). Whilst TMS uses rapid electrical current to non-invasively manipulate cortical activity (either inducing excitability or inhibition), tDCS uses low direct or alternating current. As we will discuss in the next sections, TMS has been used with chronic aphasic individuals to suppress regions potentially detrimental to recovery (Naeser et al., 2005). TMS has further been used to transiently produce 'virtual lesions' in healthy individuals, which can be clinically useful to emulate functional impairment (Devlin & Watkins, 2007).

Finally, MRI has good spatial (vs temporal) resolution, and is arguably one of the most popular techniques in terms of neuroimaging aphasia. Structural MRI is based on the interaction of nuclei (i.e., a proton; typically hydrogen) that in the presence of an external magnetic field will have a magnetic moment. When such protons are placed in MRI scanners, thus a strong magnetic field (H_0), they begin to spin, or precess about it. MRI scanners then apply a specific radio frequency pulse to excite nuclei. When the pulse ends, the excited nuclei return to their initial lower, energy state, emitting energy specific to their local environment. This energy can be measured and detected by MRI scanners, and the raw data can be converted into neural images. Functional MRI (fMRI) uses the same physical principles as structural MRI, but it focuses on the differences in magnetic properties between oxygen-rich and oxygen-poor blood to capture change in brain function. Similarly, resting state fMRI is also a blood oxygenation level dependent (BOLD) method to study function (connectivity) of the brain. Its distinguishing feature is that it measures 'spontaneous' BOLD signal fluctuations rather than response to performing a specific task. Finally, diffusion tensor imaging (DTI)- tractography is an MRI variant that allows for the virtual, *in vivo*, visualisation of white matter (WM) tracts in the brain (Basser et al., 1994; Catani et al., 2002). It is used to create 3D reconstructions of WM pathways and, being completely non-invasive compared to traditional dissecting techniques (e.g., post-mortem dissections, axonal tracing studies), it is particularly well suited for studying human brain connections.

Improvements in MRI technology has led to the developments in advanced computational techniques that allow the mapping of neural structures to behavioural function. The majority

of studies utilise univariate (performing a statistical test at individual locations/voxels) methods and two extensively-used ones are: voxel-based lesion symptom mapping (VLSM; Bates et al., 2003), and voxel-based correlational methodology (VBCM; Tyler et al., 2005), which is a variant of voxel based morphometry (VBM; Ashburner & Friston, 2000). Collectively, they have expanded our knowledge of lesion- (linguistic) symptom relations in clinical populations, including: single-word and connected-speech production (Halai et al., 2017; Seghier et al., 2014), sentence comprehension (Leff et al., 2009), repetition (Fridriksson et al., 2010b), phonology and semantics (Butler et al., 2014; Mirman et al., 2015; Schwartz et al., 2009), and morphological processing (Meteyard et al., 2013). Raw data acquired from MRI scanners can be preprocessed and converted into three-dimensional images (usually T1-weighted or T2-weighted scans). The smallest unit in an MRI scan is the voxel (comparable to a pixel), which reflects a volume measurement (i.e., 1 mm^3). Depending on the tissue weighted properties of the scan, one can derive lesion profiles, or probability maps of grey and white matter. These can subsequently be mapped to behavioural deficits. One major difference between VLSM and VBCM is that the former compares performance of subgroups with and without lesion, whereas the latter includes the data as continuous values and performs correlations (Geva et al., 2012). VLSM requires that lesions are defined (predominately this is done manually but auto or semi-automated methods exist), which is typically time-consuming and subject to potential personal biases. Manual lesion demarcation typically does not take into account regions/voxels distant to the lesion that might have been affected (e.g., due to Wallerian degeneration and gliosis; Geva et al., 2012) and statistical inference is confined to lesioned areas with a minimum/maximum number of patients present (i.e., one cannot split the data into two sufficient groups if everyone has a lesion [or not] at a location). In contrast, as VBM and VBCM assign a continuous neural value to each voxel, one can explore the effect across the whole-brain. They can thus increase the sensitivity and statistical power of the relationship between neural structure and performance (Tyler et al., 2005), and suit the study of multidimentional disorders such as stroke-aphasia. Indeed, VBCM has been extensively used to examine cognitive-linguistic impairment in aphasia (Alyahya et al., 2020; Butler et al., 2014; Halai et al., 2017; Schumacher et al., 2019; Tochadse et al., 2018). The converging evidence from such work indicates that different neuropsychological processes map to distinct neural structures. For example, phonological abilities relate to left posterior superior temporal gyrus and its underlying white matter (including the arcuate fasciculus); semantics to the anterior temporal lobe; and speech fluency to the left precentral gyrus and motor cortex. In the following section I will review the use of neuroimaging (including lesion-symptom approaches) in the

context of theories of aphasia recovery. I will apply VBCM in Chapters 2-4 to investigate spontaneous and therapy-induced change in chronic aphasia.

Second theme: Theories of aphasia recovery

Neuropsychological and neuroimaging work has shown that lesion size and site, as well as participants' demographics (e.g., age, sex, education), are crucial predictors of language outcomes in stroke aphasia (Basso et al., 1982; Goldenberg & Spatt, 1994; Gonzalez-Fernandez et al., 2011; Kertesz et al., 1993; Maas et al., 2012; Pizzamiglio et al., 1985; Watila & Balarabe, 2015). However, there is considerable debate over how exactly recovery occurs, and the role of the two hemispheres in recovery.

In contrast to the representation of motor and sensory functions in the brain, language is left-lateralised in over 60% of individuals (Catani et al., 2007). Thus, if stroke, or any other brain injury, strikes the left hemisphere the large proportion of the language system may be lost. Here, the research on the mechanisms underlying language recovery will be discussed in stroke aphasic patients. Specifically, four key hypotheses will be considered, three language-specific ones and one relating to domain-general cognitive networks (Brownsett et al., 2014; Geranmayeh et al., 2014; Geranmayeh et al., 2017). Importantly, these hypotheses are not mutually exclusive, and the interaction of multiple factors (e.g., lesion location or severity of impairment) may be central to recovery.

The perilesional hypothesis

The first hypothesis on factors driving recovery in aphasia, as defined in a review by Geranmayeh et al. (2014), is the 'Perilesional hypothesis' and it relates to the role of intact perilesional regions (Griffis et al., 2017; Heiss et al., 1999; Heiss et al., 2003; Thompson & den Ouden, 2008; Warburton et al., 1999). In this view, the perilesional tissue surrounding the lesion, which is typically premorbidly involved in linguistic functions, supports linguistic recovery. As an example of evidence for the Perilesional hypothesis, de Boissezon et al. (2005) used positron emission tomography (PET) to show that overt word production improvements in seven chronic stroke aphasic (CSA) patients was associated with activity in the left

hemisphere ITG. In another study on 210 CSA patients, Leff et al. (2009) demonstrated that aphasic patients' abilities to comprehend sentences was correlated with the preserved structural integrity of the left posterior STG and STS. On a similar note, Fridriksson et al. (2010a) found that improved naming performance in a group of 15 CSA patients correlated with functional activity in left language network areas. Using fMRI, they showed that as patients improved at naming pictures (compared to those who declined), there was an increase in blood-oxygen-level dependent (BOLD) levels in the left perilesional tissue. Finally, Robson et al. (2019) showed that neuropsychological recovery in 12 individuals with Wernicke's aphasia was related to the integrity of the spared left superior temporal cortex.

The laterality-shift hypothesis

The 'Laterality-shift hypothesis' of language recovery is concerned with the reorganisation of the language network in the right hemisphere (Geranmayeh et al., 2014). In this view, contralateral homotopic areas will reorganise after stroke such that it allow them to subserve the function of the damaged area (Musso et al., 1999; Richter et al., 2008; Skipper-Kallal et al., 2017; Weiller et al., 1995; Xing et al., 2016). This remodelling of the language network is permitted by the loss of transcallosal inhibition that occurs as a consequence of neuronal loss. The decrease in inhibition from the left hemisphere allows right regions to strengthen and create new connections to process language. It has been proposed that right hemisphere involvement in language predominantly happens when damage to the left hemisphere is substantial, affecting the both core language areas as well as large portions of neighbouring cortical and subcortical structures (Anglade et al., 2014; Heiss & Thiel, 2006). In one of the first neuroimaging studies supporting the 'Laterality-shift hypothesis', Thulborn et al. (1999) identified with fMRI a rightward shift in functional activity, a transfer from Broca's area to Broca's right-hemisphere homologue, as a person with Broca's aphasia progressively recovered language. In the same study, a person with Wernicke's aphasia started recruiting Wernicke's 'mirror structure' in the right hemisphere as she progressively recovered.

Tractography studies have suggested that right hemisphere premorbid anatomical differences and having a bilaterally distributed language network may be crucial for recovery (Bartolomeo & Thiebaut de Schotten, 2016). For example, Forkel et al. (2014) demonstrated that a higher volume of the arcuate fasciculus (specifically the direct segment) in the right hemisphere was

a good predictor of language outcomes, and that patients with a bilateral AF (compared to those with an extremely left-lateralised tract) were more likely to improve over time. Pani et al. (2016) later discovered that the integrity of the white matter underlying the right MTG, pars opercularis and precentral gyrus predicted speech fluency in aphasic patients.

The disinhibition hypothesis

The right hemisphere thus appears to be more engaged in linguistic processes in aphasic patients than healthy people, however not all evidence supports that this is beneficial for recovery (Geranmayeh et al., 2014; Naeser et al., 2005). The 'Disinhibition hypothesis' holds that after stroke the loss of callosal, inter-hemispheric, connections allows the right hemisphere to interfere with the potential for residual left language network activity (Heiss & Thiel, 2006). Contralateral language areas play a maladaptive role which is detrimental to recovery. As an example of this, Rosen et al. (2000) showed, using combined fMRI with PET methods, that patients with non-fluent aphasia had a higher than average (healthy controls) activity in the right IFG during word stem completion tasks. Furthermore, aphasic patients who had a successful recovery presented perilesional activation around left Broca's area (supporting the Perilesional hypothesis). In another fMRI study, Naeser et al. (2004) found increased neural activity in the right SMA as non-fluent CSA patients narrated stories, compared to healthy people (who activated left SMA). These differential (abnormal) patterns of activity, the authors argued, were the cause of the effortful and agrammatic speech produced by patients. In a last study and example of right hemisphere activity detrimental for recovery, Postman-Caucheteux et al. (2010) assessed CSA patients and neurologically healthy controls during a picture-naming task. It was discovered that, although correct naming responses elicited left IFG activity in patients and controls, incorrect naming was solely correlated with right IFG engagement.

Following these maladaptive right hemisphere activations, a number of researchers have attempted to suppress this activity to facilitate language recovery. For example, repetitive transcranial magnetic stimulation (rTMS) has been applied to the right pars triangularis (Naeser et al., 2005) and both right pars triangularis and opercularis (Harvey et al., 2017) in CSA patients to succesfully boost patients' naming abilities. Using a different technique which led to similar results, (Griffis et al., 2016) applied intermittent theta-burst stimulation (iTBS) to a perilesional, spared region near the left IFG in eight chronic patients. After ten iTBS sessions,

fMRI revealed a significant shift in activity from the right to the left hemisphere in patients, and a return to normal activation levels in Broca's area. Broca's functional increase in activation was correlated with significant improvements in general speech fluency.

The cognitive compensation hypothesis

The previously discussed hypotheses and the studies that support them put an emphasis on language processing and reorganisation in aphasic patients. Recently, researchers have started to investigate the role of other cognitive (e.g., executive or default mode) networks in language recovery (Salis et al., 2017). It has been proposed that changes in ipsilateral and contralateral activity are due to an increased computational effort from domain-general (non-linguistic) regions (Baumgaertner et al., 2013). Brownsett et al. (2014) examined the cingular-opercular system, involved in processing cognitively complex tasks, when CSA individuals and neurotypical speakers computed 'difficult' language. Both groups were asked to listen and repeat speech stimuli, which were either sentences of different levels of complexity (patients) or canonical sentences and noise-vocoded speech (healthy people). As hypothesised, processing difficult stimuli yielded cingular-opercular network activity in the midline frontal cortex (specifically dorsal anterior cingulate cortex and adjacent SFG) in patients and controls. This increase in activity was further correlated with participants' performance in repetition. In a longitudinal, follow-up study, Geranmayeh et al. (2017) assessed functional, language activity in patients and controls at 2 weeks (subacute phase) and 4 months post-stroke. They discovered that cingular-opercular activity in the subacute phase predicted, and was correlated with, the extent of patients' spontaneous speech production at 4 months. These results not only linked language and cognitive processes in aphasia (and indicated the cingular-network as a biomarker of language outcomes), but also presented this network as a potential candidate to be exploited in recovery. Crucially, the midline frontal cortex is seldom damaged in stroke aphasia as it is supplied by the anterior cerebral artery (ACA), and not the MCA (Geranmayeh et al., 2017). This area may thus be targeted using neurostimulation in patients where conventional language therapy does not work. In fact, rTMS over midline frontal cortex has been demonstrated to improve pseudoword learning in healthy people (Sliwinska et al., 2017).

In another fMRI study, Geranmayeh et al. (2016) investigated the combined role of different cognitive (default mode network (DMN) and cingular-opercular) and speech-specific (fronto-

temporo-parietal, FTP) networks in patients as they described pictures. One of their main findings was that the interaction between cognitive and linguistic systems, rather than linguistic system activity alone, predicted speech outcomes. In patients (and healthy controls) increased left FTP and decreased DMN activity was correlated with improved language production, while increase in right FTP compared to the DMN was associated with worse outcomes. Furthermore, Sandberg (2017) used resting state fMRI and also found a significant relationship between cognitive and resting state networks (including the DMN and the cingular-opercular/salience network) and a semantic network. Linguistic deficits in aphasic patients were correlated with hypoconnectivity of both resting state and semantic systems. In addition, the higher and more integrated connectivity within these resting state networks in patients (compared to neurotypical controls) was associated with a milder aphasia, while a decrease in connectivity with a more severe impairment.

The role of timing in hemispheric differences in recovery

Another factor that has been related to patterns of hemispheric activation (left vs right) and language outcomes in aphasic patients is timing, the amount of time which has passed since the stroke (Thiel et al., 2006). Saur et al. (2006) scanned 14 aphasic participants at three separate time points post-stroke whilst they listened to sentences and meaningless reverse speech. It was observed that participants would go through an initial stage of minimal activation of left Broca's area and neighbouring cortical regions (in the acute phase), which correlated with severe linguistic deficits. This was followed, as determined by participants' second neuropsychological testing and MRI scan, by a change in activity as the language network became bilateral and started recruiting contralateral hemisphere regions (including right Broca's area) in the subacute phase. This was associated with participants' linguistic improvements. Finally, a normalisation of activation in the left hemisphere (as detected with patients' third MRI scan) correlated with the recovered ability to process sentences in the chronic phase (determined with neuropsychological tests). This led the authors to hypothesise that right hemisphere participation in computing language is normal in the subacute phase but that, ultimately, in the chronic phase successful recovery is associated with left perilesional areas.

A review by Stefaniak et al. (2020) tried to summarise the separate hypotheses described above into a generalised frameworks. The authors proposed two neural mechanisms that might support linguistic recovery in (subacute) aphasia: degeneracy and variable neuro-displacement. Degeneracy is the process where a neural structure, which was premorbidly not specialised for a linguistic function, becomes engaged in that function. Thus, helping the patient to recover following stroke. Variable neuro-displacement refers to the fact that the brain in healthy people does not need to utilise all its available energy in 'normal' situations, and can increase its activity when needed (e.g., in cognitively complex situations). After injury, the remaining neural resources tend to work harder and at higher capacity to try to achieve similar functions that before injury were 'easy'. Importantly, neither of these processes are mutually exclusive, and they might plausibly co-occur.

Third theme: Spontaneous and induced-change in chronic aphasia

As we have so far seen, it is extremely difficult to pinpoint the neural correlates of aphasic recovery in patients because the left and right hemispheres may play both a facilitatory and inhibitory function at different stages during recovery. Saur et al. (2006)'s results indicated that linguistic improvements may continue in the chronic phase, although this research field is fairly unexplored.

It is unclear whether spontaneous recovery continues to occur years after stroke. Traditional theories suggest that linguistic improvements naturally end after a 'critical period' for recovery (Nouwens et al., 2015). However, Hope et al. (2017) demonstrated that naming difficulties (anomia), the most common persistent symptom of aphasia, continue to evolve over the course of one year in 28 already chronic patients. These changes were associated with structural changes in the brain. To evaluate behavioural change in patients and its neural basis, Hope et al. (2017) assessed patients twice (at Testing 1 and Testing 2) within an interval of 12 months at least. Patients were assessed on the whole Comprehensive Aphasia Examination (CAT; Swinburn et al., 2004), which included 22 language-specific subtests. Furthermore, a T1-weighted structural MRI scan was acquired at each time point. Results showed that there was significant change in naming abilities in chronic patients (in the 'spoken object naming' subtest, which correlated with the spoken action naming' and 'written object naming' subtests). Naming improvements were associated with structural adaptations (hypertrophy) in the right

anterior temporal cortex, a key cortical region for semantic processing in neurotypical speakers (Rice et al., 2015). Not all participants improved and naming decline was associated with hypertrophy in the right precentral gyrus. This suggested that contralateral neuroplasticity may compensate for left hemisphere damage in the chronic phase. These results are promising because they indicate untapped potential for improvement, and shine a light on a subset of the population that are typically neglected (i.e., virtually no rehabilitation pathways exist for chronic patients). One specific criticism of the Hope et al., study is that change scores focused primarily on naming ability, even though the CAT taps into a wide range of linguistic domains. One reason for the lack of extended reporting may be the fact that clinical batteries, such as the CAT, offer limited dynamic range for each subtest meaning that it is difficult to use these outcome measures to detect subtle effects longitudinally. Chapter 2 and 3 in the current Thesis, aims to replicate a core finding by Hope et al., and extend their work by investigating a range of language and executive tasks with greater dynamic range, in order to better understand the long term progression of symptoms in chronic aphasia.

Although the Hope et al. (2017) study was the first neuroimaging study to report spontaneous linguistic changes in the chronic phase, there is extensive evidence from speech and language therapy indicating that it can induce behavioural and neural changes during this period (Conroy et al., 2018; Mohr, 2017; Stark & Warburton, 2018; Wan et al., 2014). For example, Schlaug et al. (2009), used Melodic Intonation Therapy (MIT), a therapy specifically designed to engage RH mechanisms, in six severely aphasic chronic patients. The arcuate fasciculus was evaluated at two time points, namely before and after 75 sessions of MIT. It was discovered that the MIT induced increases in the number of fibres and volume of the right AF and, moreover, these structural changes correlated with improved spontaneous speech scores in patients. This study thus showed a transformation of the right direct segment occurring even in the chronic stages after stroke, favouring the 'Hemispheric shift' hypothesis of recovery. Additionally, other interventions such as brain stimulation techniques (Darkow et al., 2017; Sandars et al., 2016, 2018a) and drugs (Berthier et al., 2011; Keser et al., 2017; Woodhead et al., 2017) have induced linguistic or naming recovery in chronic individuals. In a clinical or research setting, naming is usually assessed by confrontation naming tasks such as the 64-item Cambridge naming battery (Bozeat et al., 2000) or the Boston Naming Test (Kaplan et al., 1983). Patients are shown a picture (the 'target') and are asked to produce its name verbally (Raymer, 2011). Naming errors are often related to the target and thus 'predictable' (Minkina

et al., 2016), and they can give a glimpse of the cognitive mechanisms that are disrupted in anomia (Maher & Raymer, 2004; Nickels, 1995).

Dell et al. (1997)'s dual-route interactive two-step model is based on the processes of three independent but inter-related systems, namely: semantic, lexical, and phonological (Dell, 1986; Dell et al., 1997; Dell et al., 2013). These systems can be visualised as nodes within a lexical-retrieval network, where the information flows between nodes bidirectionally. According to this model, lexical retrieval depends on two steps. The first step focuses on lexical access, and begins with the activation of the semantic features relevant to the target. This step completes once the lexical item with the highest level of activation (the highest number of semantic features) is selected. Naming errors in this phase are words (e.g., potato for 'carrot' or parrot for 'carrot'). The second step of naming is concerned with matching the lexical item to its correct phonological representation. This step begins with the activation of phonemes or phonological units that belong to the target, and ends with the selection of the phonological form with the highest level of activation. Errors within this phase are phonological and, thus, may not necessarily be a word (e.g., marrot for 'carrot'). Dell's two-step interactive model has been successfully used to simulate and predict anomic errors (Abel et al., 2009; Hanley & Nickels, 2009; Schwartz et al., 2006). Due to the inter-connectedness between phonology, semantics, and naming it is perhaps unsurprising that many popular anomic therapies are based on phonology (e.g., phonological components analysis, Leonard et al., 2008; phonemic cueing, Nardo et al., 2017) and semantics (e.g., semantic feature analysis, Ylvisaker & Szekeres, 1985; semantic categorisation, Kiran & Thompson, 2003). Repetition in the presence of a picture (RIPP) is a popular treatment that combines both phonological (in the form of word-repetition) and semantic (in terms of showing a picture) cues (Mason et al., 2011; Morris et al., 2014; Nickels, 2002). Nardo et al. (2017) used the RIPP in a longitudinal fMRI study of 18 chronic aphasic patients, where they were scanned before and after the therapy. Immediately post-RIPP therapy, patients showed an increase in naming accuracy (+29%) and faster reaction times (+17%), with these effects maintained at a three-month follow-up. By strengthening the connections within the semantic and phonological systems, RIPP may facilitate naming recovery (Howard, 2000).

Sandars et al. (2018b) thesis chapter expanded on RIPP by adding two variants: namely, i) repetition in the presence of a picture and articulation (RIPPA), where an articulatory-visual component was added to the RIPP, and ii) repetition in the presence of articulation but no

picture (ARTIC), where no picture was presented to the participants. The results revealed that all therapies led to naming gains and, importantly, the two forms of the articulatory-visual therapies yielded greater benefits than seeing a picture alone (RIPP). Subsequent lesion (VBCM) analyses showed that premotor cortex and medial anterior insula, articulatory-motor regions, mediated the articulatory ARTIC and RIPPA therapy-effects, whilst semantic regions (in the temporal lobe) related to RIPP benefits. Overall, these repetition-based therapies have much clinical potential in terms of being used with individuals who have different lesion profiles. However, this study was conducted on only six participants, so a larger cohort would be needed in order to conduct more reliable statistical analyses. We addressed this issue by recruiting a larger dataset (and increased the scope of this work to investigate predictors of therapeutic outcomes) in Chapter 4. Chapter 5 continued to explore the relative benefit of the RIPP, RIPPA and ARTIC therapies by examining their effect in participants' error-profiles.

Specific aims per chapter

This **Introductory Chapter** defines post-stroke aphasia, the key research themes and questions in this thesis, and the research aims. **Chapters 2-5** report the empirical studies that constitute the basis for the **Chapter 6: General discussion**.

Chapter 2 describes the first empirical chapter. In this study I investigate the longitudinal evolution of sentence comprehension in a chronic (> 12 months) stroke-aphasic cohort (n = 34) over a course of 26 months. I subsequently related such behavioural change to participants' grey and white matter probability maps using VBCM.

Chapter 3 presents the second empirical chapter. This project was a progression from my work in Chapter 2. I examined the potential for neuropsychological change in an extensive battery (11 detailed tests) in 26 aphasic individuals. The majority of these individuals (n = 25/26) had previously participated in the study described in Chapter 2. I further correlated the neuropsychological change with participants' grey and white matter probability maps.

Chapter 4 contains the third empirical chapter. Here I expanded on Sandars et al. (2018b)'s work by acquiring data from 26 aphasic participants (> 12 months post-stroke). The participants were recruited for this study and had not participated in the spontaneous change

studies (Chapters 2 and 3). Each therapy cycle lasted two weeks, and patients were assessed at 7-days post treatment (i.e., immediate testing) and at a 12-day follow-up (i.e., delayed testing). In addition to exploring the benefit of each therapy (and mapping naming gains to neural structures), I examined the neuropsychological factors predictive of gains (at immediate testing).

Chapter 5 includes the fourth empirical chapter. This final exploratory study examined changes in error-profiles as a result of the therapies described in Chapter 4. The same individuals participated in the studies reported in Chapters 4 and 5, as this study constituted an analysis of an additional outcome measure from Chapter 4. Most therapy work targets naming accuracy, but I hypothesise that error-rates will also decline following therapy.

The **Chapter 6: General discussion** connects the findings from **Chapters 2-5**, and integrates this knowledge within the broader field of aphasiology. This final chapter will discuss our findings in the context of the theoretical models of aphasia recovery and clinical applicability. It will further delineate potential directions for future research.

Acknowledgement of authors' contributions

Dr Anna Woollams and Dr Ajay Halai supervised all work documented in this thesis, and assisted in producing the final version of each Chapter. Prior to her departure from the University of Manchester, Dr Lauren Cloutman was part of the supervisory team, and provided helpful guidance with the realisation of each project. Dr Paul Conroy read multiple early versions of Chapter 4 and gave insightful comments. The volunteers from Chapters 2-5 were part of the Neuroscience and Aphasia Research Unit (NARU) at the University before I commenced my PhD. They had completed a neuropsychological battery and undergone MRI scanning as part of their involvement in previous studies. Sasha Johns and Dr Elin Williams helped me to collect the therapy data for Chapters 4-5. I have acknowledged this situation in the relevant sections of the four empirical chapters. I conducted all recruitment and additional behavioural testing for participants' second neuropsychological assessment in Chapters 2-3. I recruited participants in Chapters 4-5, and conducted some therapy sessions (they were split almost equally into three). I also analysed the behavioural and neuroimaging data presented here, and wrote the drafts which were subsequently commented by my supervisors.

Chapter 2: Neural Correlates of Change in Sentence Comprehension Over Time in Chronic Stroke Aphasia

Abstract

It has recently been shown that aphasic patients' naming abilities can continue to evolve many years after stroke, with these effects reflected in changes in brain structure. Such findings run against the commonly held view that stroke aphasic performance is largely stable in the chronic phase. Here we considered the potential for change over time in chronic stroke aphasia in a receptive language ability: spoken sentence comprehension. Thirty-four chronic aphasic patients (> 12 months) were assessed twice on the Spoken Sentence Comprehension subtest of the Comprehensive Aphasia Test over a time interval of at least one year, with detailed T1 images acquired at the time of their first assessment. Subsequently, normalised change per year in sentence comprehension scores were entered in voxel-based correlational methodology (VBCM) analyses of grey and white matter probability maps. In line with previous work, a modest amount of linguistic change, both positive and negative, occurred between assessments (mean time interval = 26.18 months, SD = 11.32). Whole brain analyses revealed a neural cluster systematically related with the behavioural change over time, with greater damage at the time of initial testing corresponding to greater decline. This cluster was centred in the left posterior superior temporal gyrus, and extended into the anterior superior temporal gyrus, planum temporale and central opercular cortex. Our results are consistent with the work on the left posterior temporal cortex role in sentence comprehension, and suggest that patient performance trajectories in the chronic phase can be anticipated using lesion information.

Introduction

Language deficits, or aphasia, affect approximately 30% of stroke survivors in the subacute phase, persisting chronically in 20% (Engelter et al., 2006). Following the initial days post-stroke (acute phase), most patients will recover some degree of linguistic function subacutely (~ 2 weeks - 12 months) (Lomas & Kertesz, 1978). Pedersen et al. (2004) reported a general shift in aphasia classification from more to less severe (as assessed by the Scandinavian Stroke Scale) in 270 subacute patients, with a substantial reduction in global cases (e.g., from 32% Global cases subacutely to 7% twelve months after), and an increase in milder forms of aphasia (e.g., from 25% Anomic cases subacutely to 29% twelve months after).

Neuroimaging studies have mapped spontaneous linguistic recovery in the subacute phase to neural regions in the brain, predominantly in the spared perilesional cortex (Fridriksson et al., 2010a; 2012; Griffis et al., 2017; Szaflarski et al., 2013) and homologous right hemisphere regions (Crinion & Price, 2005; Turkeltaub et al., 2012), with some contribution from domain-general cognitive areas (Brownsett et al., 2014; Geranmayeh et al., 2017). Furthermore, other functional neuroimaging work has suggested that multiple neural regions are recruited differentially throughout the recovery process (Saur et al., 2006; Stockert et al., 2020). Saur et al. (2006), who scanned 14 aphasic patients at three consecutive time points after stroke, observed minimal early activation in perilesional left hemisphere areas (in the acute phase), followed by an increase in activation in bilateral language structures, with peak activity in right Broca's area (in the subacute phase), and finally a return to normal activation levels in the remainder of the left hemisphere neural language network (in the chronic phase). These changes in cortical activation were positively associated with the progressive recovery of spoken sentence comprehension functions.

Lesion-symptom mapping studies in aphasic participants have shown an extensive neural system involved in sentence comprehension, including the left posterior and anterior temporal lobes, inferior parietal cortices, and the pars orbitalis of the IFG (Butler et al., 2014; Dronkers et al., 2004; Fridriksson et al., 2018; Halai et al., 2017; Leff et al., 2009; Lwi et al., 2021). A number of longitudinal studies have considered the process of recovery of auditory sentence comprehension in the early stages post-stroke (Lwi et al., 2021). Although some work showed a stabilisation of auditory comprehension in subacute patients, including improvements occurring between baseline testing and at 3-4 months post stroke (but not at a 6-7 months follow up) (Mazzoni et al., 1992), other behavioural studies found recovery over a longer period (Lwi

et al., 2021; Prins et al., 1978). For example, Prins et al. (1978) reported progressive sentence comprehension improvements (but not spontaneous speech) in 74 aphasic participants who were assessed at three time points over the course of one year.

Until recently it was assumed that stroke patients' physiological capacity to recover language declined over time, and hence that patients' linguistic abilities stabilised after approximately 9 - 12 months, reaching the chronic phase (Pedersen et al., 1995). There is nevertheless some evidence of spontaneous recovery (and loss) occurring in chronic patients, with these changes mirrored by structural adaptations in the brain (Elkana et al., 2013; Stefaniak et al., 2020). For example, Hope et al. (2017) were able to show using voxel-based morphometry that naming changes measured at two chronic time points in 28 aphasic patients were correlated with structural adaptations in the brain. Single-word naming improvements seen in 13 patients were associated with neural changes in the right anterior temporal lobe (aTL), whilst naming decline seen in 11 patients correlated with a cluster in the right precentral gyrus. This suggested that long-term neural plasticity could occur in chronic aphasia, in contrast to the linguistic recovery in the subacute phase primarily caused by lesioned tissue reperfusion (Hillis et al., 2006). If aphasic changes can occur multiple years post stroke then we might have to reconsider current approaches to rehabilitation, as currently most treatment focus is on the subacute phase (Palmer et al., 2018).

Given recent evidence of change in the spoken production task of naming in chronic stroke aphasia (Hope et al., 2017), the present work aimed to explore the evolution of spoken sentence comprehension for the first time in people with chronic aphasia. The present work combined structural MRI data with behavioural testing in survivors with chronic stroke aphasia to examine spoken sentence comprehension abilities longitudinally. Our main aims were: firstly, to document the extent and nature of changes in auditory comprehension abilities in chronic stroke aphasia, and secondly, to use VBCM to identify what aspects of their lesions may be associated with such behavioural change. Such knowledge could allow us to anticipate which patients are likely to improve and those who are at risk of further language loss, which in turn could facilitate long term management.

Methods

Participants

Thirty-four stroke participants with chronic aphasia were recruited for this study (11 females and 23 males; age (mean [SD] range) = 61.65 [11.49] 43 - 86 years). For additional demographic and lesion data, please refer to Table 2.1. Participants were recruited from community groups and speech and language therapy services in the North West of England. The Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1983) was used to determine participants' aphasic subtype. All subjects were in the chronic phase (> 12 months post-stroke) when they completed the round of neuropsychological and neuroimaging assessments (T1) (mean months post-stroke = 53.29, SD = 52.99). Patients were re-tested with a minimum interval of 12 months (T2) (T2 – T1 = 26). Inclusion criteria consisted of adults with normal or corrected-to-normal hearing and vision, premorbid right handedness, and English as a native language. Exclusion criteria included having suffered multiple strokes, a previous history of neurological disorders, and having any metal-implants or contraindications for MRI scanning.

All patients provided informed consent under approval from the North West Multi-Centre Research Ethics Committee (reference 01/8/94).

Table 2. 1

Patients' demographics and lesion characteristics

ID	BDAE	Age	Sex	Time post stroke	Lesion volume	ICV
09	Broca	52	M	33	11915	1452744
11	Anomia	52	F	76	9767	1317360
15	Mixed Nonfluent	68	M	14	8788	1514570
21	Broca	58	M	135	18392	1540649
31	Global	68	M	50	41379	1535539
32	Anomia	44	M	40	8437	1640831
34	Mixed Nonfluent	73	M	23	22732	1573136
36	Anomia	51	F	66	6975	1396846
37	Broca	54	M	35	18632	1538321
38	Anomia	77	F	56	13577	1441204
40	Anomia	69	F	39	9159	1396744
41	Mixed Nonfluent	78	M	36	34242	1575336
42	Anomia	68	M	21	3311	1379659
44	Broca	59	M	37	13080	1607653
45	Anomia	59	M	34	16433	1526725
46	Global	58	M	57	33239	1591013
47	Anomia	51	M	72	22948	1577505
48	Conduction	46	F	21	3897	1510325
49	Broca	82	M	13	12131	1637251
52	Anomia	44	F	37	18948	1306882
53	Transcortical Motor Aphasia	73	M	46	23863	1432364
54	Mixed Nonfluent	75	F	160	12057	1299507
58	Anomia	43	F	15	175	1343738
59	Mixed Nonfluent	64	M	29	33239	1577682
63	Anomia	58	F	278	12699	1699167
64	Conduction	67	M	13	4879	1526785
65	Global	52	M	73	37822	1366299
66	Anomia	86	M	17	8528	1635679
67	Broca	73	M	114	36877	1766844
68	Conduction	67	M	14	6557	1649370

69	Anomia	56	M	17	6974	1514072
70	Anomia	65	M	75	6607	1429488
71	Anomia	50	M	16	4538	1434621
74	Mixed Nonfluent	56	F	40	10051	1487067

Participants' IDs refer to their file number in the Manchester Aphasia Stroke Sample. Time post-stroke (in months) was the time of the first assessment. Lesion volume and intra-cranial volume are reported in mm^3. **Abbreviations:** BDAE = Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983), SCPY = sentence comprehension change per year, ICV = intra-cranial volume.

Background neuropsychological assessment

We used an extensive neuropsychological battery to measure patients' receptive and expressive linguistic and cognitive functions (Butler et al., 2014; Halai et al., 2017). This battery consisted of: i) subtests from the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) battery (Kay et al., 1992): auditory discrimination using non-word (PALPA 1) and word minimal pairs (PALPA 2), and immediate and delayed repetition of non-words (PALPA 8) and words (PALPA 9); ii) naming tests, including the Boston Naming Test (BNT) (Kaplan et al., 1983) and 64-item Cambridge naming battery (CNB; Bozeat et al., 2000); iii) single-word comprehension tests, including the 96-synonym judgement test (Jefferies et al., 2009), and tests from the Cambridge Semantic Battery (Bozeat et al., 2000): spoken word-to-picture matching, written word-to- picture matching, and a picture version of the Camel and Cactus test; iv) cognitive tests, including forward and backward digit span (Wechsler, 1987), the Brixton Spatial Rule Anticipation Task (Burgess & Shallice, 1997), and Raven's Coloured Progressive Matrices (Raven, 1962). Assessments were conducted with participants over several testing sessions with the pace and number determined by the participant. Scores in the neuropsychological battery are provided in Appendix A.

Assessment of auditory sentence comprehension abilities

Participants were assessed twice on the Spoken Sentence Comprehension subtest from the Comprehensive Aphasia Test (CAT) (Swinburn et al., 2004). This task measures patients' receptive speech comprehension skills using 20 sentence-to-picture matching trials (Howard et

al., 2010). The mean time interval between assessments was of 2.77 years (range = 371 – 2194 days; SD = 525.48 days). Behavioural scores on the CAT Spoken Sentence Comprehension subtest at the two time points are presented in Appendix B.

In order to compare scores between participants over time, we calculated sentence comprehension change per year score (SCPY) for each patient. The SCPY was estimated to control for differences in time-intervals between assessments across patients. To calculate the SCPY, we substracted the raw score at time 1 from time 2, and divided this change by the number of years (with years determined as number of days divided by 365).

Acquisition of neuroimaging data

High-resolution structural T1-weighted MRI scans were acquired on a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an eight-element SENSE head coil. A T1-weighted inversion recovery sequence with 3D acquisition was employed, with the following parameters: repetition time = 9.0 ms, echo time = 3.93 ms, slice thickness = 1 mm, flip angle = 8, 150 contiguous slices, acquired voxel size = 1.0 × 1.0 × 1.0 mm^3, matrix size = 256 × 256, field of view = 256 mm, inversion time = 1150 ms, SENSE acceleration factor 2.5, total scan acquisition time = 575 s.

Pre-processing of neuroimaging data

Patient's structural MRI scans were pre-processed with Statistical Parametric Mapping software (*SPM12*, 2012) running under Matlab 2019a. The images were first normalised into standard Montreal Neurological Institute (MNI) space using a modified unified segmentation-normalisation procedure optimised for focal lesioned brains (Seghier et al., 2008). A healthy control group (n = 22), matched for age and education, was used to determine the extent of abnormality per voxel using an automated lesion identification procedure (Seghier et al., 2008). Neuroimaging data from the 34 patients and 22 controls were then entered into the segmentation-normalisation. Images were smoothed with an 8mm full-width at half-maximum Gaussian kernel. Patients' lesions were automatically identified using a fully automated method based on fuzzy clustering (Seghier et al., 2008). The default parameters were used aside

from the lesion definition 'U-threshold', which was set to 0.5 rather than 0.3 to create a binary lesion image. This parameter was changed after comparing the results obtained from a sample of patients to what would be nominated as lesioned tissue by an expert neurologist. The T1-weighted images generated from every patient were visually inspected with respect to the original scan, and manually modified if necessary. The grey and white matter probability maps resulting from the segmentation-normalisation algorithm were used in the subsequent neuroimaging analyses.

Voxel-based correlational methodology analyses

To examine the neural correlates of sentence comprehension change, patients' SCPY scores were correlated with their grey and white matter images using voxel-based correlational methodology (VBCM) (Tyler et al., 2005). VBCM is a variant of voxel based morphometry (Ashburner & Friston, 2000), where both the behavioural and neuroimaging data are assigned a continuous, non-binary value. VBCMs were conducted with SPM12 (*SPM12*, 2012) running under Matlab 2019a. In addition to the SCPY, four regressors of no interest were entered in the VBCM model, namely: age at the scan (in years), lesion volume (i.e., the number of damaged voxels in the lesion map) (in cm^3), time post stroke (in months) and intra-cranial volume (i.e., the sum of voxels including grey matter, white matter and other tissues) (ICV, in cm^3). Anatomical areas were defined using the Harvard-Oxford atlas in MNI space (Desikan et al., 2006) and the Natbrainlab white matter tract atlas (Catani et al., 2012). All images are presented in MRIcron (Rorden et al., 2007).

Results

Behavioural results

Group-level. Paired-samples t-tests were used to compare changes in the CAT Spoken Comprehension subtest from the first to the second assessment. Rather than using the raw values at the two time points, we assessed the size of the SCPY to control for the time interval between assessments. Overall, participants' spoken comprehension abilities declined significantly between assessments ($t(33) = -2.35$, $p = 0.025$). From the 34 participants: 19

declined, 11 improved and 4 remained stable (mean SCPY change = -1.967, SD = 5.03, range = -17.23 to +6.71) (Fig. 2.1). Statistically significant correlations were found between SCPY and Minimal Pairs Words (r = 0.434, p = 0.01) and Minimal Pairs Nonwords (r = 0.475, p = 0.005) scores from the neuropsychological assessments conducted at initial testing, both of which are tasks relying on receptive spoken word processing.

Individual-level. Wilcoxon Rank Tests were used to determine the statistical significance of any sentence comprehension change from the first to the second assessment. Three participants showed a significant decline over time: patient 48 (z = -2.121, p = 0.034), 49 (z = -2.81, p = 0.005) and 66 (z = -2.46, p = 0.014). This was consistent with the general trend in our cohort to decline rather than improve.

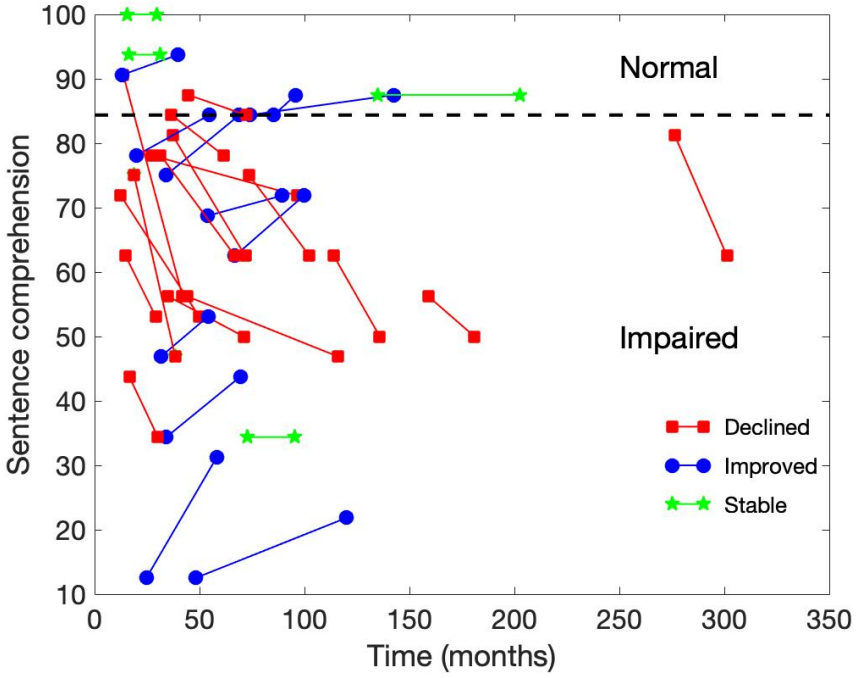


Figure 2. 1 Patients' scores in the CAT sentence comprehension subtest at the two time points in the chronic phase. The cut-off for impairment was 84.37% (Swinburn et al., 2004), and it is depicted as a dashed black line.

Neuroimaging results

Lesion overlap map. Fig. 2.2 shows the lesion overlap of the 34 participants. It primarily covers the region in the left hemisphere supplied by the middle cerebral artery (MCA) (Phan et al., 2005). The highest number of patients who presented damage to the same neural region was 29, in the left precentral gyrus (MNI coordinates: -34, 0, 24).

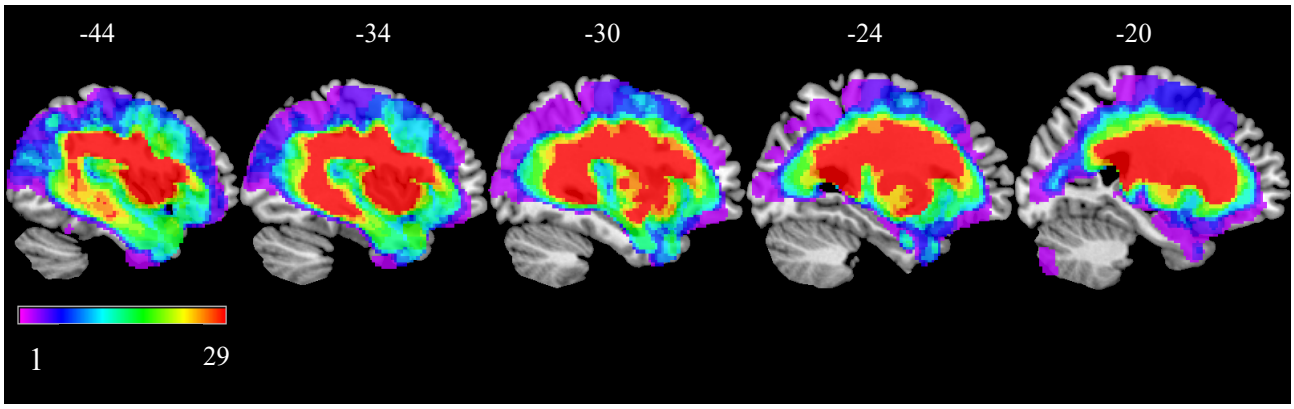


Figure 2. 2 Lesion overlap map from the 34 participants, showing the distribution of patients' lesions. Colour scale reflects the number of patients who had a lesion to a specific voxel. The brain region that was most damaged in the cohort was the left precentral gyrus (MNI coordinates: -34, 0, 24).

Identifying the neural clusters associated with behavioural change. The VBCM analysis for SCPY was conducted on grey and white matter probability maps using four regressors of no interest: age, time post stroke, intracranial volume and lesion volume. Results were thresholded at $p < 0.005$ voxel- level, $p \leq 0.05$ FWE corrected cluster-level. Fig. 2.3 shows the neural cluster in the white matter images that correlated with SCPY, with the peak MNI coordinates given in Table 2.2. The cluster occupied an area centred in the left posterior superior temporal gyrus (pSTG) and sulcus (pSTS), extending into anterior superior temporal gyrus, the planum temporale and the central opercular cortex. There were no significant clusters within the grey matter probability maps related to SCPY.

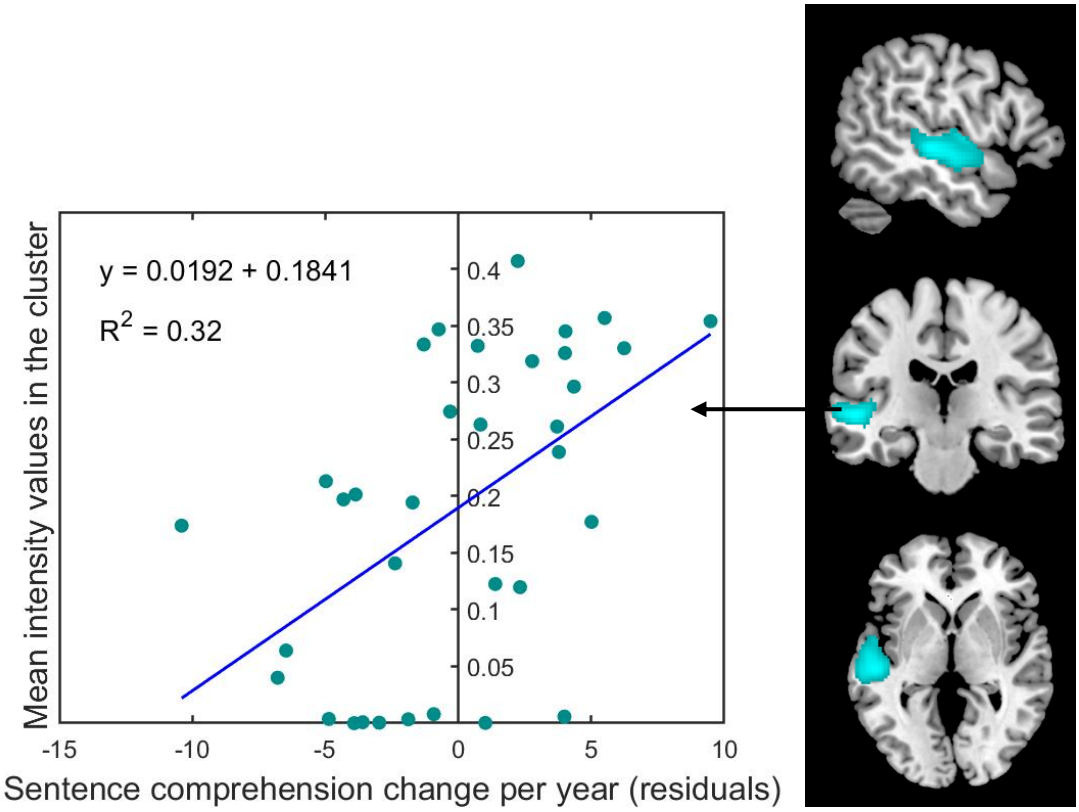


Figure 2. 3 The neural cluster positively associated with SCPY in the VBCM analyses. The x-axis shows the SCPY residuals (i.e., variance left unexplained) resulting from covarying out the effect of nuisance variables (age, time post stroke, ICV and lesion volume) from the behavioural score (SCPY). The y-axis refers to mean intensity white matter values within the cluster.

Table 2. 2

Peaks within the cluster significantly associated with decline in sentence comprehension change per year

Behavioural Regressor	Location	Extent (Voxels)	Z	MNI Coordinates		
				x	y	z
SCPY	Left Superior Temporal Gyrus	1220	3.78	-54	-22	0
	Planum Temporale		3.66	-62	-28	8
	Central Opercular Cortex		3.38	-56	-6	4

Abbreviation: SCPY = sentence comprehension change per year.

Discussion

Recent studies have extended the study of post-stroke language recovery beyond the subacute stage into the chronic phase, and have revealed both significant improvement and decline in spoken word production abilities with associated distinct right hemisphere correlates (Hope et al., 2017). These findings challenge the widely held view of stability of language functions in chronic aphasia. The present study adds to this body of evidence by examining changes in a receptive language ability, spoken sentence comprehension, in chronic stroke aphasia. Considerable behavioural variability in amount and direction of change was apparent, with the majority of the group (19/34) showed a numerical decline in performance, and fewer (11/34) showing a numerical improvement, meaning that at a group level, there was significant decline in spoken comprehension of time. The analysis of individual patient performance confirmed significant declines in three cases. Analyses of grey and white matter probability maps from scans taken at the time of initial testing identified a left superior temporal region in which greater damage was associated with greater decline spoken sentence comprehension. These results demonstrate significant change in receptive language tasks for the first time in chronic stroke aphasia, and further identify an area of left superior temporal cortex in which more extensive damage indicate a higher probability of future auditory comprehension decline.

Regarding the behavioural changes observed in speech comprehension, it is notable that decline was more prevalent than recovery. The mechanism by which this occurred is unclear, but one possibility is that it represents a form of diaschisis (Carrera & Tononi, 2014) whereby damage to the superior left temporal regions weakens input to sentence comprehension processes, decreasing their overall efficiency over time. Another possibility is that sentence comprehesion processes decline over time through disuse. As a result of partially losing their language functions, aphasic patients may be discouraged from communicating linguistically, progressively using speech less, and ultimately declining. This could be true of our patients, especially considering that over half the people who declined (13 out of 19) were more severe to begin with (i.e., were classified as having Broca's or more severe forms of aphasia). It seems unlikely the declines we observed were the consequence of aging, as there was a wide age range amongst those declining, nor did it seems that it was a consequence of post-stroke neurodegeneration (Kalaria et al., 2016), as none of the patients had been diagnosed with dementia.

Our VBCM findings that the white matter probability maps underlying the left pSTG and its surrounding tissue correlated with the SCPY is consistent with the literature indicating the involvement of left posterior temporal regions with sentence comprehension processes. For example, Leff et al. (2009) utilised voxel based morphometry to show that the left pSTG and pSTS correlated with sentence comprehension (and auditory short-term memory) in 210 aphasic stroke patients. Similarly, Lwi et al. (2021) reported that damage to the left posterior middle temporal gyrus associated with poor comprehension of sequential commands in 168 aphasic participants, while deficits in single-word and yes/no question comprehension correlated with mid- to posterior middle temporal gyrus. In a study that compared auditory single-word and sentence comprehension processes in 72 patients with primary progressive aphasia, Mesulam et al. (2015) was able to dissociate two brain regions. Atrophy to the left anterior temporal lobe correlated with word-level comprehension deficits while atrophy to left posterior temporal cortex (in addition to frontal regions) correlated with sentence-level comprehension deficits. Subsequent work by Xing et al. (2017) in 40 patients with chronic stroke aphasia showed that white matter integrity of the aTL and the uncinate fasciculus related to single-word comprehension abilities, while the white matter underlying the pTL and the inferior longitudinal fasciculus correlated with spoken sentence comprehension functions. When examining the neural correlates of sentence comprehension and production processes (using voxel-based lesion symptom mapping), Lukic et al. (2021) found a unique role for the left posterior temporal lobe. While damage to the left aTL in 76 chronic aphasic participants was associated with both sentence comprehension and production deficits, damage to pTL (and inferior parietal lobe) was additionally related to sentence comprehension impairment. PTL was further associated with deficits in processing syntactically complex (noncanonical word-order) sentences across domains.

The left posterior superior temporal cortex is further strongly associated with phonological and lexical processing, the ability to perceive speech accurately, and word recognition (Bornkessel-Schlesewsky & Schlesewsky, 2013; Hullett et al., 2016; Scott & Johnsrude, 2003; Walenski et al., 2019). For example, functional neuroimaging (PET) work by Scott et al. (2000) showed pSTS activity when eight healthy participants listened to speech stimuli containing phonetic information (i.e., normal speech, spectrally rotated speech, and noise-vocoded speech) compared to stimuli that did not sound like speech (i.e., spectrally rotated noise-vocoded speech). In contrast, the anterior STS was uniquely sensitive to intelligible stimuli (i.e., normal speech and noise-vocoded speech). The authors speculated that the pSTS is involved in the

short-term representation of phonemes, which is crucial to be able to repeat and learn new words in the long-term. This speculation was based on the finding that lesions to the posterior superior temporal cortex can lead to conduction aphasia, a phonological condition characterised by an inability to repeat words (Anderson et al., 1999; Axer et al., 2001).

Given these previous structural and functional imaging results from aphasic and healthy participants, the left posterior temporal cluster found to predict future decline in this study is logical, as arguably the ability to understand sentences taps on both sentence-level semantics and phonology. The input (phonological) deficits in our patient cohort (as assessed with MPW and MPNW) might underlie sentence comprehension decline (as determined by the Spoken Comprehension CAT Subtest) at the group level.

In conclusion, our results indicate that spoken language comprehension processes continue to evolve over the chronic period in stroke aphasia. The fact that decline was more prominent than recovery highlights the importance of identifying at-risk patients. We have identified that those with more extensive lesions within the left posterior superior temporal lobe are those most likely to show a decline in their spoken language abilities over the longer term, which could permit application of targeted treatments to stave off these deficits, improving functional outcomes.

Chapter 3: Investigating Neuropsychological Change and its Neural Correlates in Chronic Stroke Aphasia

Abstract

Language difficulties (aphasia) are one of the most common and debilitating symptoms after stroke, affecting at least one third of patients. Recent investigations have shown that aphasic recovery (and decline) can continue to occur many years after stroke, mirrored by neural changes in the brain. Due to the multi-dimensional nature of language, it is unclear if all linguistic functions can potentially change over time, and if there are any brain areas systematically related to these changes. In this study we combined extensive neuropsychological testing with neuroimaging to explore the trajectory of aphasia in 26 chronic (> 12 months) participants. Following the completion of a full neuropsychological battery and the acquisition of detailed T1-weighted MRI scans, patients were assessed again on eleven of its most sensitive tests (mean time interval = 28.37 months, SD = 12.66). Individually, some participants improved and declined in specific tasks, whilst at the group-level they marginally improved in the non-word repetition test. Normalised change per year scores in the linguistic-cognitive tasks were entered in voxel-based correlational methodology analyses of grey and white matter probability maps. Naming change per year was positively associated with a cluster in the grey matter extending from the right frontal cortex to the temporal pole, and including the uncinate fasciculus. This is in line with the anterior temporal lobes and the uncinate fasciculus being essential for naming and semantic processes. Non-word repetition change per year was positively correlated with a cluster in the right caudate and its surrounding white matter. The caudate has previously been linked to speech motor processes and inhibitory/language control. These findings indicate that linguistic processes have different recovery patterns in chronic aphasia, and that key neural areas are responsible for these.

Introduction

Human language is an incredibly rich and sophisticated system of communication. When this system is disrupted or impaired, as is common after stroke or neurodegeneration, it can lead to a multitude of linguistic impairments, collectively referred to as aphasia (Pedersen et al., 2004). It is estimated that one third of stroke survivors are affected with aphasia (Engelter et al., 2006), and for the majority of patients there will be some recovery of function over time. For around 20% of these patients aphasia will become chronic, recovery is thought to plateau, and patients are typically not offered therapy after 6 to 12 months post-stroke (Palmer et al., 2018). In the last few years, a number of studies have shown that spontaneous change, both positive and negative, can continue to occur in 'chronic' patients, at least for some linguistic functions (Hope et al., 2017). Identifying the patients at risk of decline has important clinical value as it might permit more extended or targeted therapeutic interventions to support them. This study considered for the first time neuropsychological change across an extensive battery in chronic aphasia, revealing if any neuropsychological changes could extend to similar tasks, or generalise to other functions, by examining behavioural change, and its neural correlates, in a chronic (> 12 months) stroke cohort.

Most, if not all, linguistic recovery post-stroke is thought to occur between the acute (first few days to weeks) and subacute (~ 2 weeks - 12 months) phases (Bakheit et al., 2007; Pedersen et al., 1995). For example, Pedersen et al. (2004) described an aphasic profile shift, from more to less severe (as assessed by the Scandinavian Stroke Scale), in a 270 subacute cohort. There was a significant reduction in global cases (from 32 % to 7% twelve months post-stroke), and an increase in milder forms of aphasia (that is, anomia, from 25% cases subacutely to 29% twelve months later). Structural and functional studies have associated spontaneous recovery in the subacute phase to neural structures in the brain, specifically the spared and perilesional cortex (Fridriksson et al., 2010a; Griffis et al., 2017) and contralateral right hemisphere areas (Crinion & Price, 2005; Turkeltaub et al., 2012), with some support from domain-general cognitive regions (Geranmayeh et al., 2017). Saur et al. (2006) and later Stockert et al. (2020) tried to merge these often contradictory findings by scanning patients and acquiring neuropsychological data at three different time points. In their longitudinal fMRI study, 14 participants were scanned and administered neuropsychological tests in the acute (mean = 1.8 days post-stroke), subacute (mean = 12.1 days post-stroke) and chronic phases (mean = 321 days post-stroke) (Saur et al., 2006). Results showed that different neural activation patterns in

each phase correlated with the progressive recovery of linguistic function. In the acute phase, minimal early activation was observed in perilesional left hemisphere areas, followed by an increase in activation in the subacute phase in right Broca's area and right supplementary motor area. Maximal recovery in the chronic phase was associated with a return to normal activation levels in the left hemisphere neural language network.

In terms of linguistic abilities in chronic patients, it was traditionally assumed that there was a 'critical period' for recovery, after which deficits stabilised. Nevertheless, anecdotal reports (Smania et al., 2010) as well as evidence from children who improved spontaneously many years post-stroke (Elkana et al., 2013) seemed to contradict this. Hope et al. (2017) showed that naming improvements and decline (in relatively equal measures) could continue to occur in chronic patients. This was mirrored by structural (and functional) neural adaptations: naming recovery in 13 patients was positively correlated with change in the right anterior temporal lobe, while decline in 11 participants was negatively associated with structural adaptations in the right precentral gyrus. This suggested that neural plasticity in chronic aphasia could continue to occur. Our subsequent work (Chapter 2) indicated that multi-word sentence comprehension could also evolve in chronic aphasia. The behavioural change correlated with the neural integrity of the left posterior superior temporal gyrus. This current prospective longitudinal study increases our understanding of linguistic abilities in chronic aphasia by expanding the number of assessments administered to patients to cover a variety of linguistic and non-linguistic domains. These changes were then related to the structural neural integrity of patients from scans acquired at the time of their first assessment.

Methods

Participants

Twenty-six stroke participants with chronic aphasia were recruited for this study (10 females and 16 males; age (mean [SD] range) = 59.8 [11.43] 43 - 86 years). The majority of these individuals (n = 25/26) had previously participated in the study described in Chapter 2. For additional demographic and lesion data, please refer to Table 3.1. Participants were recruited from community groups and speech and language therapy services in the North West of England. The Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1983)

was used to determine participants' aphasic subtype at both time points. All subjects were in the chronic phase (> 12 months post-stroke) when they completed the round of neuropsychological and neuroimaging assessments (T1) (mean months post-stroke = 57.02, SD = 60.21). Patients were re-tested with a minimum interval of 12 months (T2) (T2 – T1 = 26.18). Inclusion criteria consisted of adults with normal or corrected-to-normal hearing and vision, premorbid right handedness, and English as a native language. Exclusion criteria included having suffered multiple strokes, a previous history of neurological disorders, and having any metal-implants or contraindications for MRI scanning.

All patients provided informed consent under approval from the North West Multi-Centre Research Ethics Committee (reference 01/8/94).

Behavioural assessment

The participants in this study were part of a larger aphasic database (n = 97) that have detailed neuropsychology and neuroimaging, as described in Halai et al. (2017). The 'full' neuropsychological battery, that was administered to all patients when they were recruited, constituted the tests at Time 1. This battery included subtests from the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) battery (Kay et al., 1992) auditory discrimination using non-word (PALPA 1) and word minimal pairs (PALPA 2); and immediate and delayed repetition of non-words (PALPA 8) and words (PALPA 9). Tests from the 64-item Cambridge Semantic Battery (Bozeat et al., 2000) were also included: spoken and written versions of the word-to-picture matching task; Camel and Cactus Test (CCT picture); and the picture naming test (Cambridge naming battery, CNB). To increase the sensitivity to mild naming and semantic deficits we used the Boston Naming Test (BNT; Kaplan et al., 1983) and a written 96-trial synonym judgement test (Jefferies et al., 2009). The spoken sentence comprehension task from the Comprehensive Aphasia Test (CAT) (Swinburn et al., 2004) was used to assess sentential receptive skills. The additional cognitive tests included forward and backward digit span (Wechsler, 1987), the Brixton Spatial Rule Anticipation Task (Burgess & Shallice, 1997), and Raven's Coloured Progressive Matrices (Raven, 1962). Tasks that required patients to produce speech were recorded, and their answers were manually transcribed and scored. Scores in the (complete) neuropsychological battery are provided in Appendix A.

Typically it took between 6 and 10 hours of testing to administer the battery, so it was undesirable for patients to complete the whole battery again. Therefore, we decided to focus on a subtest of tests that accurately captured the aphasic profile of the full battery. Halai et al. (2020a) showed that is it possible to reduce the full battery down to approximately 2 hours of testing but retain the overall sensitivity. This battery was made of: 2 phonological tests (word and non-word repetition), 2 semantic tests (96-synonyms and spoken word-to-picture matching task), 2 naming tests (CNB and BNT), 2 executive-cognitive tests (Brixton Spatial Rule Anticipation Task and Raven's Coloured Progressive Matrices), a sentence comprehension test (CAT spoken sentence comprehension subtest), the digit forward, and the general aphasic profile test (BDAE). Assessments were conducted with participants over several testing sessions with the pace and number determined by the participant. Behavioural scores on the reduced neuropsychological battery are presented in Appendix C.

In order to compare scores between participants over time, we converted the neuropsychological values into change per year (CPY) scores. The CPY were estimated to control for differences in time-intervals between assessments across patients. To calculate the CPY we substracted the raw score at time 1 from time 2, and divided this change by the number of years (with years determined as number of days divided by 365).

Table 3. 1

Participants' demographics and lesion characteristics

ID	BDAE	Age	Sex	Time post-stroke	Lesion volume	ICV
11	Anomia	52	F	76	9767	1317360
15	Mixed Non-fluent	68	M	14	8788	1514570
21	Broca	58	M	135	18392	1540649
31	Global	68	M	50	41379	1535539
32	Anomia	44	M	40	8437	1640831
36	Anomia	51	F	66	6975	1396846
38	Anomia	77	F	56	13577	1441204
41	Mixed Non-fluent	78	M	36	34242	1575337
42	Anomia	68	M	21	3311	1379659
44	Broca	59	M	37	13080	1607653
45	Anomia	59	M	34	16433	1526726
47	Anomia	51	M	72	22948	1577506
48	Conduction	46	F	21	3897	1510325
52	Anomia	44	F	13	18948	1306883
54	Mixed Non-fluent	75	F	160	12057	1299507
58	Anomia	43	F	15	175	1343738
63	Anomia	58	F	278	12699	1699168
64	Conduction	67	M	13	4879	1526785
65	Global	52	M	73	37822	1366299
66	Anomia	86	M	17	8528	1635680
68	Conduction	67	M	14	6557	1649371
69	Anomia	56	M	17	6974	1514073
70	Anomia	65	M	75	6607	1429488
71	Anomia	50	M	16	4538	1434622
74	Mixed Non-fluent	56	F	40	10051	1487067

82	Anomia	57	F	21	10027	1461015

Participants' IDs were taken from the Manchester Aphasic Stroke Sample. Time post-stroke (in months) was the time of the first assessment. Lesion volume and intra-cranial volume are reported in mm^3. **Abbreviations:** BDAE = Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983), ICV = intra-cranial volume.

Acquisition of neuroimaging data

High-resolution structural T1-weighted MRI scans were acquired on a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an eight-element SENSE head coil. A T1-weighted inversion recovery sequence with 3D acquisition was employed, with the following parameters: repetition time = 9.0 ms, echo time = 3.93 ms, slice thickness = 1 mm, flip angle = 8, 150 contiguous slices, acquired voxel size = 1.0 × 1.0 × 1.0 mm^3, matrix size = 256 × 256, field of view = 256 mm, inversion time = 1150 ms, SENSE acceleration factor 2.5, total scan acquisition time = 575 s.

Preprocessing of neuroimaging data

Patient's structural MRI scans were pre-processed with Statistical Parametric Mapping software (*SPM12*, 2012) running under Matlab 2019a. The images were first normalised into standard Montreal Neurological Institute (MNI) space using a modified unified segmentation-normalisation procedure optimised for focal lesioned brains. A healthy control group (n = 22), matched for age and education, was used to determine the extent of abnormality per voxel using an automated lesion identification procedure (ALI V3) (Seghier et al., 2008). Neuroimaging data from the 26 patients and 22 controls were then entered into the segmentation-normalisation. Images were smoothed with an 8mm full-width at half-maximum Gaussian kernel. Patients' lesions were automatically identified using a fully automated method based on fuzzy clustering (Seghier et al., 2008). The default parameters were used aside from the lesion definition 'U-threshold', which was set to 0.5 rather than 0.3 to create a binary lesion image. The parameters were changed after comparing the results obtained from a sample of patients to what would be nominated as lesioned tissue by an expert neurologist. The T1-weighted images generated from every patient were visually inspected with respect to the original scan, and manually modified if necessary. The smoothed grey and white matter

probability maps resulting from the segmentation-normalisation algorithm in MNI space were used in the subsequent neuroimaging analyses.

Voxel-based correlational methodology analyses

To examine the neural correlates of linguistic change, patients' behavioural scores were mapped onto their grey and white matter images using voxel-based correlational methodology (VBCM; Tyler et al., 2005). VBCM is a variant of voxel based morphometry (Ashburner & Friston, 2000), where both the behavioural and neuroimaging data are assigned a continuous, non-binary value. VBCMs were conducted with SPM12 (*SPM12*, 2012) running under Matlab 2019a. We computed two models, a grey matter and a white matter, for each neuropsychological measure. In addition, four regressors of no interest were entered in the models, namely: age at the scan (in years), lesion volume (LV, in mm^3), time post-stroke (in months) and intra-cranial volume (ICV, in mm^3). The LV was calculated using the outputs from the ALI toolbox, thus the binarised lesion fuzzy map, and then extracting the number of voxels in that lesion map. We converted that number to volume by multiplying it by the volume of the voxel. The ICV was calculated by converting the SPM ICV template mask into subject native space then counting the number of voxels (and again multiplying it by the volume of the voxel). Anatomical areas were defined using labels based on the Harvard-Oxford atlas in MNI space (Desikan et al., 2006) and the Natbrainlab white matter tract atlas (Catani et al., 2012). All images are were created using MRIcron and MRIcroGL (Rorden et al., 2007).

Results

Neuropsychology

Group-level. Paired-samples t-tests were used to compare changes in the neuropsychological tasks from the first to the second assessment. We assessed the size of the change per year values as this controls for the variable time interval between assessments. Participants declined significantly in the CAT Spoken Comprehension subtest ($t(25) = -2.15$, $p = 0.041$). From the 26 participants: 14 declined, 9 improved and 3 remained stable (mean SCPY change = -2.03, SD = 4.82, range = -17.23 to +3.55). This result replicated our finding from a previous study

on 34 participants (25 included in this study), which focussed on sentence comprehension abilities in chronic aphasia (Chapter 2). Participants further marginally improved in the Non-word Repetition test ($t(25) = 1.85$, $p = 0.056$). In this task, 14 patients improved, 8 declined and 4 remained stable (mean NCPY change = 0.35, SD = 0.96, range = -1.31 to +2.61).

Spearman's rank-order correlation coefficient was used to detect the strength of correlation between change scores per neuropsychological test. We found a significant correlation between the following pairs: 1) Word repetition and CNB ($r = 0.423$, $p = 0.031$); 2) Boston naming test and CNB ($r = 0.54$, $p = 0.004$); and 3) Raven's progressive matrices and Brixton spatial anticipation tests ($r = 0.451$, $p = 0.021$). These correlations indicate that such scores must be included in separate VBCM models.

Individual-level. McNemar's Tests and Wilcoxon Rank Tests were used to determine statistical significant change in each neuropsychological task from the first to the second assessment. As reported in Table 3.2, 12 patients changed significantly across 7 tasks measuring naming, repetition, sentence comprehension, and executive-cognitive functions. No patients changed significantly in the single-word comprehension tasks and the digits forward. Patients' scores for the tests where they changed significantly are shown in Fig. 3.1. The figure for the CAT sentence comprehension was not included because it was so similar to Fig. 2.1.

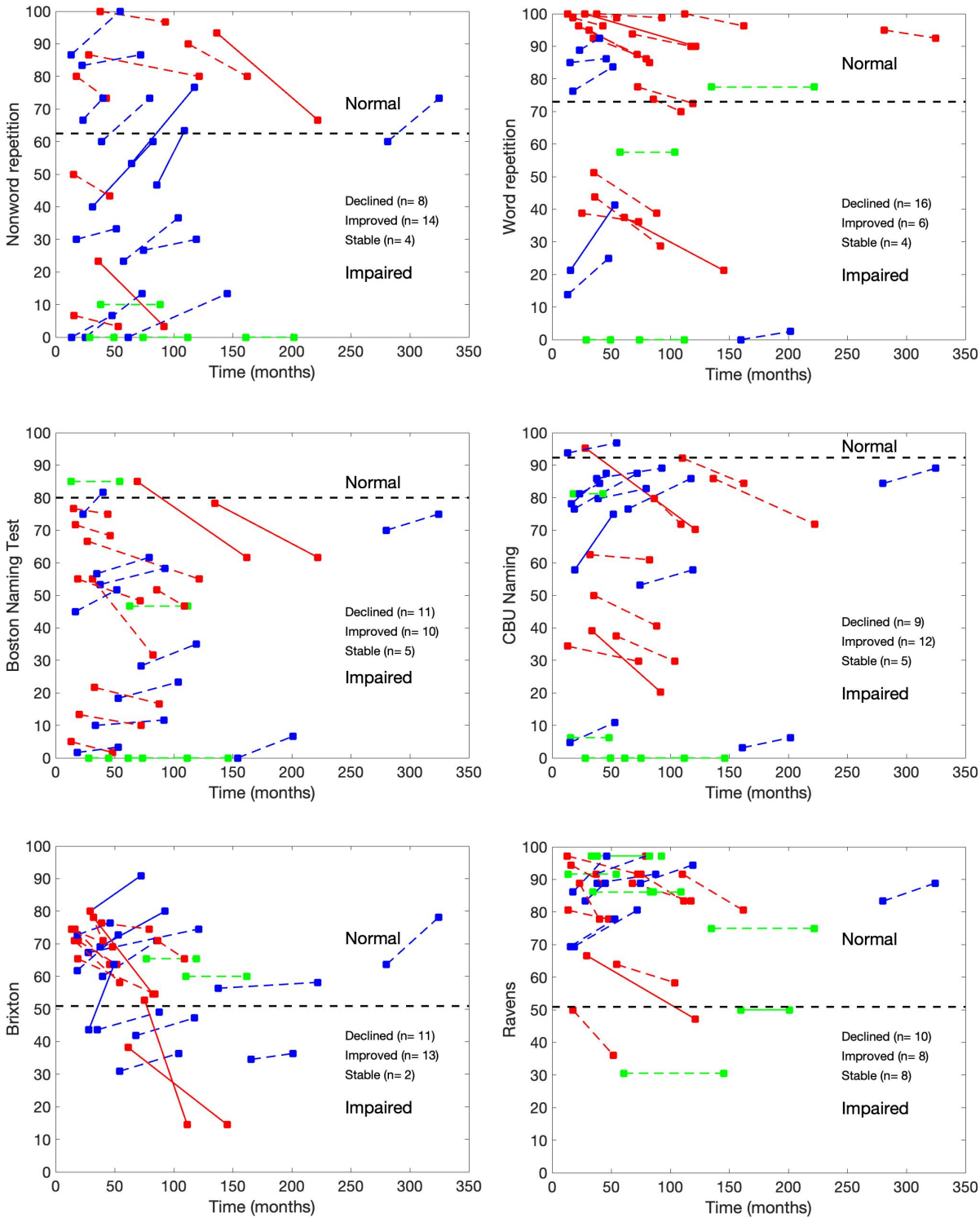


Figure 3. 1 Scores in the neuropsychological battery at the first and second assessments. The continuous line represents a significant change (improvement or decline) between assessments. The dashed line represents no significant change between tests. Blue = improvement, Green = stable, Red = declined.

Table 3. 2

McNemar and Wilcoxon Rank tests for the patients who changed significantly over time in a task

ID	Test	McNemar	Wilcoxon	Direction of change
11	BNT	$p < 0.001$		Decline
15	Word repetition	$p = 0.008$		Decline
	CNB	$p < 0.001$		Decline
	Raven's	$p = 0.039$		Decline
21	Non-word repetition	$p = 0.039$		Decline
	BNT	$p = 0.021$		Decline
31	Word repetition	$p = 0.021$		Decline
	Brixton	$p = 0.015$		Decline
32	Brixton	$p = 0.031$		Improvement
41	Non-word repetition	$p = 0.031$		Decline
	CNB	$p = 0.017$		Decline
45	Non-word repetition	$p = 0.041$		Decline
	BNT	$p = 0.004$		Decline
	Brixton	$p = 0.007$		Decline
48	CAT Comprehension		$p = 0.034$ $z = -2.121$	Decline
	Brixton	$p = 0.031$		Improvement
65	Brixton	$p < 0.001$		Decline
66	CNB	$p = 0.019$		Improvement
	CAT Comprehension		$p = 0.014$ $z = -2.46$	Decline
68	Word repetition	$p = 0.018$		Improvement
74	Brixton	$p = 0.027$		Improvement

Abbreviations: BNT = Boston Naming Test (Kaplan et al., 1983), CAT = Comprehensive Aphasia Test (Swinburn et al., 2004), CNB = Cambridge naming battery (Bozeat et al., 2000).

Neuroimaging

Lesion overlap map. Fig. 3.2 shows the lesion overlap of the 26 participants. It principally covered the left hemisphere region supplied by the middle cerebral artery (Phan et al., 2005). The highest number of patients who presented damage to the same neural region was 20, in the left precentral gyrus (MNI coordinates: -27, 10, 26).

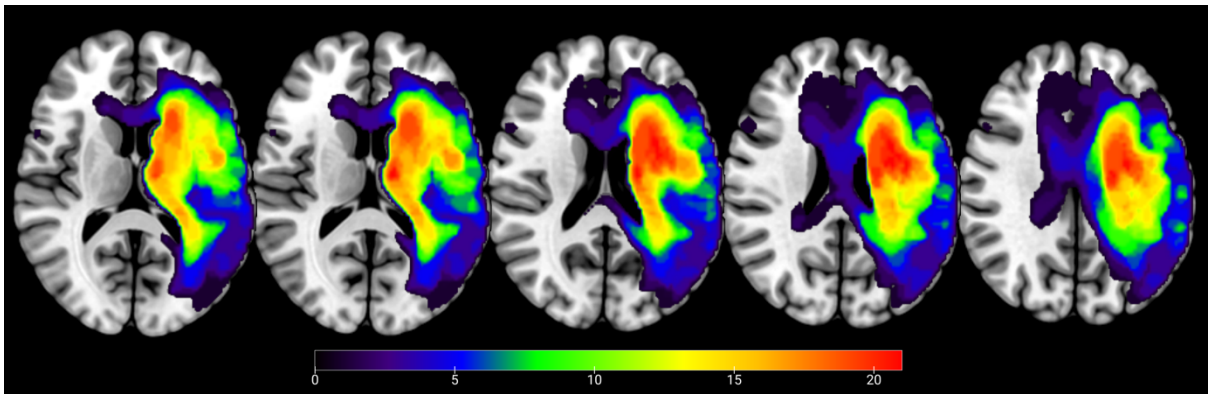


Figure 3. 2 Lesion overlap map showing the distribution of patients' (n = 26) lesions. The neural region that was most damaged in the cohort was the left precentral gyrus (MNI coordinates: -27, 10, 26).

Identifying the neural correlates of behavioural change

The second aim was to map the change per year scores to underlying brain structures, therefore two separate VBCM models (reflecting grey and white matter maps) were created for each neuropsychological test. The results revealed two unique clusters, one in the grey matter and another in the white matter, that were associated with linguistic change over time (Table 3.3). The results were thresholded at $p < 0.005$ voxel- level, $p \leq 0.05$ FWE corrected cluster-level. First, we observed a positive correlation with grey matter probability and change in CNB within the right frontal cortex (frontal pole, medial and orbital cortex), insula, temporal fusiform gyrus and temporal pole. The cluster also overlapped with the uncinate fasciculus, a key tract for semantic processing (Catani et al., 2013) (Fig. 3.3). Second, we observed a positive correlation with white matter probability and change in non-word repetition. This cluster was centred on white matter surrounding the right caudate and anterior cingulate (i.e., the cingulum, corpus

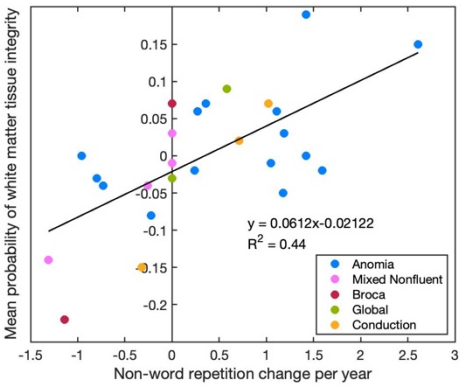
callosum and internal capsule), whose damage is directly related to multiple types of aphasia (Hillis et al., 2004).

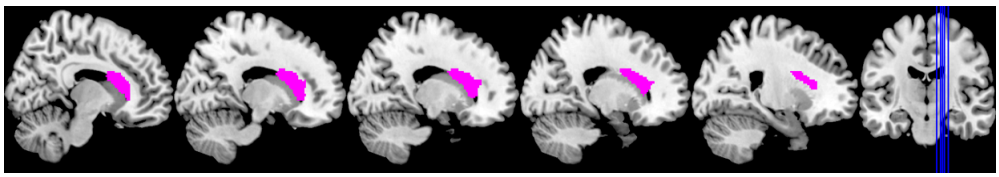
Table 3.3

Peaks within the neural clusters associated with the normalised change per year scores

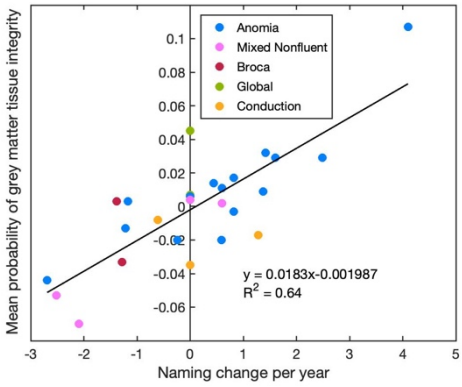
Covariate	Image type	Anatomy	Extent (voxels)	Z	MNI coordinates		
					x	y	z
NCPY	swc1T1		548	3.51	32	-4	-2
				3.26	26	-4	-8
		Frontal orbital R		2.23	22	20	-14
	swc2T1	/					
N-RCPY	swc1T1	/					
	swc2T1	Corpus callosum R	943	3.54	14	20	14
		Corpus callosum R		3.48	18	12	20
				2.83	26	30	12

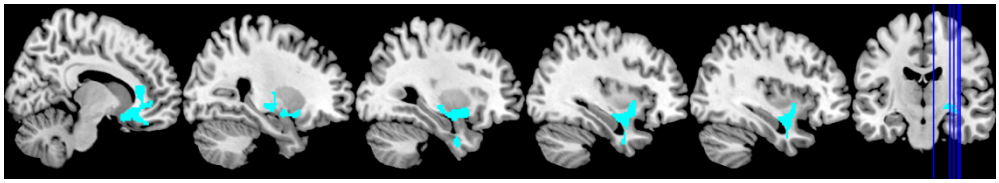
Abbreviations: NCPY = naming change per year, N-RCPY = non-word repetition change per year, swc1T1 = smoothed warped (normalised) corrected grey matter, swc2T1 = smoothed warped (normalised) corrected white matter.





x = 10	x = 14	x = 16	x = 18	x = 22





x = 10	x = 26	x = 30	x = 34	x = 36

Figure 3. 3 Significant neural clusters associated with recovery and decline.

Top panel. The neural cluster positively associated with Non-word Repetition Change per Year (N-RCPY). Left panel. The x-axis shows the N-RCPY residuals (i.e., variance left unexplained) resulting from covarying out the effect of nuisance variables (age, time post-stroke, lesion volume and ICV) from the behavioural score (N-RCPY). The y-axis refers to mean intensity white matter values within the cluster. Right panel. Neural region centred in the right caudate and underlying white matter found to correlate with N-RCPY. Bottom panel. The neural cluster associated with Naming Change per Year (NCPY). Left panel. The x-axis represents the NCPY residuals resulting from covarying out the effect of nuisance variables from the NCPY. The y-axis are the mean intensity grey matter values within the cluster. Right panel. Neural region centred in the frontal cortex extending into the temporal pole that correlated with NCPY.

Discussion

Understanding the trajectory of linguistic symptoms is essential both for building theoretical models of aphasia recovery and to inform clinical practice. Current literature indicates that chronic patients' abilities are not as static as previously thought, and that specific linguistic functions can continue to evolve over time. This said, no work has addressed yet neuropsychological change across a battery, which would lead to a more comprehensive knowledge of symptoms in chronic aphasia. This longitudinal study assessed chronic participants twice in a neuropsychological battery, and mapped their behavioural change per year scores to their neural data acquired at the first assessment. Our results expanded our knowledge of recovery in post-stroke aphasia, and found that: i) not every neuropsychological test changed in the chronic phase; ii) a portion of participants improved and declined between assessments, in contrast to the subacute phase were change is predominantly positive; iii) and the functions that changed were systematically related to specific areas in the right hemisphere. Overall, our results are consistent with the view that the right hemisphere is implicated in cognitive and linguistic processes in aphasia, both in the subacute and chronic phases.

At the group-level there was significant neuropsychological change in two tasks: sentence comprehension and (marginally) non-word repetition. This is consistent with the view that there is no exact time point where recovery (or decline) ceases, although arguably change in the chronic phase occurs to a lesser extent than in the subacute phase (Holland et al., 2017; Johnson et al., 2019). These results also indicate that there are different patterns of recovery among neuropsychological tasks, and that some patients are more predisposed to change than others. Lesion size and site, initial aphasic severity and possibly patient-related factors (e.g., family or living situation, socioeconomic status) might play a role in predicting patients' long-term linguistic outcomes (Plowman et al., 2012).

Change in non-word repetition was positively associated with the right caudate, anterior cingulate and its neighbouring white matter. That is, higher probability of tissue integrity in these regions at time of first assessment was associated with a higher chance of recovery. Non-word repetition is a cognitively complex function, involving the fusion of phonological working memory with word learning (Coady & Evans, 2008). The caudate bilaterally is required for language control mechanisms, including translation (Price et al., 1999), language

switching (e.g., in bilingualism) (Abutalebi et al., 2008; Crinion et al., 2006) and the control of word interference (Price, 2010, 2012). An fMRI study by Ali et al. (2010) reported left caudate activity when participants suppressed irrelevant words in the Stroop task, as opposed to irrelevant visual stimuli. The anterior cingulate is also associated with error detection, and is a node within the cognitive neural network that is involved in guiding behaviour (Seeley et al., 2007). It has been proposed that the caudate mediates cortical activation in the anterior cingulate during changing the focus of attention different between stimuli (Hedden & Gabrieli, 2010). Our findings suggest that the right caudate and anterior cingulate work together to support the cognitive mechanisms controlling non-word repetition, while at the same time suppressing conflicting stimuli and word interference (e.g., that might result in erroneously producing an existing word).

Change in naming abilities was positively correlated with a cluster encompassing frontal and temporal cortices, and the uncinate fasciculus that connects them, where higher integrity in these regions at first assessment corresponding to greater recovery over time. This result is in line with the literature that links naming and semantic processing with the uncinate fasciculus (Catani et al., 2013) and the anterior temporal lobes (ATLs), more prominently in the left hemisphere (Lambon Ralph et al., 2017; Patterson et al., 2007). Electrical stimulation (anodal transcranial direct stimulation) of the ATLs improves naming recall in both young adults (Ross et al., 2010) and elderly people (Ross et al., 2011), although for the elderly only the left ATL yielded a significant result. On a related note, inhibitory repetitive transcranial magnetic stimulation in healthy individuals caused disruption of picture naming in the left but not right ATL (Woollams et al., 2017). In stroke-aphasic patients, lesion-symptom studies have mapped naming retrieval errors to the left ATL, particularly the anterior middle temporal gyrus (Schwartz et al., 2009). VBCM work has consistently related principal component analysis (PCA)-derived semantic factors (i.e., a behavioural reduction technique, as applied to the same 'full' neuropsychological battery as used in this study) to anterior temporal regions (Butler et al., 2014; Halai et al., 2017; Halai et al., 2020b). Furthermore, functional neuroimaging studies have shown that semantic tasks elicit bilateral ATL activity, which tends to be greater in the left ATL than the right (Humphreys et al., 2015; Rice et al., 2015; Visser et al., 2010). In terms of the uncinate fasciculus, it is atrophied in semantic dementia (Agosta et al., 2010; Galantucci et al., 2011) and damaged in stroke-aphasia (Basilakos et al., 2014). Removal of this tract leads to naming deficits (Papagno, 2011). Our results indicate that the interaction of right frontal and

temporal regions connected through the uncinate fasciculus underlie change in naming abilities in chronic aphasia.

As noted above, we related changes to scans taken at first assessment, and therefore cannot say exactly how changes in the brain over time relate to aphasia - specifically, whether it is premorbid anatomy or neural plasticity that is driving the naming changes. However, Hope et al. (2017), who conducted a longitudinal neuroimaging study assessing naming, identified structural adaptations in a similar cluster predictive of naming recovery. This suggests that actual neural plasticity was related to changes in performance, although a second MRI scan would be needed to confirm this in our sample.

In conclusion, this study shows that linguistic impairments in post-stroke chronic aphasia do not constitute a single, unitary 'entity', but they have different recovery patterns. Future work can disentangle the specific neural regions that are relevant and predictive of recovery and decline, for example by acquiring two MRI scans and examining change in neural structures longitudinally.

Chapter 4: Correlates of Naming Gains from Repetition-based Therapeutic Intervention

Abstract

Repetition in the presence of a picture (RIPP) is a widely used naming treatment for people with post-stroke aphasia. Recent evidence has indicated that adding a visual articulatory component to RIPP, that is, repetition in the presence of a picture and articulation (RIPPA), or even substituting the picture in the RIPP with an articulatory component (ARTIC), may be equally beneficial, if not more. Clinically, it would be useful to determine the neural and neuropsychological correlates of (successful) outcome in these therapies, so that the patients most likely to benefit from such interventions can be prospectively identified. In the current study, 26 participants with chronic (> 12 months) stroke aphasia underwent three rounds of therapy each (RIPP, RIPPA and ARTIC) over a course of nine weeks. The participants had not previously participated in the spontaneous change studies, and they were recruited from community groups and speech and language therapy services in the North West of England. At the group-level, all therapies were successful in terms of improving the naming performance (for the treated words) one-week post-treatment, with no therapy effect for the untreated (control) items. Principal Component Analysis (PCA) was applied to the naming scores post-therapy, which revealed two components: a component related to treated gains, and a component related to untreated gains. This reflected that, fundamentally, all repetition-based therapies were beneficial compared to no therapy. Subsequently, we investigated whether participants' pre-therapy neuropsychological abilities (derived from a battery consisting of 21 measures), both in raw form and PCA-derived components, correlated with the treated and untreated gain components. Furthermore, we related the therapy components to participants' grey and white matter maps using voxel-based correlational methodology. Results showed that naming and PCA-derived phonological scores correlated with the treated gains component. In addition, a neural cluster in the right precentral gyrus and superior parietal lobule was related to the therapeutic gains. Overall, this suggests that participants' naming and phonological abilities, as well as neural structures in the right hemisphere, are good predictors of therapeutic outcomes in these repetition-based therapies.

Introduction

One of the most common and frustrating symptoms in post-stroke aphasia is anomia, or word-finding difficulty (Fridriksson et al., 2012; Pedersen et al., 2004). Anomia affects around one third of left hemisphere stroke patients (Berthier, 2005), and can have a substantial adverse effect on their social and work lives (Ferro et al., 1999; Sarno, 1997), and mental health (Mitchell et al., 2017). It is therefore important to find effective therapies for word finding difficulties in chronic aphasia.

Repetition in the presence of a picture (RIPP) is a widely used speech and language therapy to improve patient's word-finding abilities (Mason et al., 2011; Morris et al., 2014; Nickels, 2002; Sandars et al., 2018b). It consists in showing the individual a picture of an object (or a verb) along with the auditory presentation of its name, and asking him/her to repeat the word. Providing the complete word to the patient, rather than for example just the initial or final phonemes as cues, it might be less cognitively demanding on the participant and more enjoyable. In fact therapies, such as the RIPP, are used as a way of minimising naming errors in the therapy, and although they may lead to more errors in terms of outcomes, they are quicker to implement (Conroy et al., 2009). Nardo et al. (2017) used the RIPP in a longitudinal fMRI study of 18 chronic aphasic patients, where they were scanned before and after the therapy. Immediately post-RIPP therapy, patients showed an increase in naming accuracy (+29%, SD = 3.45) and faster reaction times (+17%, SD = 1.83), with these effects maintained at a 3 month follow-up. Processing of these complete word cues activated bilateral cortical areas, including the right angular gyrus. Interestingly, providing patients with other types of phonemic cues (i.e., word-initial and word-initial cues) was associated with the recruitment of different cortical areas. Theoretically, the main case in support of RIPP is an errorless one, wherein both the semantics (picture) and phonology (auditory input) of target words are reinforced through Hebbian learning (Hebb, 1949). That is, anomia can result from disrupted semantics and/or phonology (Dell & Oseaghdha, 1992; Dell et al., 2013), and, by strengthening the connection within these systems, RIPP may facilitate naming recovery (Howard, 2000).

Based on the literature that showed a common neural substrate for some language production and comprehension areas (Fridriksson et al., 2008; Grodzinsky & Santi, 2008; Ojanen et al., 2005; Pickering & Garrod, 2013; Skipper et al., 2007), Sandars et al. (2018b) decided to add an articulatory-visual component to the RIPP, turning this therapy into the repetition in the presence of a picture and articulation (RIPPA). Previous work by Fridriksson et al. (2009) had

identified that including a video of a word being articulated in a picture-word matching therapy enhanced patients' naming gains. Similarly, in an apraxia of speech programme called SWORD (Sheffield WORD – 'Structured speech therapy'), Varley et al. (2016) used this video imitation method as an advanced form of errorless learning, making error production even less likely than in RIPP. Besides the RIPPA, Sandars et al. (2018b) administered the RIPP and another form of articulatory-visual therapy, repetition in the presence of articulation but no picture (ARTIC). ARTIC was thus used in order to provide some experimental control, and delineate which aspect of RIPPA was driving treatment gains. Importantly, these were all repetition-based therapies, where the six chronic aphasic participants were asked to repeat the treated words. The results revealed that both forms of the articulatory-visual therapies led to naming gains (RIPPA: +31%, SD = 6.53; and ARTIC: +29%, SD = 10.75 compared to baseline), as did RIPP (+24%, SD = 6.26). Subsequent lesion overlap analyses revealed that different neural areas in the left hemisphere mediated each therapy effect: the premotor cortex was associated with the benefit for RIPPA; the inferior temporal and fusiform gyri correlated with treatment effects of the RIPP; and the medial anterior insula was related to the treatment gains following ARTIC. It should be noted that this was an exploratory study, and due to the relatively small sample size it is difficult to generalise to a broader aphasic population.

Principal Component Analysis (PCA) is a statistical decomposition method that has recently been used to investigate and identify latent factors amongst aphasic behavioural data (Butler et al., 2014; Halai et al., 2017; Kummerer et al., 2013; Mirman et al., 2015; Schumacher et al., 2019). Essentially, it can capture the graded variations in a multi-dimensional continuous space, and is therefore suited for a heterogeneous condition such as aphasia. Studies using this technique hace consistently reported four distinct factors within the aphasic continuum, namely phonology, semantics, speech fluency and cognitive-executive function (Halai et al., 2017). Lesion-mapping analyses have related these PCA-derived factors to distinct brain areas, including the left superior temporal gyrus and its underlying white matter for phonology; the anterior temporal lobe for semantics; and the left motor cortex for speech fluency.

In this study we expanded on Sandars et al. (2018b)'s work by acquiring behavioural and neural data from a larger patient cohort of 26 chronic aphasic patients. The key aims of this study were: (i) to assess and compare the linguistic (naming) benefit of each therapy type; (ii) to relate patients' background behavioural abilities, both neuropsychology alone as well as its PCA-derived components, to their therapeutic gains (both raw and PCA-components); and (iii)

to map these PCA-derived therapeutic gains to patients' lesion profiles. A more comprehensive understanding of the neuropsychological and neuroimaging predictors of therapy outcomes has important and valuable clinical applications.

Methods

Participants

Twenty-six stroke participants with chronic aphasia were recruited for this study (9 females and 17 males; age (mean [SD] range) = 62.42 [12.55] 39 - 86 years). The patients were recruited for this study and had not participated in the spontaneous change studies (described in Chapters 2 and 3). For additional demographic and lesion data, please refer to Table 4.1. Participants were recruited from community groups and speech and language therapy services in the North West of England. Inclusion criteria consisted of adults with normal or corrected-to-normal hearing and vision, premorbid right handedness, and English as a native language. Exclusion criteria included having suffered multiple strokes, a previous history of neurological disorders, and having any metal-implants or contraindications for MRI scanning. The Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1983) was used to determine participants' aphasic subtype.

Three patients were excluded from the final analyses due to the following reasons: second stroke (N=1); no visible lesion on MRI (N=1); and COVID-19 pandemic interruption (N=1).

This study obtained Local Research Ethics Committee approval (reference 13/NW/0844) and informed consent or proxy consent was obtained from each participant.

Table 4.1

Participants' demographics and lesion characteristics

ID	BDAE	Age	Sex	Time post-stroke	Lesion volume	ICV
11	Anomia	52	F	76	9767	1317360
15	Mixed Non-fluent	68	M	14	8788	1514570
21	Broca	58	M	135	18392	1540649
32	Anomia	44	M	40	8437	1640831
38	Anomia	77	F	56	13577	1441204
41	Mixed Non-fluent	78	M	36	34242	1575337
42	Anomia	68	M	21	3311	1379659
45	Anomia	59	M	34	16433	1526726
52	Anomia	44	F	37	18948	1306883
59	Mixed Non-fluent	64	M	29	234000	1495940
63	Anomia	58	F	278	12699	1699168
66	Anomia	86	M	17	53064	1551295
69	Anomia	56	M	17	6974	1514073
71	Anomia	50	M	16	4538	1434622
73	Anomia	56	M	26	96600	1395693
75	Broca	70	M	83	267496	1310857
78	Mixed Non-fluent	77	F	20	48736	1161181
81	Global	78	M	17	86360	1546924
82	Anomia	58	F	21	69040	1377100
85	Anomia	70	F	14	7928	1302080
90	Broca	39	F	16	134352	1356064
91	Broca	52	M	20	157168	1586675
92	Broca	54	F	43	69312	1398938
94	Broca	71	M	24	109512	1492296
95	Anomia	55	M	39	16696	1519276
96	Wernicke	81	M	210	133048	1318175

Participants' IDs refer to their file number in the Manchester Aphasia Stroke Sample. Time post-stroke (in months) was the time of the neuropsychological assessment. Lesion volume and intra-cranial volume are reported in mm^3. **Abbreviations:** BDAE = Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983), ICV = intra-cranial volume.

Neuropsychological assessment

In order to test patients' initial expressive and receptive semantic, phonological and cognitive functions they were assessed on a comprehensive neuropsychological battery, previously described by Butler et al. (2014) and Halai et al. (2017).

The battery included subtests from the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) battery (Kay et al., 1992): auditory discrimination using non-word (PALPA 1) and word minimal pairs (PALPA 2); and immediate and delayed repetition of non-words (PALPA 8) and words (PALPA 9). Tests from the 64-item Cambridge Semantic Battery (Bozeat et al., 2000) were included: spoken and written versions of the word-to-picture matching task; Camel and Cactus Test (CCT picture); and the picture naming test. To increase the sensitivity to mild naming and semantic deficits we used the Boston Naming Test (BNT) (Kaplan et al., 1983) and a written 96-trial synonym judgement test (Jefferies et al., 2009). The spoken sentence comprehension task from the Comprehensive Aphasia Test (CAT) (Swinburn et al., 2004) was used to assess sentential receptive skills. The additional cognitive tests included forward and backward digit span (Wechsler, 1987), the Brixton Spatial Rule Anticipation Task (Burgess & Shallice, 1997), and Raven's Coloured Progressive Matrices (Raven, 1962). Tasks that required patients to produce speech were recorded ("Cookie theft" picture description task), and their answers were manually transcribed and scored for number of tokens, words per minute, mean length of utterances and type/token ratio. Scores in the neuropsychological battery are provided in Appendix A.

Accuracy was measured on the basis of participants' first spoken response, although we transcribed their full responses. Assessments were conducted with participants over several testing sessions with the pace and number determined by the participant.

Since this study relied on participants' abilities to repeat, we decided to include only participants who were generally able to repeat, and who scored over 50% in the PALPA immediate word repetition task. Equally, we wanted to avoid naming ceiling effects from participants who were too mild, and thus we decided to have a cut-off of 85% in the BNT. In order to show the distribution of patients selected for therapy, we plotted participants repetition and BNT scores in Fig. 4.1 (red), along with scores from the full database (blue). The majority

of participants selected for the therapy study had relatively spared repetition abilities (n = 23/26), and could name well but not perfectly (n = 25/26).

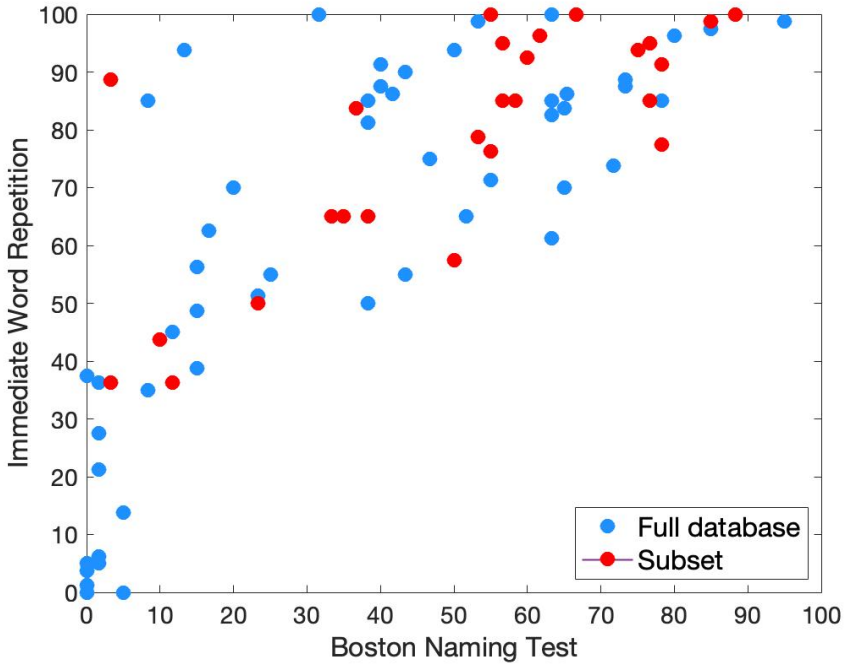


Figure 4. 1 Participants' scores in the Boston naming test (x-axis) and immediate word repetition (y-axis). Red circles represent the people (n = 26) who participated in this study, while blue circles refer to the rest of participants (n = 59) belonging to the Manchester Aphasic Stroke Sample.

Stimuli

Before administering the therapy, participants went through two initial naming assessments where they were asked to name 408 nouns (black-and-white pictures) from the International Picture Naming Project (IPNP, 2000, https://crl.ucsd.edu/experiments/ipnp/1stimuli.html) (shown in Appendix D). The items were presented on a laptop computer using E-Prime (Psychology Software Tools Inc., Sharpsberg, Philadephia), in eight blocks of 51 items. The blocks were matched on length in phonemes, number of syllables, frequency, and age of acquisition, using values provided by the IPNP. Participants completed the blocks from 1 to 8

(i.e., in ascending order) in the first naming assessment, and in the reverse order (i.e., from 8-1) in the second session. Participants had 10 seconds to name each item, after which the picture would time out automatically, and change to the following one. Naming accuracy was scored on the basis of the first verbal attempt, so for example: 'tab, erm, table' for the target 'table' would be scored as 'incorrect'. Patients' responses were recorded, and the second session was conducted within one week of the first assessment.

We then created personalised sets for each participant depending on the words they could name correctly and incorrectly. The stimuli sets were made of 20 items each, and each patient was shown three stimuli sets in every therapy (i.e., 60 different words per therapy type). The treated items sets were made of words patients would consistently name incorrectly, as determined by the two initial naming assessments (i.e., both naming attempts incorrect). Coloured pictures of the treated items were used in the actual therapy. The untreated items set was composed of words patients had also difficulty naming, but these were not treated in the therapy. Finally, the correct set was comprised of words patients could name correctly (consistently: on both trials). When creating the stimulus sets, they were each matched for length in phonemes, number of syllables, frequency, and age of acquisition, using values provided by the IPNP.

There was a small subgroup of patients (n= 7/26) whose naming abilities were relatively preserved and who named too many correct nouns in the initial assessments (≥ 50% or 204/408 correct nouns). For these patients, in addition to the noun assessments, there were two other verb naming assessments pre-therapy, also taken from the IPNP (available in Appendix E). The purpose of this was to make sure these patients had enough incorrect items for the Treated and Untreated sets, as verbs are typically more difficult to name than nouns (due to lower imageability and frequency compared to nouns) (Berndt et al., 2002; Luzzatti et al., 2002).

Therapy procedure

Participants received the three therapies over the course of a 7 week period (9 weeks including the initial naming assessments) (Fig. 4.2). Therapies were administered by three researchers (E.W., S.J. and N.D.S.) following the guidelines described in Sandars et al. (2018b)'s thesis chapter (Fig. 4.3). The order in which the therapies were administered was counterbalanced across patients in order of enlistment. The therapies were presented using Microsoft

PowerPoint slides, and participants were instructed to listen to the name of the treated word and to repeat it out loud. On the first day of each therapy, patients would be asked to name the Treated, Untreated and Correct items (Re-Baseline Condition). This was followed by the therapy session, and two more therapy sessions in the next two days. After the third session, patients would be shown the same items sets as the Re-Baseline, although in a different order, and asked to name them (Immediate Assessment). Participants would then be reassessed after 12 days on the same item sets (Follow-up Assessment). If possible, participants would start the next therapy (i.e., the next Re-Baseline and therapy session) on the same day as the Follow-up Assessment.

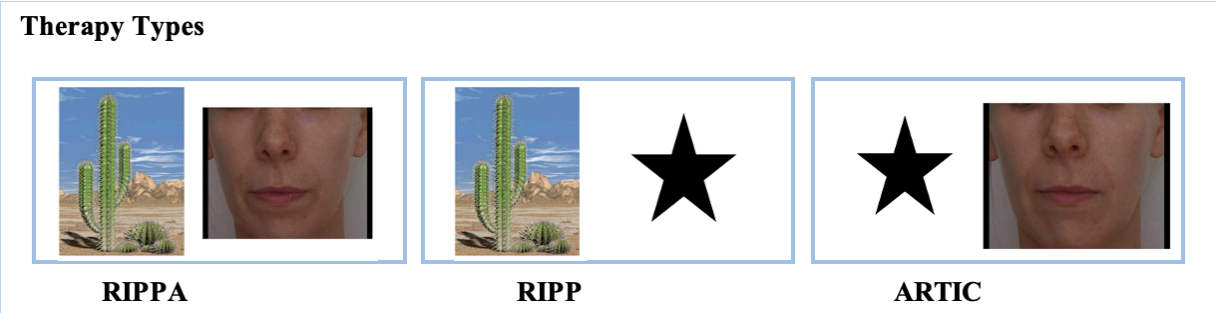


Figure 4.2 Example slides of the three therapy conditions. The left picture shows repetition in the presence of a picture and articulation (RIPPA). The middle represents repetition in the presence of a picture (RIPP). The right illustrates repetition in the presence of articulation but no picture (ARTIC).

Statistical analyses

Statistical analyses were conducted on SPSS software version 27. Paired-samples t-tests were used to compare mean changes in percentage naming accuracy (at the group-level) between baseline and post-therapy (immediate and follow-up testing) in each therapy condition. McNemar's Tests were used to determine significant change in each therapy (at the individual-level) from baseline to post-therapy. A one-way analysis of variance (ANOVA) between therapies was used to compare the differences in naming gains. In order to examine the underlying (cognitive) component structure of participants' neuropsychological abilities we

applied a varimax rotated PCA to participants' pre-therapy scores. We applied the PCA to our full patient database (n = 85), and then extracted the relevant values for the participants in this study, to increase the statistical power of our analyses. Rotated PCA was further applied to participants' post-therapy naming scores to investigate commonalities in outcomes. Spearman's rho was used to describe the strength and the direction of the relationship between participants neuropsychological abilities (both raw form and PCA-derived) and therapy outcomes.

Acquisition of neuroimaging data

High-resolution structural T1-weighted MRI scans were acquired on a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an eight-element SENSE head coil. A T1-weighted inversion recovery sequence with 3D acquisition was employed, with the following parameters: repetition time = 9.0 ms, echo time = 3.93 ms, slice thickness = 1 mm, flip angle = 8, 150 contiguous slices, acquired voxel size = 1.0 × 1.0 × 1.0 mm^3, matrix size = 256 × 256, field of view = 256 mm, inversion time = 1150 ms, SENSE acceleration factor 2.5, total scan acquisition time = 575 s.

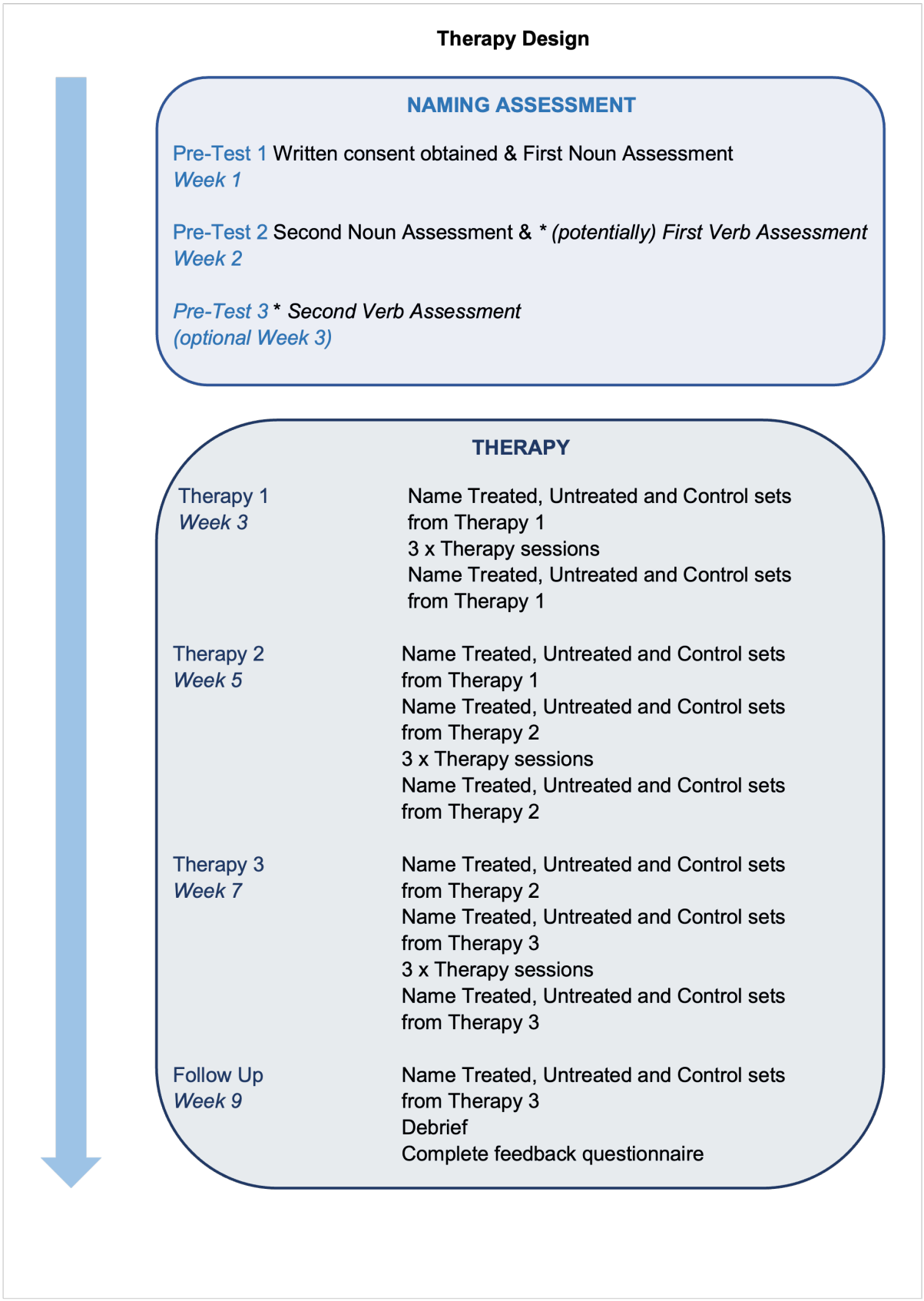


Figure 4.3 Schematic representation of the therapy design.

Analysis of neuroimaging data

Patient's structural MRI scans were pre-processed with Statistical Parametric Mapping software (SPM12, 2012) running under MATLAB 2019a. The images were first normalised into standard Montreal Neurological Institute (MNI) space using a modified unified segmentation-normalisation procedure optimised for focal lesioned brains. A healthy control group (n = 22), matched for age and education, was used to determine the extent of abnormality per voxel using an automated lesion identification procedure (Seghier et al., 2008). Neuroimaging data from the 26 patients and 22 controls were then entered into the segmentation-normalisation. Images were smoothed with an 8mm full-width at half-maximum Gaussian kernel. Patients' lesions were automatically identified using a fully automated method based on fuzzy clustering (Seghier et al., 2008). The default parameters were used aside from the lesion definition 'U-threshold', which was set to 0.5 rather than 0.3 to create a binary lesion image. The parameters were changed after comparing the results obtained from a sample of patients to what would be nominated as lesioned tissue by an expert neurologist. The T1-weighted images generated from every patient were visually inspected with respect to the original scan, and manually modified if necessary. They were used to create a lesion overlap map (Fig. 4.4A), which primarily covered the left hemisphere region supplied by the middle cerebral artery (MCA) (Phan et al., 2005). The grey (swc1T1) and white (swc2T1) matter probability maps resulting from the segmentation-normalisation algorithm were used in the subsequent neuroimaging analyses.

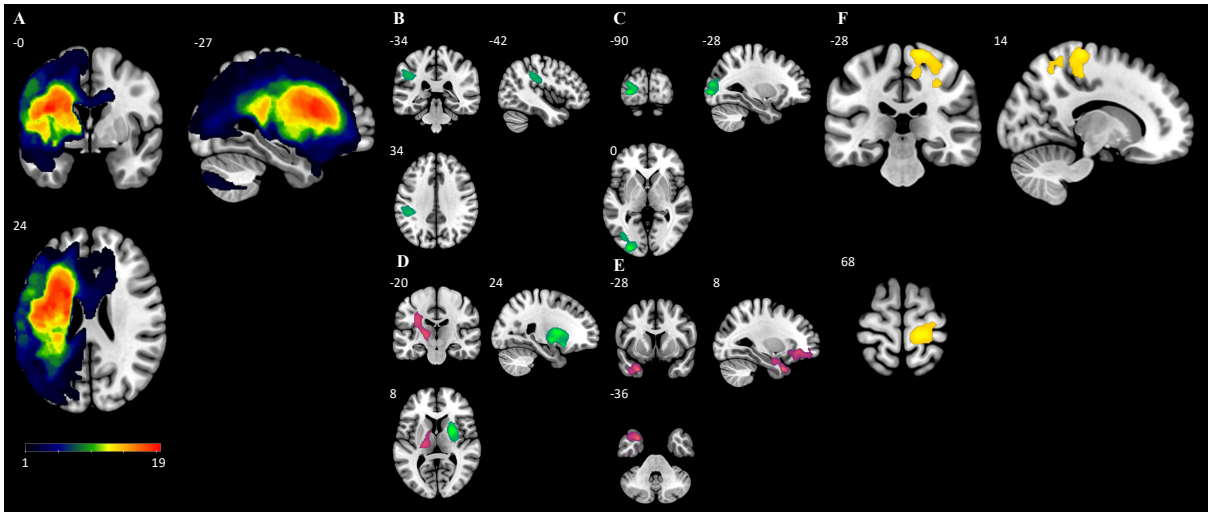


Figure 4.4 Neuroimaging results (A) Lesion overlap map from the 26 participants. Colour scale illustrates the number of participants with damage in that voxel. The regions with the highest damage in our cohort (n = 19) were the left precentral gyrus (MNI coordinates: -37 0 24) and central opercular cortex (MNI coordinates: -37 -3 22). (B) Neural cluster related to phonological component. (C) Neural cluster related to cognitive (visuospatial) component. (D) Neural cluster related to speech fluency. (E) Neural cluster related to semantics. Blue/green = cluster underlying the white matter. Magenta= cluster in the grey matter. (F) Neural cluster associated with therapeutic gains.

Voxel-based correlational methodology analyses

Voxel-based correlational methodology (VBCM, Tyler et al., 2005) analyses were used to examine the neural correlates of patients' PCA-derived behavioural abilities and PCA-derived therapeutic gains. VBCM is a variant of voxel based morphometry (Ashburner & Friston, 2000), where both the behavioural and neuroimaging data are assigned a continuous, non-binary value. We used maps of grey and white matter probabilities in our VBCM models. Three regressors of no interest were entered in the model, namely: age at the scan (in years), time post-stroke (in months) and intra-cranial volume (ICV, in mm^3). Anatomical areas were defined using labels based on the Harvard-Oxford atlas in MNI space (Desikan et al., 2006) and the Natbrainlab white matter tract atlas (Catani et al., 2012). All images were prepared using MRIcron and MRIcroGL (Rorden et al., 2007).

Results

Therapeutic gains

Group-level. The first aim of this study was to assess the naming gains, as measured by naming accuracy scores, in the three repetition-based therapies. The distribution and accuracy scores for every patient's treated items are illustrated in Fig. 4.5. Mean percentage naming accuracy increased significantly in all conditions (RIPPA: 34.04% - 66.92%, $t(25) = -10.77$, $p \leq 0.001$; RIPP: 30.19% - 63.65%, $t(25) = -9.51$, $p \leq 0.001$; ARTIC: 32.88% - 61.15%, $t(25) = -8.16$, $p \leq 0.001$). The effects were maintained at a twelve-days follow-up (RIPPA: 34.04% - 54.25%, $t(25) = -7.16$, $p \leq 0.001$; RIPP: 30.19% - 51.55%, $t(25) = -6.71$, $p \leq 0.001$; ARTIC: 32.88% - 47.88%, $t(25) = -4.87$, $p \leq 0.001$). ANOVA between therapy gains showed no significant differences in therapy types at immediate ($F(2,75) = 0.492$; $p = 0.613$) and follow-up testing ($F(2,75) = 0.852$; $p = 0.431$), compared to baseline. These results indicate that, fundamentally, all therapies were equally successful when considered at the group level. For the untreated sets there were no significant differences in naming accuracy between baseline and post-therapy, indicating that therapies did not generalise to untreated words.

Individual level. Participants responded differently for each therapy, with RIPPA being the most beneficial for: 15/26 patients, followed by RIPP: 14/26, and ARTIC: 11/26. Participants' scores for the treated words are presented in Appendix F, and McNemar results in each therapy condition are shown in Table 4.2. No participants at the individual level showed significant improvements for the untreated items.

Principal component analyses of patients' neuropsychological abilities and therapeutic gains

The second aim was to explore the relationship between patients' neuropsychological abilities, and the associated principal component factor (PCA) scores with therapeutic gains. The separate principal component analyses for the patients' Neuropsychology and Therapy scores yielded four components for the neuropsychology (accounting for 79.3% of the variance, Kaiser-Meyer-Olkin (KMO) = 0.85) that were interpreted as: (i) phonology, (ii) cognition, (iii) semantics and (iv) speech fluency (Table 4.3); and two components for the therapy scores

(accounting for 60.9% of the variance, KMO = 0.63), interpreted as: (i) treated gains and (ii) untreated gains (i.e., no therapy effect) (Table 4.4).

Relationship between patients' neuropsychological functions and treated gains

We used Spearman's rho correlations to describe the strength and direction of the relationship between patients' neuropsychological abilities and their therapeutic gains. Gains in the RIPPA were positively correlated with the delayed word and non-word repetition tests ($r = 0.444$, $p = 0.023$ and $r = 0.435$, $p = 0.026$, respectively), Camel & Cactus ($r = 0.47$, $p = 0.015$), CNT ($r = 0. .493$, $p = 0.01$), BNT ($r = 0.431$, $p = 0.028$), 96-synonyms ($r = 0.563$, $p = 0.003$), and Brixton ($r = 0.474$, $p = 0.015$). Naming improvements in the RIPP were positively correlated with the immediate and delayed word-repetition tests ($r = 0.437$, $p = 0.026$ and $r = 0.451$, $p = 0.021$, respectively) and immediate and delayed non-word-repetition tests ($r = 0.529$, $p = 0.005$ and $r = 0.468$, $p = 0.016$, respectively), written Words-to-Picture Matching ($r = 0 .418$, $p = 0.034$), CNT ($r = 0.603$, $p = 0.001$), BNT ($r = 0.544$, $p = 0.004$), 96-synonyms ($r = 0 .526$, $p = 0.006$), Spoken CAT comprehension ($r = 0.400$, $p = 0.043$), and Camel & Cactus ($r = 0.402$, $p = 0.042$). Finally, naming benefits in the ARTIC were positively correlated with CNT and BNT ($r = 0.495$, $p = 0.01$ and $r = 0.448$, $p = 0.022$, respectively) and Camel & Cactus ($r = 0.41$, $p = 0.037$). All these associations except for gains in the RIPPA and CNT disappeared when we used a Bonferroni correction of $p = 0.0024$ (correcting for 21 tests).

The PCA-derived phonology factor was positively correlated with the PCA-derived therapeutic gains factor ($r = 0.599$, $p \leq 0.001$). This result showed that, at its core, having good phonological (repetition) abilities was related to positive benefits from the therapies.

Table 4. 2

McNemar's tests for each therapy condition

Participant ID	McNemar test (p-value)		
	ARTIC	RIPP	RIPPA
11	**0.021***	0.125	**0.031***
15	0.289	**0.013***	0.18
21	**0.002****	**0.004****	**0.004****
32	**0.002****	**0.004****	**0.008****
38	0.7	0.375	**0.002****
41	0.289	1	**0.016***
42	0.289	**0.003****	0.109
45	**0.039***	0.375	**0.001****
52	0.125	**0.006****	0.375
59	0.25	1	0.125
63	**0.016***	0.07	**0.021***
66	**0.031***	**0.012***	**0.008****
69	**0.039***	**0.008****	**0.001****
71	0.125	0.219	0.219
73	1	0.219	0.453
75	0.289	0.07	0.219
78	1	1	1
81	0.125	0.453	0.687
82	**0.002****	**0.008****	**0.008****
85	**0.012***	**0.001****	**0.002****
90	0.289	0.125	**0.012***
91	0.625	**0.006****	$p = 0.375$
92	0.25	**0.039***	**0.008****
94	**0.001****	**0.008****	**0.016***
95	1	**0.031***	$p = 0.219$
96	**0.001****	**0.001****	**0.003****

* $p < 0.05$, ** $p \leq 0.01$. **Abbreviations:** ARTIC = repetition in the presence of articulation but no picture, RIPP = repetition in the presence of a picture, RIPPA = repetition in the presence of a picture and articulation.

Table 4. 3

Factor loadings from the neuropsychological battery on 85 patients

	Phonology (51.27 %)	**Cognitive (10.23 %)**	**Semantic (8.40 %)**	**Fluency (6.21 %)**
Delayed Repetition – Non-word	**0.88**	0.24	0.02	0.15
Delayed Repetition - Word	**0.87**	0.23	0.25	0.19
Immediate Repetition – Non-word	**0.85**	0.20	0.09	0.18
Immediate Repetition - Word	**0.84**	0.14	0.28	0.20
Boston Naming Test	**0.81**	0.12	0.35	0.15
Cambridge Naming Test	**0.81**	0.16	0.40	0.16
Forward Digit Span	**0.73**	0.24	0.23	0.05
Backward Digit Span	**0.59**	0.22	0.16	0.34
Spoken Sentence Comprehension - CAT	0.47	0.45	0.46	0.11
Minimal Pairs – Non-word	0.37	**0.81**	0.10	-0.04
Raven Coloured Progressive Matrices	0.09	**0.76**	0.27	0.13
Minimal Pairs – Word Spoken	0.42	**0.72**	0.25	0.10
Brixton Spatial Rule Anticipation Test	0.13	**0.67**	0.05	0.27
Word-Picture Matching	0.26	0.29	**0.79**	0.18
Type/Token Ratio	0.30	-0.05	**0.79**	-0.06
Camel and Cactus - Pictures	0.13	0.51	**0.68**	0.24
96 Synonym Judgement	0.35	0.38	**0.66**	0.32
Written Word-Picture Matching	0.21	**0.55**	**0.62**	0.16
Tokens	0.06	0.19	0.03	**0.89**
Words Per Minute	0.30	0.13	0.26	**0.83**
Mean Length of Utterances	0.33	0.08	0.11	**0.77**

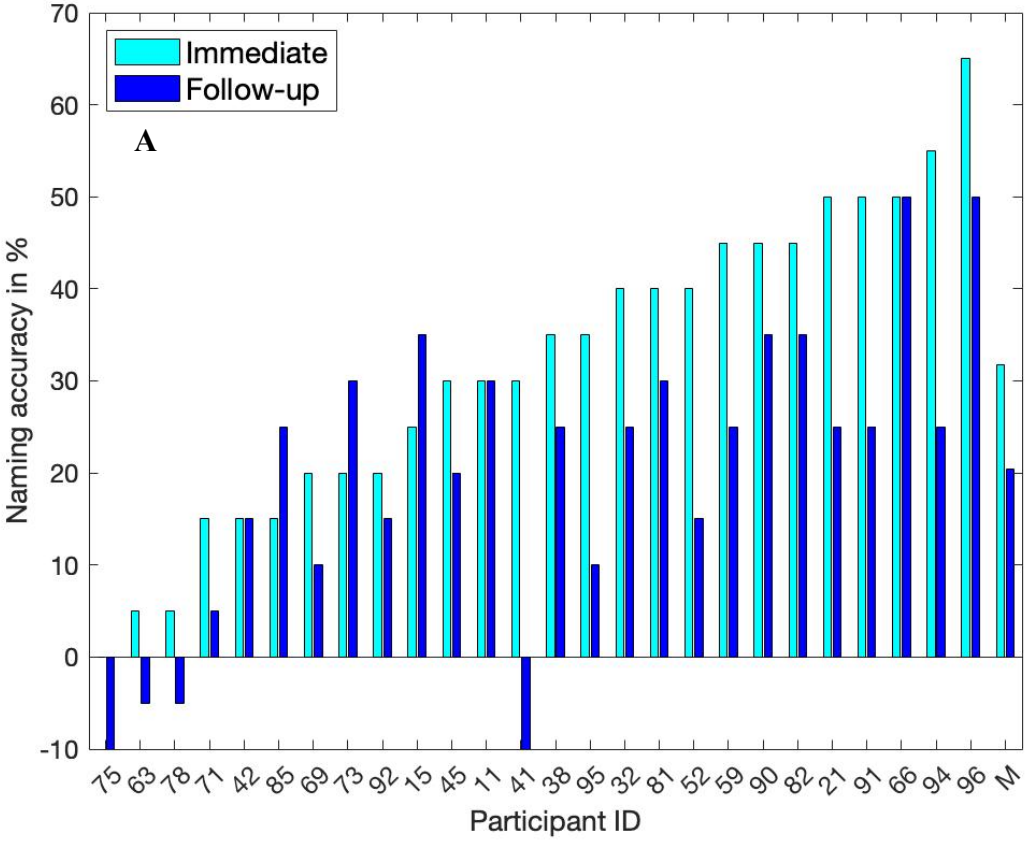
Abbreviation: CAT = comprehensive aphasia test.

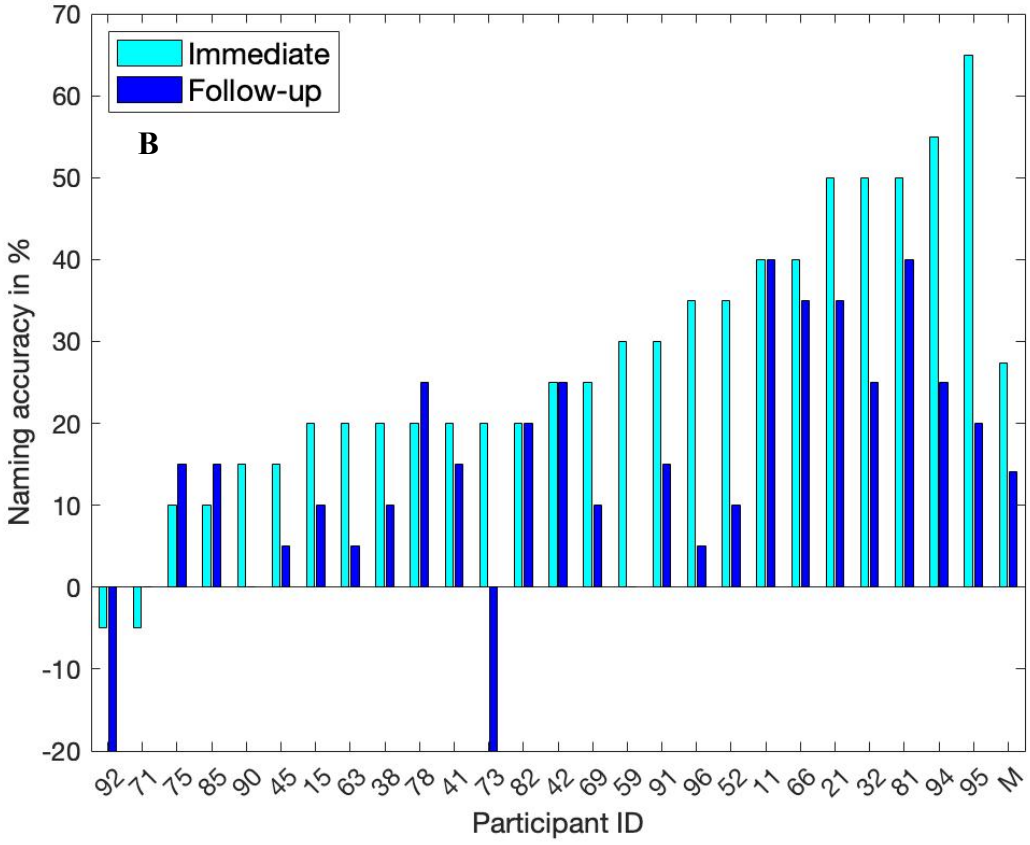
Table 4. 4

Factor loadings from the treated and untreated therapy gains

	Treated (39.44 %)	**Untreated (21.46 %)**
Total RIPP Gains	**0.856**	-0.236
Total RIPPA Gains	**0.83**	0.203
Total ARTIC Gains	**0.773**	0.349
Untreated RIPPA Gains	0.073	**-0.797**
Untreated RIPP Gains	0.154	**0.692**
Untreated ARTIC Gains	0.343	0.395

Abbreviations: ARTIC = repetition in the presence of articulation but no picture, RIPP = repetition in the presence of a picture, RIPPA = repetition in the presence of a picture and articulation.


Immediate
Follow-up
A
Naming accuracy in %
70
60
50
40
30
20
10
0
-10
75 63 78 71 42 85 69 73 92 15 45 11 41 38 95 32 81 52 59 90 82 21 91 66 94 96 M
Participant ID


Immediate
Follow-up
B
Naming accuracy in %
70
60
50
40
30
20
10
0
-10
-20
92 71 75 85 90 45 15 63 38 78 41 73 82 42 69 59 91 96 52 11 66 21 32 81 94 95 M
Participant ID

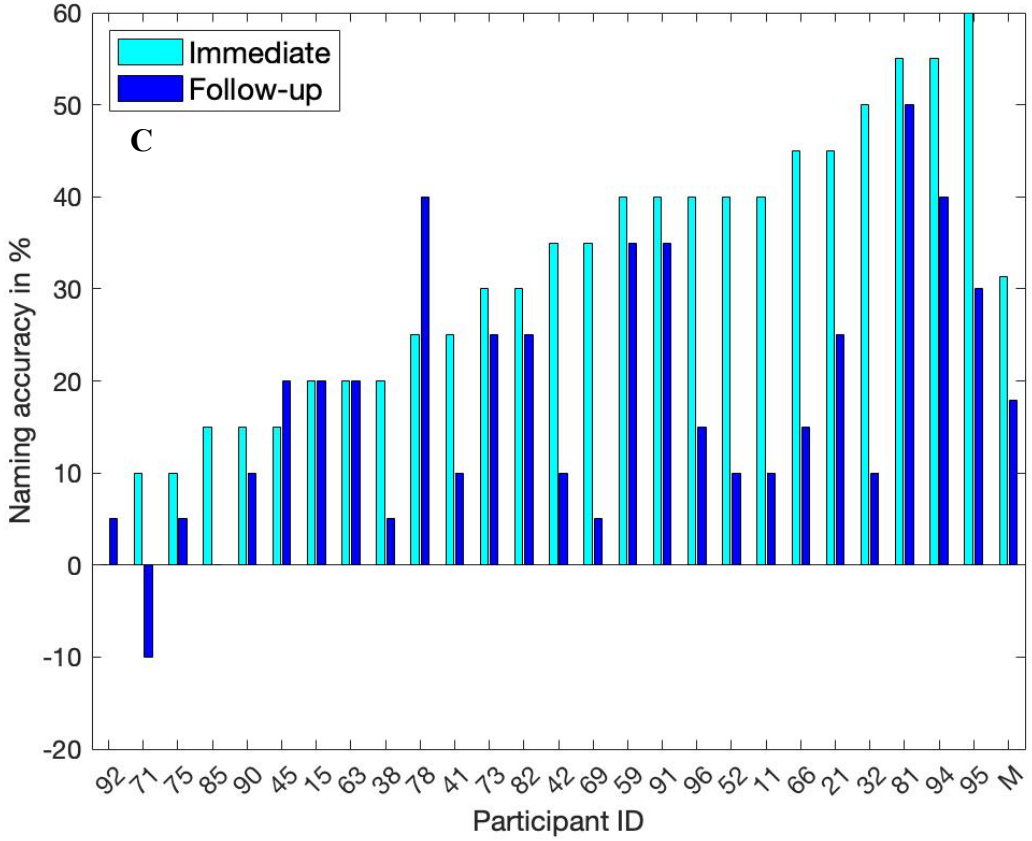


Figure 4.5 Treated gains in the therapies. Participant scores are shown from smaller to larger therapy gains (at immediate testing). **(A)** Repetition in the presence of a picture; **(B)** Repetition in the presence of articulation but no picture; **(C)** Repetition in the presence of a picture and articulation. Immediate represents the change in naming accuracy between baseline and immediate testing. Follow-up reflects the change in naming accuracy between baseline and follow-up testing. **Abbreviation:** M = mean.

Structural correlates

Another aim of this study was to map behavioural scores, that is the neuropsychological components and the therapeutic gains, to neural structures in the brain. We used grey (swc1T1) and white (swc2T1) matter probability maps in our voxel-based correlational methodology (VBCM) models (Tyler et al., 2005) so we could examine both the neural regions and their underlying connections (albeit not from formal diffusion based imaging). Age, time post-stroke and intra-cranial volume were used as additional regressors of no interest. Results were

thresholded at $p < 0.005$ voxel-level, $p < 0.05$ family-wise error (FWE) corrected cluster-level. Further details on the clusters (including peak MNI coordinates) are illustrated in Appendices G and H.

Identifying the neural correlates of the neuropsychological components. VBCM revealed four unique neural clusters associated with the PCA-derived neuropsychological components (Fig. 4.4B-E). Phonology related to the white matter underlying the left supramarginal gyrus, postcentral gyrus, central opercular cortex, and parietal operculum. This cluster included portions of the arcuate fasciculus white matter tract. Cognitive abilities related to a white matter cluster located in the left peripheral MCA region, in the lateral occipital cortex. Semantics related to a grey matter cluster extending from the left temporal pole to the frontal orbital cortex, and including the uncinate fasciculus (UF) and inferior fronto-occipital fasciculus (IFOF). Speech fluency related to the grey and white matter in the left pre- and postcentral gyri and middle frontal gyrus (MFG), and was further associated with the right insula, UF, and IFOF. The fact that some of these (cognitive-linguistic) components related to the same overlapping regions (e.g., the frontal and temporal cortices) may be a reflection of their shared neural substrates.

Mapping therapeutic gains to neural structures. VBCM models identified a neural cluster centred in the right precentral gyrus extending into the superior parietal lobule (SPL) associated with therapeutic gains (Fig. 4.5F). These regions are involved in speech articulation (the precentral gyrus, Basilakos et al., 2018) and integration or manipulation of information (the SPL, Koenigs et al., 2009), and thus seems sensible in terms of predicting naming outcomes. Interestingly, the inclusion of lesion volume to the model (as a regressor of no interest) led to the disappearance of the cluster associated with therapeutic gains. There were no significant clusters associated with untreated outcomes.

Discussion

In the present study we compared the therapeutic benefit (as determined by increased naming accuracy) of three repetition-based therapies in an attempt to replicate and extend the study of Sandars et al. (2018b). Furthermore, we investigated if patients' background neuropsychological abilities before therapy could predict therapy outcomes, and searched for

neural structures associated with naming improvements. Similarly to the work by Sandars et al. (2018b), we found that all therapies were effective. In addition, we showed that: i) the therapies were equally beneficial (regardless of input modality) and participants did not improve in the untreated items; ii) participants' initial phonological functions (and CNT) correlated with their therapeutic gains; and iii) neural structures in the right hemisphere were associated with these gains.

Overall, our results showed that patients' initial naming and phonological abilities were strongly related to their therapeutic (naming) gains. That is, to succeed in any therapy participants needed to have relatively preserved phonological or naming functions. In fact, from the participants who did not improve in any therapy (n = 7/26), the majority (n = 5/7) presented low phonological (≤ 50% in the Immediate Word Repetition) or naming (< 38.33% in the Boston Naming Test) scores. Interestingly, phonology correlated with gains even in the RIPP, which intuitively has a more marked semantic component than phonological, reflecting the importance of initial phonological abilities.

The VBCM models on the neuropsychological components identified four unique neural clusters. These clusters effectively replicated results from previous work (Butler et al., 2014; Halai et al., 2020a; Halai et al., 2017). Phonology related to a cluster that included the white matter underlying the left supramarginal gyrus, the postcentral gyrus, and the AF. These regions are well-known to be involved in phonological (Berthier et al., 2012; Deschamps et al., 2014; Forkel et al., 2020; Hartwigsen et al., 2010) and articulatory speech processes (Nakamichi et al., 2018; Skipper et al., 2017). Cognitive functions related to a white matter cluster found at the edge of the left hemisphere, in the lateral occipital cortex. This was not unsurprising as both the Brixton Spatial Rule Anticipation Test and the Raven's Coloured Progressive Matrices tap on visuospatial functions. Semantics related to a neural cluster encompassing the left temporal and frontal poles, and the connections between them. This result is in line with the plethora of evidence that has linked these regions to semantics (single-word processing) and conceptual representations (Catani et al., 2013; Jefferies, 2013; Lambon Ralph et al., 2017). Finally, speech fluency correlated with two clusters in the grey and white matter, one centred in the left precentral gyrus and MFG, areas involved in fluency and articulation (Mirman et al., 2015), and another in the right insula and UF/IFOF. Since these participants have damage to left frontal regions, then contralateral areas in the right hemisphere may become predictive of their fluency performance.

Therapeutic gains were related to the grey matter integrity of the right precentral gyrus and superior parietal lobule. This result is consistent with the literature that has associated right hemisphere regions with therapeutic improvements (mainly from intonation-based therapies, but not exclusively) (Harnish et al., 2008; Sandberg et al., 2015; Vines et al., 2011; Wan et al., 2014). In a study by Richter et al. (2008), 16 chronic participants with aphasia underwent constraint-induced aphasia therapy (CIAT) and were scanned twice (pre- and post-intervention). Therapeutic improvement, as determined by increases in a global score (calculated from subtests in the Aachen Aphasia Test (Huber et al., 1984) and Amsterdam-Nijmegen Everyday Language Test (Blomert et al., 1994)), was positively correlated with neural activation (fMRI) in right precentral gyrus and middle temporal gyrus.

Importantly, the left precentral gyrus and SPL were some of the areas damaged in our cohort (in n = 19/26 and n = 1/26, respectively) and thus they were necessarily implicated in phonological processing (and, indeed, correlated with phonological scores). The fact that therapy gains were linked to neural density in homologous right hemisphere regions suggests that these areas may support improved naming in these patients. Of course, this association might be due to weaker language lateralisation pre-stroke (Forkel et al., 2014). However, it is also possible that the additional use post-stroke of these areas in an attempt to compensate for phonological deficits led to their increased tissue density (Chen et al., 2021; Hope et al., 2017). That is, structural compensatory mechanisms in the right hemisphere might be driving naming gains in this aphasic cohort.

The inclusion of lesion volume to the VBCM model led to the disappearance of the neural cluster, indicating that the result was dependent on the lesion. This result suggests that following the lesion to the left precentral gyrus and SPL, homologouos regions in the contralateral hemisphere became more important for naming processes. This finding highlights the importance of lesion size (and site) in predicting therapeutic outcomes post-stroke.

In conclusion, integrating articulatory, phonological and semantic cues in repetition-based therapies led to naming gains in people with chronic stroke aphasia. Higher gains were associated with spared phonological and naming abilities, indicating that perhaps these therapies would benefit the most people with milder forms of aphasia. Finally, the right precentral gyrus and superior parietal lobule were related to therapeutic improvements, suggesting that the right hemisphere mediates intervention induced naming gains in chronic stroke aphasia.

Chapter 5: Beyond Accuracy: Naming Therapy Gains as Manifest in a Shift in Error Types

Abstract

Repetition-based therapies have been shown to increase naming accuracy in individuals with chronic stroke aphasia. That is, following intervention, anomic participants produce more correct responses and fewer errors. To date, however, the possibility for therapy effects to manifest in the quality and the trajectory of error remains largely unexplored. In this study we compared error-profiles pre- and post-therapy in twenty-six participants with chronic stroke aphasia (> 12 months). Specifically, we concentrated on changes in the error categories farthest from and closest to the target in terms of their phonological similarity. These were, in increasing proximity to the target: omissions (i.e., no verbal response), distant phonological (i.e., < 30% phonological overlap with the target), close phonological (i.e., > 30% phonological overlap with the target), and correct eventually (i.e., the first response was incorrect, so it was an error, but it was followed by the correct response). The naming errors were made by participants completing a sequence of repetition-based therapies, which included: repetition in the presence of a picture (RIPP), repetition in the presence of a picture and articulation (RIPPA), and repetition in the presence of articulation but no picture (ARTIC). Overall, there was a significant decrease in the number of errors following therapy (7 days), which was maintained at follow-up (12 days). Further, there was a significant decrease in the proportion of omissions and distant phonological errors from baseline to immediate and follow-up testing. Finally, there was a significany increase in the proportion of correct eventually from baseline to follow-up. These results indicate that naming errors are becoming phonologically closer to the target following therapy, which may result in higher functional communication in people with chronic aphasia. Investigating participants' errors may help us understand the mechanisms of therapeutic improvement, which has important clinical value and applications.

Introduction

It is critical to have a comprehensive understanding of anomic interventions for people with post-stroke aphasia, an acquired language disorder that affects at least one-third of left-hemisphere stroke survivors (Engelter et al., 2006). Almost universally, therapeutic effectiveness is measured in changes in accuracy, and sometimes is also associated with changes in functional communication (Palmer et al., 2019). What has rarely been explored is the possibility for changes in error types, such that therapy may induce closer approximations to the target. This current study explored the evolution of error-profiles across a sequence of three repetition-based therapies, with the goal of exploring if there would be a decrease in the proportion of errors most distant to the target, and an increase in the proportion of errors more closely related to the target.

Models of speech errors in people with aphasia can be used to describe the cognitive mechanisms supporting linguistic processes, and how disruptions to this system can lead to difficulties in word-retrieval. Dell (1986) developed a model first used to simulate word-production errors by neurotypical speakers, which was subsequently adapted for speakers with aphasia (Dell et al., 1997; Dell et al., 2013; Schwartz et al., 2012). Dell et al. (2013)'s dual-route interactive two-step model consists of 3 separate and interconnected systems, namely semantic, lexical, and phonological, that are involved in lexical-retrieval (naming) and (word and non-word) repetition (Fig 5.1). In this model, (output) phonology connects to a further component, auditory verbal output (input phonology). These systems can be visualised as nodes within a lexical-retrieval network, where the information flows between nodes bidirectionally. Semantics (*s weight*) refers to the strength of the connection between semantic and lexical nodes, phonology (*p weight*) describes the link between lexical and output phonology, and non-lexical (*nl weight*) determines the connection between output phonological and auditory input nodes. The model distinguishes two steps involved in lexical-retrieval. The first step begins with the activation of semantic features related the target. After a fixed period of time, the word with the highest level of semantic activation (from the appropriate grammatical category) is selected. Selection errors in this step are words (e.g., cat for 'dog' or cat for 'mat'), and they reflect disruption to the *s weight*. The second step in naming begins with the activation of phonemes or phonological units belonging to the target, and ends with the selection of the phonological form with the highest level of activation. Errors in this step are phonological and, thus, not necessarily words (e.g., cag for 'cat' or cap for 'cat'). Such

errors are a consequence of damage to the *p weight*. The common goal across all therapies was to strengthen the *p weight*, as they all involved repetition. Dell's model has been successfully used to simulate and predict errors cross-linguistically in individuals with aphasia (Abel et al., 2009; Hanley & Nickels, 2009; Schwartz et al., 2006; Tochadse et al., 2018). For example, Schwartz et al. (2006) successfully used the dual-route interactive two-step model to explain 94.5% of variance in naming errors made by 94 participants with stroke aphasia. A further goal of this study was to contextualise error changes from our participants using Dell's model.

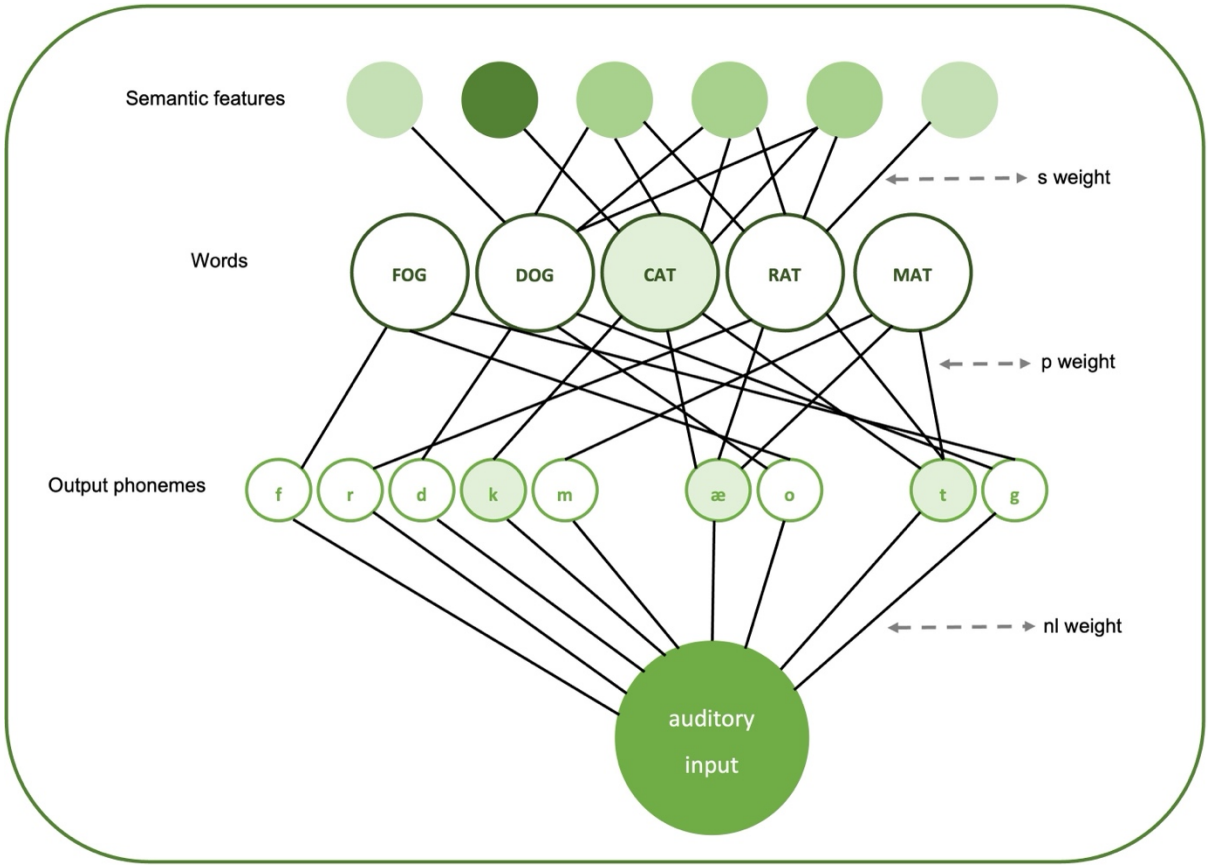


Figure 5. 1 Schematic representation of Dell's dual-route interactive two-step model. Modified from Dell et al. (2013).

To date, a few small case-series studies have considered the evolution of error patterns following speech and language therapy (Bose, 2013; Gordon, 2007; Kiran & Thompson, 2003; Ross et al., 2019). Drew and Thompson (1999) examined the effect of using a semantic

treatment, which focused on strengthening the semantic associations/features of the target word (i.e., semantic feature analysis, Ylvisaker & Szekeres, 1985), in four participants with severe naming deficits. This treatment was used alone, and in combination with orthographic and phonological (i.e., word) cues about the target. Post-semantic treatment alone (no other cues), Participant 4 showed a decrease in omissions compared to baseline, whilst Participant 2 presented an an increase in semantic errors. For the two other participants, the error changes were not significant. Following the semantic treatment with the addition of word cues, Participants 1 and 4 showed a decrease in general error profiles (i.e., non-specific responses and omissions), and an increase in the proportion of specific errors (i.e., more specific word responses but they were still inaccurate). Specifically, Participant 1 had an increase in perseverations, whereas Participant 4's errors evolved to almost all semantic. For Participant 2 the addition of word cues led to an increase in phonological errors, and for Participant 3 to a decrease in the total number of errors. Interestingly, semantic feature analysis has been found to generalise to untreated languages in bilingual aphasic speakers (Edmonds & Kiran, 2006). This was shown in four bilingual patients who produced more semantic errors (e.g., in both the trained and untrained languages) following treatment (Kiran & Roberts, 2010).

Minkina et al. (2016) considered error responses from 24 individuals with chronic stroke aphasia were compared pre- and post- phonomotor treatment. Although the results were not significant, the authors noted a general decrease in the proportion of omission responses immediately post-therapy (for the treated words) and at three-month follow-up (for the treated and untreated words). A post hoc analysis on the participants with the lowest naming accuracy showed a significant decrease in omissions at three-month follow-up for the treated words. This indicated that the most severe participants (in terms of naming abilities) were driving the reduction in omission rates. Overall, the collective findings from these studies indicated that therapies may benefit patients differently, and that errors can become more related to the target following treatment.

Non-linguistic therapy conditions have further elicited error improvements in individuals with aphasia. Hanlon et al. (1990) assessed the effect of simultaneous gesturing during a picture-naming task in 24 participants with stroke aphasia. In the non-fluent patients, gestures that targeted the activation of the proximal (shoulder) musculature of the right paralytic limb (i.e., pointing with the right arm) led to a reduction in word-production errors compared to pointing

with the left arm or making a fist with the right arm. Specifically, pointing with the right arm led to a decrease (-30%) in misarticulations and initiation errors relative to the other conditions.

There are parallels between the therapy-induced error changes observed in aphasic speakers, and the ones associated with spontaneous (untreated) recovery. As aphasic individuals recover linguistic function over time, their errors appear to "recover" as well. Kohn and Smith (1994) evaluated the spontaneous trajectory of neologistic jargon in an individual with acute aphasia who was assessed at 3 days, 6 weeks, 3 months and 5 months post-stroke. The neuropsychological evaluation included picture-naming, conversation, and picture-description tasks. At the initial assessment, the participant was severely impaired in picture-naming, and produced a high number (18/27) of omission errors and empty remarks (e.g., "I used to make them"). At the next assessment, the errors (19/30) had mainly evolved to unrelated verbal paraphasias (74%) and neologisms and phonemic paraphasias (26%). At 3 months post-stroke, the proportion of circomlocutions had significantly dropped from 74% to 24% (compared to 6 weeks) which was maintained at five months (28%). Finally, at the last assessment, there was an increase in the proportion of phonic verbal paraphasias (39%) relative to the previous assessment. These findings were replicated by Kohn et al. (1996) in two additional patients, who further showed that lack of recovery (in another two participants) was associated with extensive damage to the posterior temporal association cortex. The authors interpreted these findings as showing that this was a key region for retrieving entries in the phonological lexicon.

In this study we focused on errors from 26 chronic stroke aphasic participants completing a sequence of three repetition therapies: repetition in the presence of a picture (RIPP) (Morris et al., 2014; Nickels, 2002), repetition in the presence of a picture and articulation (RIPPA), and repetition in the presence of articulation but no picture (ARTIC) (Sandars et al., 2018b). As reported in the previous chapter, all therapies produced significant gains in accuracy across a group of 26 participants, but did not examine errors as a therapeutic outcome, and it may be clinically interesting to focus on changes in error-profiles. We classified error responses into eighteen unique categories, with the farthest category from the target being "omissions" (i.e., no verbal response) and the closest "correct eventually" (i.e., participant's first response was incorrect but it was followed by the correct answer). Intermediate to these extremes on the phonological continuum of similarity to the target were distant and close phonological errors. We would expect that therapeutic intervention should decrease the number of omission and

distant phonological errors and increase the number of close phonological and correct eventually responses.

Methods

Participants

Twenty-six stroke participants with chronic aphasia were recruited for this study (9 females and 17 males; age (mean [SD] range) = 62.42 [12.55] 39 - 86 years). This study included the same participants as Chapter 4. For additional demographic and lesion data, please refer to Table 5.1. Participants were recruited from community groups and speech and language therapy services in the North West of England. Inclusion criteria consisted of adults with normal or corrected-to-normal hearing and vision, premorbid right handedness, and English as a native language. Exclusion criteria included having suffered multiple strokes, a previous history of neurological disorders, and having any metal-implants or contraindications for MRI scanning. The Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1983) was used to determine participants' aphasic subtype.

Three patients were excluded from the final analyses due to the following reasons: second stroke (N=1); no visible lesion on MRI (N=1); and COVID-19 pandemic interruption (N=1).

This study obtained Local Research Ethics Committee approval (reference 13/NW/0844) and informed consent or proxy consent was obtained from each participant.

Table 5. 1

Participants' demographics and lesion characteristics

ID	BDAE	Age	Sex	Time post-stroke	Lesion volume	ICV
11	Anomia	52	F	76	9767	1317360
15	Mixed Non-fluent	68	M	14	8788	1514570
21	Broca	58	M	135	18392	1540649
32	Anomia	44	M	40	8437	1640831
38	Anomia	77	F	56	13577	1441204
41	Mixed Non-fluent	78	M	36	34242	1575337
42	Anomia	68	M	21	3311	1379659
45	Anomia	59	M	34	16433	1526726
52	Anomia	44	F	37	18948	1306883
59	Mixed Non-fluent	64	M	29	234000	1495940
63	Anomia	58	F	278	12699	1699168
66	Anomia	86	M	17	53064	1551295
69	Anomia	56	M	17	6974	1514073
71	Anomia	50	M	16	4538	1434622
73	Anomia	56	M	26	96600	1395693
75	Broca	70	M	83	267496	1310857
78	Mixed Non-fluent	77	F	20	48736	1161181
81	Global	78	M	17	86360	1546924
82	Anomia	58	F	21	69040	1377100
85	Anomia	70	F	14	7928	1302080
90	Broca	39	F	16	134352	1356064
91	Broca	52	M	20	157168	1586675
92	Broca	54	F	43	69312	1398938
94	Broca	71	M	24	109512	1492296
95	Anomia	55	M	39	16696	1519276

96	Wernicke	81	M	210	133048	1318175

Participants' IDs were taken from the Manchester Aphasic Stroke Sample. Time post-stroke (in months) was the time of the neuropsychological assessment. Lesion volume and intra-cranial volume are reported in mm^3. **Abbreviation:** BDAE = Boston Diagnostic Aphasia Examination, ICV = intra-cranial volume.

Neuropsychological assessment

In order to test patients' initial expressive and receptive semantic, phonological and cognitive functions they were assessed on a comprehensive neuropsychological battery, previously described by Butler et al. (2014) and Halai et al. (2017).

The battery included subtests from the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) battery (Kay et al., 1992): auditory discrimination using non-word (PALPA 1) and word minimal pairs (PALPA 2); and immediate and delayed repetition of non-words (PALPA 8) and words (PALPA 9). Tests from the 64-item Cambridge Semantic Battery (Bozeat et al., 2000) were included: spoken and written versions of the word-to-picture matching task; Camel and Cactus Test (CCT picture); and the picture naming test. To increase the sensitivity to mild naming and semantic deficits we used the Boston Naming Test (BNT) (Kaplan et al., 1983) and a written 96-trial synonym judgement test (Jefferies et al., 2009). The spoken sentence comprehension task from the Comprehensive Aphasia Test (CAT) (Swinburn et al., 2004) was used to assess sentential receptive skills. The additional cognitive tests included forward and backward digit span (Wechsler, 1987), the Brixton Spatial Rule Anticipation Task (Burgess & Shallice, 1997), and Raven's Coloured Progressive Matrices (Raven, 1962). Tasks that required patients to produce speech were recorded ("Cookie theft" picture description task), and their answers were manually transcribed and scored for number of tokens, words per minute, mean length of utterances and type/token ratio. Accuracy was measured on the basis of their first spoken response, although we transcribed their full responses. Assessments were conducted with participants over several testing sessions with the pace and number determined by the participant. Scores in the neuropsychological battery are provided in Appendix A.

Following the initial neuropsychological assessment, participants were administered three rounds of therapy each (i.e., RIPP, RIPPA, and ARTIC) with the order counterbalanced across participants. The therapy procedure was described in Chapter 4. Example slides for each

therapy condition are shown in Fig. 5.2. Post-therapy, mean percentage naming accuracy increased significantly in all conditions (RIPPA: 34.04% - 66.92%, $t(25) = -10.77$, $p \leq 0.001$; RIPP: 30.19% - 63.65%, $t(25) = -9.51$, $p \leq 0.001$; ARTIC: 32.88% - 61.15%, $t(25) = -8.16$, $p \leq 0.001$). The effects were maintained at a twelve-days follow-up (RIPPA: 34.04% - 54.25%, $t(25) = -7.16$, $p \leq 0.001$; RIPP: 30.19% - 51.55%, $t(25) = -6.71$, $p \leq 0.001$; ARTIC: 32.88% - 47.88%, $t(25) = -4.87$, $p \leq 0.001$). There were no statistically significant differences between therapy types in terms of the improvement in accuracy (as determined with a one-way ANOVA in the previous chapter). We therefore collapsed across error-types within session for treated items and untreated items separately, in order to increase power in our error based analyses.

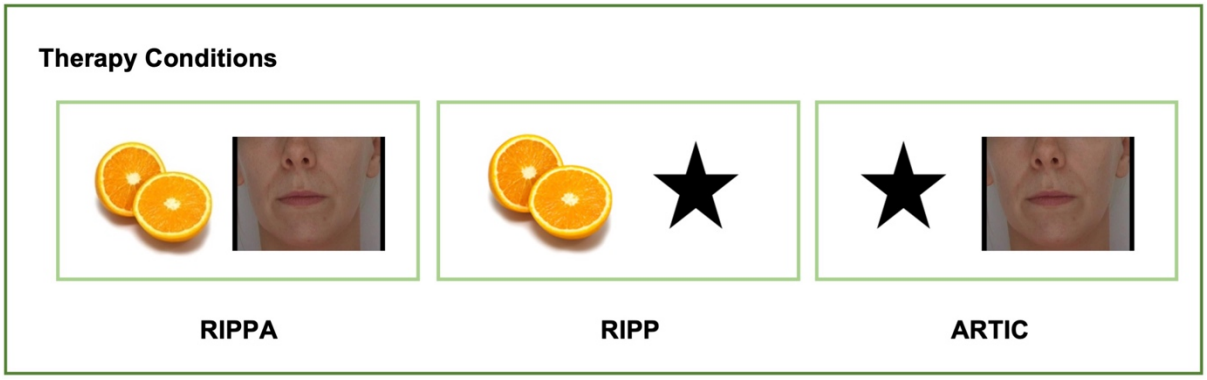


Figure 5. 2 Example slides of the three therapy conditions. The left picture shows repetition in the presence of a picture and articulation (RIPPA). The middle represents repetition in the presence of a picture (RIPP). The right illustrates repetition in the presence of articulation but no picture (ARTIC).

Error profiles and analyses

The criteria we used to code each error was modified from Halai et al. (2018). We recorded and manually transcribed the full verbal response uttered by the participant, and used his/her first response to determine the naming accuracy. Errors were classified in eighteen categories described in what follows. Some of the following errors were actual responses given by the participants, and others were created for explanatory purposes. Semantic errors were semantically-related to the target, and were either sub-ordinate (e.g., poodle for 'dog'), super-

ordinate (e.g., animal for ‘dog’) or associative (e.g., tail for ‘dog’); unrelated errors were semantically unrelated to the target (e.g., lamp post for ‘dog’); close phonological were non-words that shared a 30% phonological overlap with the target (e.g., dof for ‘dog’); distant phonological (~ neologism) were phonologically unrelated non-words (e.g., arla for ‘dog’); initial were the first phoneme or the beginning part of the target (e.g., d… for ‘dog’); disfluency were corrected repaired responses (e.g., d… do… dog for ‘dog’); formal were phonologically related (i.e., > 30 % overlap with target) words but semantically unrelated (e.g., fog for ‘dog’); mixed were phonologically and semantically related words (e.g., dog for ‘dogsled’); morphological included a grammatical error such as pluralisation (e.g., dogs for ‘dog’, scissor for ‘scissors’), or converting a noun into a verb (e.g., ‘ice creaming’ for melting, wolf for ‘to howl’); ‘not a’ correct were responses that began with ‘not a’ followed by the target (e.g., not a dog for ‘dog’); ‘not an’ incorrect were responses that began with ‘not a’ followed by an incorrect word (e.g., not a cat for ‘dog’); perseveration were repetitions of words a participant had previously uttered (e.g., a previous target); informative circomlocution were descriptions of the target (e.g., it’s furry, it’s got four legs… for ‘dog’); empty circomlocution were nonexplanatory descriptions of the target (e.g., I know what it is… over here… for ‘dog’); correct eventually were correct responses that were not uttered as a first response, so they were scored as incorrect (e.g., a pet, erm, it’s a dog for ‘dog’). Finally, any other errors that did not belong to these categories were classed as ‘other’, with the responses in this category being less than 2% of the total errors.

We then calculated the rate of each error type, averaged across all sessions and therapy types. Appendix I illustrates the error proportions for each error-category.

Statistical analyses

All statistical analyses were conducted on SPSS software version 27. Paired-samples t-tests were used to compare changes in error proportions across the phonological continuum (omissions, distant phonological, close phonological, and correct eventually). Graphs were made using Matlab version 21.b.

Results

The main aim of this study was to assess change in error categories (the phonologically farthest and closest to the target) following a set of repetition-based therapies. Changes in error-profiles (for the treated words) are shown in Fig. 5.3. There was a significant decrease in omission error proportions between baseline and immediate post-therapy (-5.45%, $t(25) = 4.2$, $p \leq 0.001$), which was maintained at follow-up (-3.97%, $t(25) = 3.35$, $p \leq 0.001$). There was a further significant reduction in distant phonological error proportions post-therapy (-2.95%, $t(25) = 2.41$, $p = 0.02$) and (marginally) at follow-up (-2.31 %, $t(25) = 1.93$, $p = 0.07$). No significant changes were observed for close phonological error proportions. Finally, there was a significant increase in the proportion of correct eventually responses that only emerged at follow-up (+1.67%, $t(25) = 0.54$, $p = 0.01$).

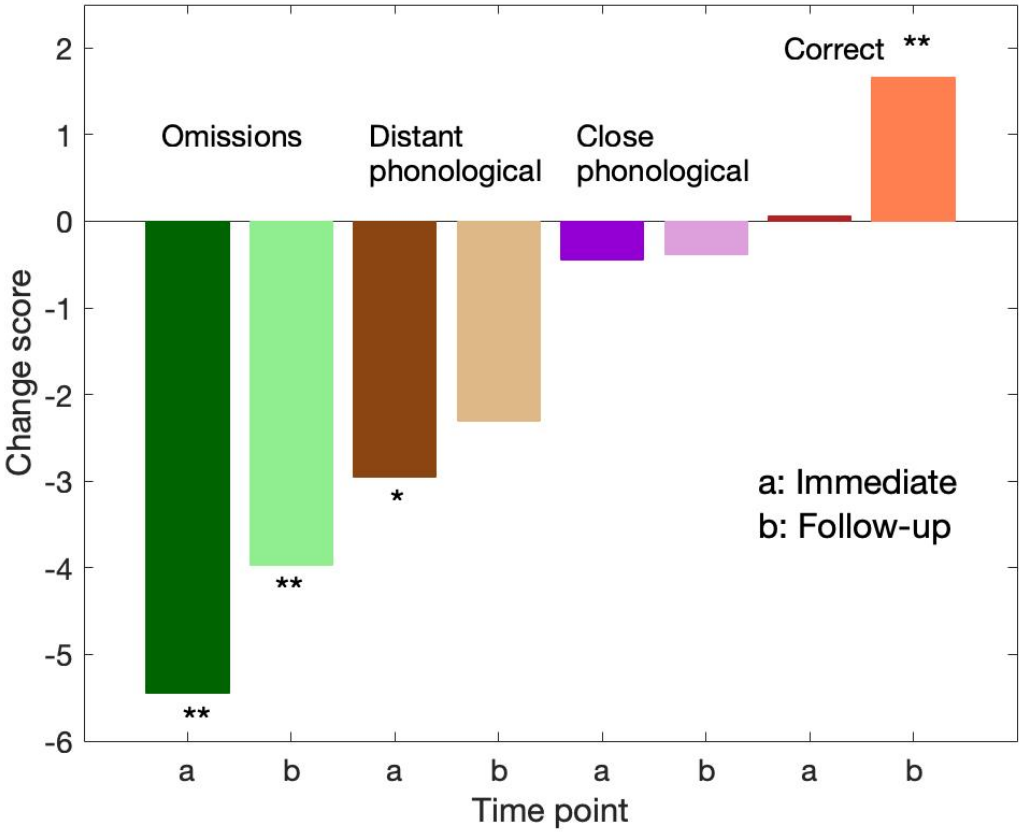


Figure 5. 3 Changes in error profiles for treated items post-therapy. Immediate represents the change in error profile between baseline and immediate testing. Follow-up reflects the change in error profile between baseline and follow-up testing. There was a significant reduction in omissions and distant phonological errors post-therapy, and a significant increase in correct eventually (at follow-up). * $p < 0.05$ and ** $p < 0.01$ compared to baseline.

Table 5. 2

Participants' treated errors in the farthest and closest phonological error-categories to the target. Data are presented in percentages

ID	Omissions			Distant Phonological			Close Phonological			Correct eventually		
	B	I	F	B	I	F	B	I	F	B	I	F
11	1.7	0.0	0.0	0.0	0.0	1.7	0.0	0.0	0.0	5.0	5.0	5.0
15	11.7	3.3	6.7	1.7	3.3	1.7	0.0	1.7	0.0	5.0	1.7	3.3
21	6.7	5.0	0.0	10.0	5.0	1.7	3.3	1.7	1.7	3.3	0.0	3.3
32	6.7	1.7	5.0	3.3	0.0	0.0	0.0	0.0	0.0	1.7	0.0	0.0
38	5.0	5.0	0.0	35.0	16.7	15.0	23.3	35.0	13.3	0.0	3.3	5.0
41	11.7	5.0	8.3	1.7	0.0	1.7	0.0	0.0	0.0	8.3	5.0	10.0
42	3.3	3.3	3.3	5.0	3.3	5.0	15.0	3.3	3.3	0.0	3.3	3.3
45	5.0	3.3	1.7	8.3	3.3	8.3	0.0	3.3	3.3	1.7	1.7	6.7
52	1.7	1.7	0.0	1.7	1.7	1.7	0.0	5.0	3.3	3.3	1.7	6.7
59	11.7	8.3	18.3	0.0	0.0	3.3	0.0	5.0	3.3	1.7	6.7	8.3
63	0.0	0.0	0.0	1.7	3.3	0.0	1.7	0.0	0.0	5.0	3.3	8.3
66	20.0	1.7	6.7	5.0	1.7	0.0	5.0	1.7	3.3	13.3	8.3	10.0
69	11.7	1.7	0.0	1.7	3.3	1.7	0.0	0.0	0.0	0.0	1.7	1.7
71	0.0	0.0	0.0	20.0	8.3	11.7	1.7	10.0	8.3	10.0	18.3	13.3
73	3.3	1.7	1.7	1.7	11.7	0.0	3.3	10.0	10.0	0.0	1.7	0.0
75	23.3	10.0	18.3	8.3	10.0	6.7	8.3	10.0	10.0	1.7	0.0	0.0
78	20.0	20.0	30.0	1.7	0.0	1.7	8.3	3.3	1.7	3.3	0.0	3.3
81	40.0	20.0	25.0	11.7	6.7	10.0	33.3	25.0	33.3	1.7	8.3	6.7
82	15.0	0.0	1.7	11.7	3.3	8.3	35.0	33.3	36.7	1.7	0.0	3.3
85	1.7	0.0	0.0	13.3	10.0	18.3	30.0	28.3	25.0	6.7	5.0	3.3
90	3.3	1.7	0.0	25.0	8.3	6.7	15.0	16.7	8.3	3.3	5.0	6.7
91	6.7	0.0	1.7	1.7	3.3	10.0	23.3	8.3	21.7	1.7	3.3	6.7
92	5.0	8.3	6.7	10.0	0.0	8.3	3.3	1.7	13.3	6.7	1.7	10.0
94	15.0	1.7	3.3	3.3	8.3	5.0	3.3	3.3	6.7	5.0	5.0	11.7
95	0.0	0.0	0.0	10.0	5.0	5.0	5.0	1.7	5.0	11.7	6.7	8.3
96	16.7	1.7	5.0	3.3	3.3	3.3	5.0	3.3	1.7	11.7	8.3	6.7

M	9.5	4.0	5.5	7.6	4.6	5.3	8.6	8.1	8.2	4.4	4.0	5.8

Participants' IDs were taken from the Manchester Aphasic Stroke Sample. **Abbreviations:** B = baseline, I = immediate, F = follow-up; M = mean.

Discussion

Although the majority of studies assessing the efficacy of speech and language anomia treatments measure naming accuracy, given that error responses vary in their proximity to the target, it is therefore valuable to examine participants' error profiles. This study significantly advanced our understanding of the evolution of error-categories post-therapy by showing a decrease in the proportion of omissions and distant phonological errors, and an increase in correct eventually. This indicates that, fundamentally, the repetition-based therapies we administered had a beneficial effect even of participants' incorrect responses, potentially enhancing their functional communication.

Regarding the reduction in omissions and distant phonological errors, this indicates that aphasic individuals made fewer severe errors post-treatment and more "smart errors" in relation to the target (Minkina et al., 2016). Depending on how close to the target the error was, this may mean that in a real-life setting people would be able to comprehend the intended name. That is, indirectly, aphasic individuals could gain higher functional communication from therapies above and beyond increases in accuracy. For instance, Falconer and Antonucci (2012) showed that following (successful) semantic feature analysis, 4 participants improved in communicative efficiency compared to baseline, as determined through increased rate of content production in discourse (+ 28, SD = 4.37) and a picture-description task (+ 26, SD = 8.21).

Overall, our findings explained in the context of Dell et al. (1997)'s model indicate that the therapies strengthened the phonological nodes (*p weight*) mapping lexical with output phonology representations. A possible explanation for the trend towards decline in close phonological errors post-therapy could be that it was a consequence of participants making more correct eventually responses.

Interestingly, participants produced a high number of semantic errors following the therapies. Both the RIPP and RIPPA include a semantic element, namely the presentation of the picture, which might have driven the increase in errors post-therapy. Furthermore, the Cambridge Naming Test predicted therapeutic gains in the RIPPA (as shown in Chapter 4), and naming difficulties in aphasia can be conceptualised as a reflection of semantic and phonological deficits (Lambon Ralph et al., 2002).

It should also be noted that there are different ways of coding errors, which can change the results and their interpretation. We chose to analyse errors along the phonological continuum since our patient cohort has a fundamental phonological impairment (as identified by the PCA in Chapter 4) and, indeed, participants' initial phonological abilities predicted their therapeutic outcomes. Our error classification was inspired by the Phonological Overlap Index (Schwartz et al., 2004), which was expanded so we could have multiple phonological error types for non-words (i.e., close and distant phonological) to measure the phonological distance from the target. Future studies would ideally conduct reliability checks for error coding and analyse change across all error types, including semantic.

In conclusion, this study investigated changes in error-profiles following a set of three repetition-based therapies. The results showed a shift in error proportions towards becoming closer, or more related to the target. Naming errors are often considered a negative outcome post-therapy; however, they can actually give us a glimpse of the mechanisms that support (induced) linguistic recovery. Future work should consider how error-changes post-therapy relate to changes in everyday functional communication.

Chapter 6: General Discussion

Overview

The overarching purpose of this thesis was to investigate linguistic change in people with chronic stroke aphasia. Longitudinal work including neuropsychological testing and neuroimaging analyses was used in four empirical chapters to assess and compare spontaneous and therapy-induced changes. A major goal of such work, as presented in Chapters 2-3, was to evaluate the potential for spontaneous systematic change, be it improvement or decline, in the chronic phase, as this field is largely unexplored. **Chapter 2** included a retrospective longitudinal study that explored the trajectory of sentence comprehension functions in chronic aphasia. Building on Chapter 2, **Chapter 3** was the first prospective longitudinal study to systematically examine neuropsychological change (using an in-depth psycholinguistic battery) in chronic participants. VBCM was further utilised in **Chapters 2-3** to map change in behavioural data to neural (grey matter and white matter) structures of patients at the time of their first assessment. In order to get a comprehensive representation of linguistic abilities in the chronic phase, the second half of the thesis focused on therapy-induced changes. The primary aim of **Chapter 4** was to identify the predictors of successful therapeutic outcome in chronic individuals who underwent a range of aphasia repetition-based treatments, an existing one (RIPP), and two novel variants (ARTIC and RIPPA). This empirical study related therapeutic outcomes to participants' pre-treatment neuropsychological scores and lesion profiles. Finally, **Chapter 5** expanded our understanding of repetition-based therapies further by targeting an often unexplored outcome in intervention studies, namely error-profiles. The aim of this chapter was to monitor the effect of therapy on errors that varied along the continuum of phonological similarity to the target (from most distant omissions to the closest correct eventually responses). This final **General Discussion Chapter** begins by briefly reviewing the findings from the empirical Chapters 2-5, and contextualising them within current knowledge of aphasia recovery. Theoretical and clinical implications from the findings will further be discussed. This chapter will end by outlining potential directions for future research.

Chapter 2 explored the evolution of spoken sentence comprehension functions in 34 people with chronic stroke aphasia. In this retrospective longitudinal study, participants were tested twice on the Spoken Sentence Comprehension test of the Comprehensive Aphasia Test (Swinburn et al., 2004) over a time interval of at least 12 months. They further underwent detailed structural MRI scanning at the time of their first assessment. Participants' normalised change per year scores were subsequently entered into VBCM models of grey matter and white matter probability maps. Behavioural results showed that a modest amount of spoken sentence comprehension change occurred between assessments (relative to the amount of change seen over the subacute phase), with some individuals continuing to improve and others actually declining. In fact, at the group-level, participants declined significantly. This result is consistent with the current (longitudinal) literature indicating that, unlike in the acute and subacute phases, 'chronic' change can be negative (Basilakos et al., 2019; Hope et al., 2017). Neuroimaging analyses revealed that behavioural decline related to a cluster centred in the left posterior superior temporal sulcus (pSTS) and gyrus (pSTG), and including the anterior temporal cortex, the planum temporale, and central opercular cortex. This finding was in line with the view that the pSTS and pSTG play a role in sentence comprehension processes (Scott et al., 2000; Scott & Johnsrude, 2003). The findings in Chapter 2 motivated the empirical study described in Chapter 3 to prospectively explore chronic linguistic change.

Chapter 3 focused on the potential for neuropsychological change and its neural correlates in a detailed psycholinguistically focused battery. Twenty-six individuals with chronic stroke aphasia were initially assessed on a complete linguistic-cognitive battery and, after 12 months, were re-assessed on 11 of its most sensitive tests (as determined by Halai et al., 2020a who used the complete battery to create a 'reduced' version, retaining the underlying sensitivity of the complete one). Normalised change per year scores from each of these tests were related to participants' lesion profiles (grey and white matter maps) from T1 imaging acquired at first assessment using VBCM. At the individual-level, some patients appeared to improve in specific tasks, whilst others declined. At the group-level, participants significantly declined in the CAT spoken sentence comprehension subtest (Swinburn et al., 2004), consistent with the results of Chapter 2, and marginally improved in the non-word repetition test (Kay et al., 1992). VBCM analyses, which are sensitive to individual performance, revealed two clusters associated with neuropsychological change. Improvement in non-word repetition related to a

cluster in the white matter underlying the right caudate and surrounding tissue. The caudate has been associated with processing cognitively complex functions (Price, 2010, 2012), which could arguably include non-word repetition. Interestingly, naming abilities (which did not change significantly at the group-level, although they did for some individuals- both improvement and decline) related to a grey matter cluster in the right temporal pole, frontal cortex, and uncinate fasciculus. This result is in line with the current knowledge on the role of anterior temporal and frontal lobes (and the connections between) in naming processes (Catani et al., 2013; Lambon Ralph et al., 2017; Patterson et al., 2007). Whilst picture naming is usually more associated with these structures in the left hemisphere, given this is damaged in our sample, it is not surprising to find that it is their right hemisphere homologues that predict performance. Although decline in spoken sentence comprehension function was significant in both studies, only Chapter 2 found significant neural correlates. This might be due to the smaller participant subset in Chapter 3 (i.e., n = 26) compared to Chapter 2 (n = 34), which reduced the statistical power of the analyses.

Chapter 4 included a study on predictors of performance in a repetition-based set of therapies. Twenty-six individuals with chronic stroke aphasia were administered three rounds of therapies each (i.e., repetition in the presence of a picture- RIPP; repetition in the presence of a picture and articulation- RIPPA; and repetition in the presence of articulation but no picture- ARTIC). All therapies led to naming gains (for the treated words) and were, essentially, equally beneficial. Phonological abilities derived from principal component analyses (PCA) on participants' pre-therapy neuropsychological scores, as well as naming (in the CBU Naming Test) correlated with gains in the therapies. Phonology is a function involved in naming (Lambon Ralph et al., 2002) which is often impaired in stroke-aphasia. Subsequent VBCM analyses revealed that the right precentral gyrus and superior parietal lobule were associated with the therapy-induced naming gains. Overall, these results suggested that participants with relatively spared phonological and naming abilities benefitted from the therapies, and that specific regions in the right hemisphere were involved in therapeutic improvements.

Chapter 5 examined outcomes in the therapies described in Chapter 4 from a different perspective, that is changes in error-profiles. Participants' errors were classified into 18

categories. We focused on four categories in this study, along the continuum of phonological similarity to the target, from the farthest (omissions) through distant and close phonological errors to those reflect an abnormally delayed correct response to the target (correct eventually). Following the therapies, there was a significant reduction in omissions and distant phonological error proportions, and an increase in correct eventually. There were no changes in error types for the untreated items. These findings indicated that participants made more 'smart' errors (Minkina et al., 2016), or closer errors in relation to the target.

Spontaneous change

Chapters 2 and 3 collectively showed that some amount of spontaneous linguistic change continued to occur in the chronic phase. Change in the subacute phase is exclusively associated with recovery, and there is often a shift in aphasia classification (from more to less severe) as reported in previous subacute-to-chronic work (Pedersen et al., 2004). In contrast, the studies reported here demonstrate that in the chronic phase it can be both positive and negative. There was variation in degree and direction of change across the individuals within the group. This indicates that language recovery in the chronic phase is more subtle than that seen during the first year post stroke. Although there was little evidence of improvement at the group level, certain individuals did improve in specific tasks. People who significantly improved (Chapter 3) included: participant 66 in naming (CNB; Bozeat et al., 2000); participant 68 in word-repetition (PALPA 9; Kay et al., 1992); and participants 32, 48 and 74 in an executive-cognitive test (Brixton; Burgess & Shallice, 1997). There are two possible (neural) explanations as to why these people recovered. The first is that premorbid anatomical differences underlaid linguistic recovery in the chronic phase. Forkel et al. (2014) showed that patients with a more symmetrically distributed (direct segment of the) arcuate fasciculus were more likely to recover than those with an extremely left-lateralised tract during the acute to subacute phase. It could be that these participants had a more bilaterally distributed language network that allowed them to utilise the spared right hemisphere for continued recovery. The other option is that structural adaptations were related to recovery. Hope et al. (2017) found that neural plasticity in 28 aphasic individuals was associated with spontaneous naming improvements (in the right ATL) and decline (in the right precentral gyrus). The fact that some of the neural findings in Chapter 3 (e.g., the right caudate) are more cognitive-general than linguistic-specific regions suggests

that plasticity occurred, although a second MRI scan would be needed to confirm this interpretation.

Regarding the linguistic decline in the chronic phase, it was much more prevalent than anticipated. At least three possible explanations for this decline exist. The first is that it reflects some form of functional diaschisis, where damage to a focal brain region disrupts the effective connectivity to anatomically distant regions, leading to further functional impairment over time (Carrera & Tononi, 2014). Functional neuroimaging work by Price et al. (2001) in four individuals with (chronic) Broca's aphasia revealed that damage to left inferior frontal gyrus was associated with abnormal activity (compared to healthy controls) in the undamaged left posterior inferior temporal lobe. Development of dementia offers a second explanation for decline, although none of the participants in Chapters 2-3 had been diagnosed with dementia, Stroke survivors are statistically more likely to suffer another stroke (or transient ischaemic stroke) (Kalaria et al., 2016). Other predictors of spontaneous decline are initial aphasia severity and leukoaraiosis (pathological white matter hyperintensity) as found in 35 participants with chronic (> 6 months) stroke aphasia (Basilakos et al., 2019). A final explanation for decline relates to patients' environment and their use (or disuse) of language. People, especially those with more severe forms of aphasia, might be discouraged from interacting or communicating linguistically, and this could lead to a even more reduction of function over time. In fact, some of the participants who declined (significantly and not) in sentence comprehension in Chapters 2 and 3 were initially diagnosed with severe forms of aphasia (i.e., Broca's or more severe) (i.e., n = 13 and n = 3, respectively).

The findings from my work and the previous neuropsychological literature indicate that there are two key variables predictive of recovery in aphasia: time post-stroke and lesion size. In the subacute phase, the left hemisphere language network has been disrupted, it cannot process language, and thus homologous right hemisphere regions are predictive of linguistic function (de Boissezon et al., 2005; Raboyeau et al., 2008). In the chronic phase, there is a reorganisation and normalisation of activity in the spared left hemisphere, which predicts (further) linguistic improvements (Saur et al., 2006). Optimal recovery years post-stroke (in chronic individuals) is associated with the engagement of neural regions in the left hemisphere that were premorbidly specialised for language. Indeed, the linguistic engagement of the right hemisphere in chronic patients (who suffered relatively "minor" lesions) is maladaptive. Importantly, the above holds true if the lesion or stroke did not disrupt the whole language

network, and there are some spared neural areas. If the lesion is so extensive that the whole left hemisphere has been disrupted, then the right hemisphere will play a role in recovery beyond the subacute phase. Recovery in these individuals (who have severe forms of aphasia subacutely) might be suboptimal compared to other patients (with smaller lesions), but it is some recovery nonetheless. Since the language network has been majorly affected, domain-general cognitive networks might start to support linguistic function (Brownsett et al., 2014; Geranmayeh et al., 2017), and may be stimulated to enhance recovery (Baker et al., 2010; Matar et al., 2022). In terms of the neuroimaging results in this thesis, in Chapter 2 spontaneous decline in sentence comprehension was positively associated with the left posterior superior temporal cortex. That is, the larger the lesion in this area was associated with greater functional decline. Conversely, in Chapter 3 marginal improvement in non-word repetition was positively associated with the right caudate. Thus, increased recovery in non-word repetition was related to higher neural density in the right hemisphere/caudate.

Although the spontaneous change studies were not therapy work, they have important clinical value and applicability. Chapters 2 and 3 showed that sentence comprehension decline in the chronic phase was associated with the left posterior superior temporal gyrus and sulcus, whilst naming decline was related to right anterior temporal and frontal cortex regions. We could use this knowledge to identify which individuals are more likely to decline on the basis of their initial brain scan, and hence direct resources to them to try to prevent this.

Therapy-induced change

Three repetition based therapies for anomia were explored in this thesis: a visual articulatory component (ARTIC therapy); a semantic component (RIPP); and a combined approach (RIPPA). Interestingly, all therapies led to an essentially equivalent significant and lasting gain for treated items, after only three therapy sessions, which is much less that that considered necessary for improvement (Brady et al., 2016; Leff et al., 2021). In addition, this was a computerised therapy that could potentially be self-administered. Both therapy format and duration needed for significant improvement indicate that these kind of therapies may be useful for chronic aphasia, particularly in the context of the limited clinical resources available (Palmer et al., 2018).

The equivalence of gains across these therapies suggests that the key ingredient was the act of repetition. It is worth of note that the participants selected for inclusion in this study were required to have a basic level of competence in immediate word repetition, and performance during the training task showed very high accuracy across the group. Consideration of the neuropsychological and therapy data using principle component analysis revealed better phonological abilities were associated with better therapy outcomes. As such, these therapies seem most suited to patients of mild to moderate severity.

In Chapter 5, there was a significant shift in errors across the phonological continuum towards becoming more related to the target. That is, there was a reduction in omission and distant phonological errors, and an increase in correct eventually responses. The repetition therapies strengthened the *p weight*, connecting lexical with output phonological nodes. A goal of future research would be to assess to what extent this increases functional communication or conversational abilities in people with aphasia. This could be assessed in multiple ways: for example, using self-rating (e.g., the 20-item Communication Outcome After Stroke (COAST) scale; Long et al., 2018), interacting with another person (e.g., the Scenario Test; van der Meulen et al., 2010) or being assessed by a speech and language therapist (e.g., with the Functional Communication Profile; Sarno, 1969).

Directions for future research

As the longitudinal behavioural studies in Chapters 2-3 employed one MRI scan, results cannot establish that the observed improvements or declines corresponded to neural change. The fact that some neural clusters were in regions not pre-morbidly specialised for language is suggestive of neural change rather than differences in pre-morbid language lateralisation. To address this, future studies should acquire two MRI scans from patients at the two different language testing time points, such that change in behaviour can be correlated with neural change, rather than initial integrity. Nevertheless, the neural correlates of change at initial testing have clinically relevant application. They can be used to build models predictive of longitudinal performance, as shown in the PLORAS system, which uses single structural MRI data to Predict Language Outcome and Recovery After Stroke (Seghier et al., 2016).

To date, there are only a handful (neuroimaging) spontaneous longitudinal studies in aphasia (Lwi et al., 2021; Saur et al., 2006; Stockert et al., 2020) and even fewer in chronic individuals (Basilakos et al., 2019; Hope et al., 2017). The fact that these chronic studies are relatively recent (< 5 years) is promising, as it suggests this research field is evolving.

A major goal of the research conducted in this thesis, and particularly the work in Chapter 3 was to collect very detailed (longitudinal) neuropsychological data. Halai et al. (2020a) showed that the neuropsychological battery I used in Chapter 3 was more sensitive to qualifying aphasic symptoms (in 75 chronic patients) than more clinically-targeted batteries such as the CAT. Yet most of the tests comprising the neuropsychological battery did not include control or longitudinal neuropsychometric data. This meant that it was difficulty to establish if any observed changes were within bounds of test re-test reliability of the measures. Nevertheless, the fact that significant recovery/decline was observed at the individual and group levels suggests that the change observed was systematic and reliable.

A further methodological limitation concerns the nature of VBCM, a correlational method that cannot be used to infer a cause-effect relation between brain and behaviour. That is, VBCM does not show whether neural change drives behavioural recovery or vice versa. In addition, univariate voxel-wise approaches might not be as sensitive to precise anatomical location (i.e., mislocalisation; Mah et al., 2014) as multivariate approaches, although the latter require larger samples (> 35/40 participants). It might be useful in future investigations to combine univariate and multivariate analyses to get a more comprehensive understanding of lesion-longitudinal change relationships.

The follow-up period in the intervention reported here was only 12 days beyond completion, and it would obviously be desirable to establish how long the observed benefits persisted. Future research involving self-administration of these therapies remotely may permit larger sample sizes and longer follow up periods. Indeed, remote therapies can provide people with chronic aphasia with affordable and effective rehabilitation and persistent therapeutic improvements (Cramer, 2019; Fleming et al., 2021; Palmer et al., 2019). For example, the trials of self-administered computerised therapies reported by Palmer et al. (2019) and Fleming et al. (2021) showed significant benefits lasting six months for 83 and 35 chronic stroke aphasic individuals, respectively. Fleming et al. (2021) also used VBM analyses on a subgroup of participants (n = 25) to show that right hemisphere white matter (pre-therapy, including temporal and frontal cortices and subcortical structures), as well as grey matter tissue intensity

in the bilateral temporal lobes (post-therapy) predicted therapeutic gains. These neural findings were consistent with the therapy results in Chapter 4 that showed an association between right hemisphere structures and therapeutic outcomes.

The right hemispheric involvement in spontaneous and therapy-induced recovery in Chapters 3 and 4 provide evidence for the 'compensatory' hypothesis (Fleming et al., 2021; Hope et al., 2017; Thulborn et al., 1999; Xing et al., 2016). This is the view that the role of the right hemisphere in linguistic processes in aphasia is beneficial, especially in individuals with large left-hemisphere lesions. In Chapter 3, a white matter cluster centred in the right caudate was associated with spontaneous improvement in non-word repetition. In Chapter 4, a grey matter cluster in the superior parietal lobule and precentral gyrus was related to induced improvement in naming. Future work could use neurostimulation to the right hemisphere in conjunction with therapy to enhance naming recovery further.

Conclusions

Chronic aphasia can have a substantial adverse effect on multiple aspects of stroke survivors' lives and on those of their loved ones. The yearly increase in stroke rates and people living with aphasia has led to significant personal and societal costs. It is therefore important to understand and predict the evolution of linguistic symptoms in aphasia, so that aphasic individuals can be supported further. Longitudinal studies are particularly valuable as they control for inter-patient variability as well as participants commencing at different time-points.

This thesis showed that an amount of spontaneous neuropsychological change continued to occur in the chronic phase. Importantly, chronic phase change was both positive and negative, with significant decline (e.g., in sentence comprehension) occurring in some people in contrast to the acute and subacute phases. Both the left and right hemispheres appeared to be implicated in change in chronic aphasia, indicating that multiple interconnected neural areas are involved. Additional longitudinal behavioural and neural data will allow us to predict performance more accurately in chronic aphasia.

Through providing a short course of repetition based therapy, this thesis demonstrated a beneficial effect in chronic individuals, both in terms of enhancing naming accuracy and

shifting error-profiles closer to the target. Moreover, variation in right hemisphere structures related to therapeutic naming gains, suggesting it had a positive role, in this study at least. Future work could explore the extent to which these therapeutic benefits apply to real-life social interactions. Overall, chronic individuals do not seem so 'chronic' after all, and neurorehabilitation can be a key tool to prevent further decline or improve linguistic abilities. Understanding aphasic symptoms longitudinally should ultimately lead to better quality of life for people with chronic stroke aphasia.

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Appendices

APPENDIX A

Participants' scores in background neuropsychological tests.

ID	MPNW	MPW	Rep NW-I	Rep NW-D	Rep W-I	Rep W-D	WPM -S	WPM -W	CNB	BNT	CC	Syn	CAT	Ravens	Brixton	DigitF	DigitB	WpM	TTR	MLU	TOK
9	80.56	93.06	60	10	73.75	68.75	98.44	98.44	75.00	71.67	98.44	95.83	56.25	91.67	50.91	37.5	0	32.57	0.74	6.86	38
11	91.67	100	90	90	100	98.75	100	100	93.75	88.33	79.69	93.75	84.38	91.67	60	87.5	85.71	211.76	0.75	11.83	60
15	93.06	94.44	86.67	80	100	96.25	98.44	93.75	95.31	66.67	73.44	83.33	78.13	66.67	67.27	62.5	57.14	50.67	0.68	8.17	38
21	100	98.61	73.33	83.33	77.5	87.5	100	100	87.5	78.33	75	89.58	87.5	75	56.36	100	100	18	0.7	7.40	30
31	22.22	52.78	0	0	37.5	0	57.81	31.25	0	0	53.13	48.96	12.5	30.56	38.18	25	0	87.27	0.47	8.20	32
32	98.61	97.22	100	90	100	100	100	100	89.06	55	90.63	90.63	87.5	97.22	69.09	50	57.14	56.00	0.66	14.8	56
34	98.61	98.61	26.67	16.67	50	61.25	96.88	93.75	46.88	38.33	59.38	57.29	12.5	38.89	58.18	37.5	28.57	7.42	0.18	3.18	33
36	90.28	95.83	53.33	10.00	93.75	41.25	100	96.88	87.50	50	92.19	78.13	62.5	88.89	43.64	37.5	28.57	49.47	0.72	10	47
37	91.67	97.22	0	0	0	0	100	98.44	4.69	0	82.81	78.13	75	88.89	76.36	37.5	42.86	105.54	0.48	19	146
38	95.83	93.06	23.33	13.33	57.5	55	96.88	98.44	53.13	50	85.94	82.29	68.75	63.89	30.91	75	42.86	25.42	0.60	4	25
40	75	93.06	50	46.67	90	88.75	100	100	89.06	43.33	95.31	96.88	81.25	100	65.45	50	57.14	106.18	0.47	19.63	315
41	95.83	93.06	23.33	6.67	43.75	35	100	96.88	39.06	10	73.44	65.63	34.38	86.11	60	75	42.86	5.16	0.91	1.4	11
42	95.83	95.83	83.33	70	96.25	96.25	100	100	84.38	61.67	84.38	79.17	78.13	77.78	65.45	87.5	42.86	92.50	0.73	13	74
44	88.89	86.11	10	3.33	51.25	42.5	98.44	100	54.69	23.33	92.19	82.29	56.25	88.89	43.64	25	28.57	29.52	0.68	6.83	31
45	98.61	95.83	43.33	46.67	95	95	98.44	100	71.88	56.67	93.75	89.58	78.13	97.22	78.18	37.5	28.57	56.40	0.52	11.89	94
46	81.94	77.78	0	0	1.25	0	78.13	93.75	0	0	67.19	75	46.88	91.67	91.67	25	0	0	0	0	0
47	80.56	87.50	26.67	13.33	86.25	63.75	95.31	98.44	76.56	41.67	79.69	75	75	88.89	88.89	37.5	28.57	56.31	0.52	16.56	122
48	79.17	80.56	0	0	38.75	23.75	100	100	34.38	15	92.19	89.58	71.88	97.22	80	37.5	0	27.47	0.55	3.15	38
49	86.11	81.94	33.33	16.67	65	66.25	96.88	98.44	65.63	38.33	81.25	85.42	90.63	88.89	61.82	87.5	28.57	17.14	0.83	8	18

52	95.83	97.22	60	40	92.5	88.75	100	100	84.38	60	90.63	87.5	84.38	91.67	76.36	50	28.57	23.75	0.61	6.83	38
53	80.56	94.44	56.67	43.33	85	91.25	100	100	60.94	38.33	84.38	83.33	87.5	80.56	50.91	75	0	19.74	0.64	4.71	25
54	73.61	84.72	0	0	0	0	100	95.31	4.69	5	78.13	73.96	56.25	50	34.55	25	0	15.33	0.39	5.22	46
58	98.61	98.61	86.67	80	100	100	98.44	98.44	93.75	88.33	84.38	86.46	90.63	94.44	70.91	62.5	57.14	69.47	0.91	10.33	22
59	97.22	86.11	53.33	20	88.75	38.75	62.5	92.19	14.06	3.33	65.63	46.88	46.88	83.33	65.45	37.5	0	32.83	0.29	5.17	58
63	81.94	91.67	60	56.67	95.00	93.75	98.44	98.44	84.38	76.67	82.81	88.54	81.25	83.33	63.64	62.5	0	37.30	0.87	4.67	23
64	93.06	98.61	0	3.33	13.75	7.5	100	98.44	6.25	5	89.06	69.79	59.38	80.56	74.55	20	28.57	110.00	0.65	9.29	55
65	84.72	86.11	0	0	0	0	59.38	65.63	0	0	62.5	52.08	34.38	88.89	52.73	0	0	0	0	0	0
66	79.17	76.39	30	10	76.25	71.25	98.44	98.44	54.69	55	75	94.79	75	52.78	70.91	62.5	42.86	97.60	0.57	17	122
67	91.67	93.06	10	13.33	65	55	92.19	98.44	59.38	51.67	65.63	69.79	62.5	47.22	30.91	25	28.57	19.66	0.63	3.29	19
68	95.83	95.83	3.33	3.33	21.25	5	96.88	96.88	3.13	1.67	89.06	89.58	62.5	83.33	61.82	25	28.57	94.42	0.51	19	203
69	86.11	93.06	80	46.67	91.25	98.75	95.31	96.88	87.50	78.33	92.19	95.83	93.75	83.33	69.09	50	42.86	47.67	0.55	16.75	116
70	87.5	91.67	46.67	30	71.25	67.5	100	100	78.13	55	87.5	87.5	84.38	91.67	70.91	62.5	42.86	55.20	0.59	11.57	69
73	95.83	94.44	96.66	43.33	98.75	95	100	100	90.62	85	95.31	80.2	62.5	80.55	69.09	62.5	42.86	74.00	0.46	6.69	74
71	87.50	97.22	50.00	36.67	85	90	100	100	78.13	76.67	92.19	95.83	100	94.44	74.55	62.5	42.86	49.47	0.51	13.63	94
74	75.00	70.83	0	0	0	0	53.12	90.62	0	0	71.88	69.8	43.75	66.67	46.64	0	0	0	0	0	0
75	45.83	55.55	6.66	6.66	50	28.75	84.37	92.18	48.44	23.33	40.62	69.79	43.75	55.56	49.49	25	28.57	46.59	0.53	11.71	73
78	56.94	61.11	36.25	0	36.25	0	89.06	28.12	10.93	3.33	70.31	0	78.12	47.22	41.81	0	0	38.5	0.53	8.2	77
81	59.72	52.78	10.00	0	36.25	0	78.12	65.62	35.93	11.67	60.93	42.7	34.37	33.33	52.72	12.5	0	14.00	0.64	4.67	14
82	95.83	95.83	66.67	70	93.75	93.75	100	100	93.75	75	87.5	80.2	87.5	88.89	80	75	42.86	40.93	0.49	11	79
85	73.61	83.33	70	60	85	65	76.56	95.31	85.93	56.67	79.68	83.33	43.75	83.33	76.36	50	28.57	89.61	0.56	10.73	115
90	94.44	94.44	10	13.33	65	68.75	93.75	98.44	40.63	38.33	87.5	83.33	75	94.44	78.18	25	0	23.41	0.83	8.67	23
91	84.72	93.05	23.33	23.33	65	50	98.43	100	52	35	87.5	80.21	93.75	90.77	47.27	37.5	0	23.87	0.63	5.14	32
92	80.55	94.44	17	6.66	65	58.75	93.75	93.75	42	33.33	75	71.88	93.75	88.88	67.27	37.5	0	30.45	0.84	6.6	25
94	93.05	90.27	63.33	60	83.75	82.5	92.19	93.75	50	36.66	73.44	75	78.13	80.55	61.82	50	0	70.38	0.46	11.57	61
95	83.33	83.33	95.83	3.33	85	62.5	98.44	98.44	67.19	58.33	90	85.42	87.5	91.66	74.55	0	0	42.29	0.7	12.75	43

96	72.22	80.56	46.67	13.33	78.75	72.5	93.75	100	73.44	53.33	79.69	67.71	37.50	88.89	9.09	0	0	67.4	0.7	50.67	118

Scores are given as %. **Abbreviations:** MP = minimal pairs NW = non-words, W = words, Rep = repetition, I = immediate, D = delayed (Psycholinguistic Assessments of Language Processing in Aphasia; Kay et al., 1992); WPM = word-to-picture matching, S = spoken, W = written, CNB = Cambridge naming Battery (Bozeat et al., 2000); BNT = Boston Naming Test (Kaplan et al., 1983); CC = camel & cactus, Syn = 96-trial synonym judgment test (Jefferies, et al., 2009); CAT = spoken sentence comprehension subtest from the Comprehensive Aphasia Test (Swinburn et al., 2004); R = Ravens (Raven, 1962); B = Brixton (Burgess & Shallice, 1997); DigitF = digit forward; B = backward (Wechsler, 1987); WpM = words-per-minute, TOK = number of tokens, TTR = type-to-token ration, MLU = mean length of utterance in morphemes.

APPENDIX B

Participants' behavioural scores at the two time points, time interval between assessments and the change per year scores used in the VBCM analyses.

Participant ID	Score 1 (%)	Score 2 (%)	Time interval (days)	SCPY (%)
9	56.25	46.87	2194	-1.56
11	84.38	87.5	2089	0.55
15	78.13	71.87	2115	-1.08
21	87.5	87.5	2064	0
31	12.5	21.87	2192	1.56
32	87.5	93.37	979	2.19
34	12.5	31.25	1020	6.71
36	62.5	71.87	999	3.42
37	75	84.37	1066	3.21
38	68.75	71.87	1072	1.06
40	81.25	62.5	1056	-6.48
41	34.375	43.75	1071	3.2
42	78.125	84.37	1052	2.17
44	56.25	50	1099	-2.08
45	78.125	62.5	1079	-5.29
46	46.875	37.5	949	-3.61
47	75	62.5	872	-5.23
48	71.875	53.12	1135	**-6.03 ***
49	90.625	56.25	1163	**-10.79 ****
52	84.375	78.12	755	-3.02
53	87.5	84.37	835	-1.37
54	56.25	50	671	-3.4
58	90.625	93.75	809	1.41
59	46.875	53.12	686	3.32
63	81.25	62.5	757	-9.04
64	59.375	59.375	610	0
65	34.375	34.375	683	0

66	75	46.87	596	**-17.23** **
67	62.5	50	666	-6.85
68	62.5	53.12	434	-7.89
69	93.75	93.75	456	0
70	84.375	87.5	371	3.55
71	100	100	420	0
74	43.75	34.37	414	-8.27

Abbreviation: SCPY = sentence comprehension change per year. To calculate the SCPY, we substracted the raw score at time 1 from time 2, and divided this change by the number of years (with years determined as number of days divided by 365). * $p < 0.05$ ** $p < 0.01$ compared to baseline.

APPENDIX C

Participants' scores in the neuropsychological battery at the two time points.

ID	Rep NW-I T1	Rep NW-I T2	Rep W-I T1	Rep W-I T2	CNB T1	CNB T2	BNT T1	BNT T2	Syn T1	Syn T2	CAT T1	CAT T2	Ravens T1	Ravens T2	Brixton T1	Brixton T2
11	90	80	100	96.25	92.19	84.38	85	**61.67**	93.75	90.63	84.38	78.13	91.67	80.56	60	60
15	86.67	80	100	**90**	95.31	**70.31**	66.67	55	83.33	85.42	78.13	75	66.67	**47.22**	67.27	74.55
21	93.33	**66.67**	77.5	77.5	85.94	71.88	78.33	**61.67**	89.58	88.54	87.5	93.75	75	75	56.36	58.18
31	0	13.33	37.5	**21.25**	0	0	0	0	48.96	48.96	12.5	28.13	30.56	30.56	38.18	**14.55**
32	100	96.67	100	98.75	85.94	89.06	53.33	58.33	90.63	91.67	87.5	84.38	97.22	97.22	69.09	**80**
36	53.33	76.67	93.75	90	76.56	85.94	46.67	46.67	78.13	78.13	62.5	68.75	88.89	83.33	41.82	47.27
38	23.33	36.67	57.5	57.5	37.5	29.69	18.33	23.33	83.33	83.33	68.75	78.13	63.89	58.33	30.91	36.36
41	23.33	**3.33**	43.75	28.75	39.06	**20.31**	10	11.67	65.63	70.83	34.38	43.75	86.11	86.11	60	70.91
42	83.33	86.67	96.25	87.5	76.56	87.5	55	48.33	79.17	77.08	78.13	78.13	69.44	80.56	65.45	54.55
44	10	10	51.25	38.75	50	40.63	21.67	16.67	82.29	83.33	56.25	46.88	88.89	91.67	43.64	49.09
45	60	**40**	95	85	62.5	60.94	55	**31.67**	89.58	92.71	71.88	65.63	97.22	97.22	78.18	**54.55**
47	26.67	30	77.5	72.5	53.13	57.81	28.33	35	75	75	75	62.5	88.89	94.44	65.45	65.45
48	0	13.33	38.75	36.25	34.38	29.69	13.33	10	89.58	87.5	71.88	**53.12**	97.22	91.67	80	**90.91**
52	60	73.33	92.5	86.25	79.69	82.81	56.67	61.67	87.5	87.5	84.38	81.25	91.67	97.22	76.36	74.55
54	0	0	0	2.5	3.13	6.25	0	6.67	73.96	65.63	56.25	46.88	50	50	34.55	36.36
58	86.67	100	100	98.75	93.75	96.88	85	85	86.46	90.63	90.63	93.75	91.67	91.67	70.91	58.18
63	60	73.33	95	92.5	84.38	89.06	70	75	88.54	84.38	81.25	84.38	83.33	88.89	63.64	78.18
64	0	6.67	13.75	25	6.25	6.25	5	1.67	69.79	68.75	59.38	62.5	80.56	77.78	74.55	69.09

65	0	0	0	0	0	0	0	0	52.08	53.13	65.63	65.63	91.67	83.33	52.73	**14.55**
66	30.00	33.33	76.25	83.75	57.81	**75**	45	51.67	94.79	90.63	75	**46.87**	50	46.11	70.91	63.64
68	6.67	3.33	21.25	**41.25**	4.69	10.94	1.67	3.33	89.58	96.88	34.38	43.75	69.44	77.78	61.82	72.73
69	80	73.33	98.75	96.25	81.25	81.25	71.67	68.33	95.83	98.96	81.25	81.25	86.11	97.22	72.73	76.36
70	46.67	63.33	73.75	70	79.69	71.88	51.67	46.67	87.5	90.63	84.38	84.38	86.11	86.11	70.91	65.45
71	50	43.33	85	86.25	78.13	87.50	76.67	75	95.83	94.79	100	93.75	94.44	88.89	74.55	63.64
74	0	0	0	0	0	0	0	0	69.79	60.42	43.75	43.75	83.33	88.89	43.64	**63.64**
82	66.67	73.33	88.75	92.5	81.25	84.38	75	81.67	80.21	90.63	87.5	78.13	88.89	77.78	80	70.91

Abbreviations: Rep = repetition, NW = non-words, W = words, I = immediate (Psycholinguistic Assessments of Language Processing in Aphasia; Kay et al., 1992); WPM = word-to-picture matching, S = spoken, CNB = Cambridge naming battery (Bozeat et al., 2000); BNT = Boston Naming Test (Kaplan et al., 1983); Syn = 96-trial synonym judgment test (Jefferies, et al., 2009); CAT = spoken sentence comprehension subtest from the Comprehensive Aphasia Test (Swinburn et al., 2004); R = Ravens (Raven, 1962); B = Brixton (Burgess & Shallice, 1997). Scores are reported in percentages. Significant change ($p < 0.05$) is given in bold.

APPENDIX D

Words in the 408-item (noun) 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	tire	asparagus	wolf
heart	box	slide	bomb
ax	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 E

Words in the 255-item (verb) picture naming assessment

Stimuli				
drink	erupt	massage	saw	swing
ski	shock	measure	reach	save
cut	follow	drill	punish	serve
blow	buckle	meditate	scoop	teach
argue	scare	melt	scratch	tear
wake up	bury	milk	carve	peck
win	deliver	conduct	sell	spill
bake	swim	miss	howl	think
sniff	glue	smile	pinch	fix
boil	shake	mix	sew	throw
shout	cook	mop	shampoo	propose
carry	grind	cry	open	tie
climb	salute	oil	shave	frost
slam	hammer	feed	shear	strain
comb	brush	parachute	sleep	tow
cook	cheer	peel	dance	trip
cough	bounce	wag	shoot	shine
crash	carve	pet	sing	type
camp	arrest	fold	sink	operate
crawl	hang	slide	sit	vacuum
curtsey	polish	pick	skate	wade
cry	hatch	plant	cut	wait
decorate	drive	kiss	slip	walk
tornado	hit	break	smell	wash
dig	drip	play	smoke	watch
bark	hug	plough	lassoo	water
dip	iron	plug	sneeze	wave
break	jump	hitchhike	snow	weigh

drown	catch	wrap	somersault	whisper
dust	buy	pop	point	yawn
eat	kick	drag	sort	win
dump	kneel	pray	sow	wink
erase	burn	pull	run	spread
stretch	hunt	hide	spit	twist
float	knight	listen	splash	squeeze
explode	knit	push	rain	write
box	fence	raise	roar	paint
scared	make	balance	spray	swat
fall	juggle	rake	stack	shout
fight	clap	read	stand	tickle
file	relax	give	steal	load
fill	celebrate	lift	sting	zip
fish	talk	knock	stir	beg
bow	unlock	marry	relax	whistle
dive	laugh	dry	suck	sweep
run	cross	sort	bowl	shower
mine	mail	wish	sunbathe	light
shake	bite	chew	surf	
count	march	ride	look	
golf	chase	row	roast	
fly	curl	magnify	sweat	
pour	lick	sail	sharpen	

APPENDIX F

Participants' naming accuracy for treated words in the therapy conditions.

Participant ID	ARTIC			RIPP			RIPPA		
	B	I	F	B	I	F	B	I	F
11	50	**90** *	**90** *	55	80	**90** *	65	**95** *	90
15	55	75	65	30	**80** *	55	50	75	**90** **
21	20	**70** **	**55** *	35	**80** **	**70** *	35	**80** **	60
32	45	**95** **	70	50	**95** **	75	55	**95** **	**90** *
38	15	45	30	5	20	20	15	**65** **	25
41	15	35	25	25	25	15	10	**45** **	20
42	25	45	40	30	**85** **	55	40	70	65
45	25	**60** *	30	40	55	65	30	**90** **	60
52	60	85	85	30	**80** **	**80** **	70	85	80
59	5	20	10	20	25	15	5	30	15
63	30	**65** *	40	35	65	**65** *	30	**70** *	45
66	50	**80** *	50	35	**80** *	**70** *	40	**80** **	50
69	35	**75** *	70	50	**90** **	75	45	**100****	**95** **
71	70	95	80	70	90	85	75	95	95
73	70	65	70	45	65	75	55	70	55
75	30	50	10	15	45	5	30	50	50
78	0	10	15	10	15	5	5	5	10
81	10	80	35	20	35	25	30	40	35
82	45	**95** **	**85** **	60	**100****	90	55	**95** **	90
85	30	**75** *	**60** *	15	**80** **	**50** *	20	**70** **	**70** **
90	30	50	50	15	**50** *	40	20	**65** *	35
91	35	45	50	20	**70** **	45	35	50	55
92	10	25	10	15	**50** *	25	10	**50** **	20
94	20	**85** **	40	15	**55** **	30	15	**50** *	20
95	50	45	30	40	**70** *	60	35	55	40
96	25	**80** **	**50** *	5	**70** **	55	10	**65** **	**50** **

Mean	32.88	63.08	47.88	30.19	63.65	51.54	34.04	66.92	54.23

Accuracy scores are reported in percentage. * $p < 0.05$, ** $p < 0.01$ compared to baseline. **Abbreviations:** B = baseline, I = immediate testing, F = follow-up testing, ARTIC = repetition in the presence of articulation, RIPP = repetition in the presence of a picture, RIPPA = repetition in the presence of a picture and articulation.

APPENDIX G

Peaks within the neural clusters associated with the neuropsychological components

Covariate	Image type	Anatomy	Extent (voxels)	Z	MNI coordinates		
					x	y	z
Phonology	swc1T1	/					
	swc2T1	Supramarginal anterior L	634	3.17	-42	-34	34
		Parietal operculum L		3.04	-46	-24	24
		Supramarginal anterior L		2.75	-60	-24	28
Cognition	swc1T1	/					
	swc2T1	Lateral occipital inferior L	841	4.24	-28	-90	0
		Lateral occipital superior L		3.73	-26	-86	10
		Intracalcarine L		3.7	-18	-84	8
Semantics	swc1T1	Temporal pole L	592	4.02	-28	8	-36
		Temporal pole L		3.56	-38	4	-42
		Parahippocampal L		3.38	-28	-6	-24
		Frontal orbital L	626	3.69	-26	32	-8
		Frontal pole L		3.67	-24	40	-14
		Frontal pole L		3.47	-32	52	-12
	swc2T1	/					
Fluency	swc1T1		1422	4.23	24	2	8
				4.06	28	-4	-4
		Insular R		3.63	26	12	-12
		Precentral L	1384	3.73	-64	0	16
		Postcentral L		3.71	-56	-8	16
		Middle frontal L		3.56	-38	2	54
		Superior frontal L	654	3.62	-6	20	58
		Superior frontal R		3.42	6	20	58
		Paracingulate L		3.29	-6	24	36
	swc2T1		878	3.31	-32	-24	20

	Cortico-spinal L	3.28	-18	-18	6
	Cortico-spinal L	2.77	-12	-2	4

Abbreviations: swc1T1 = smoothed warped (normalised) corrected grey matter (derived from T1), swc2T1 = smoothed warped (normalised) corrected white matter (derived from T1).

APPENDIX H

Peaks within the neural clusters associated with the therapy gains component

Covariate	Image type	Anatomy	Extent (voxels)	Z	MNI coordinates		
					x	y	z
Gains	swc1T1	Precentral R	1004	3.93	14	-28	68
		Precentral R		3.5	14	-30	56
		Superior Parietal R		3.45	28	-50	60

Abbreviations: swc1T1 = smoothed warped (normalised) corrected grey matter (derived from T1), swc2T1 = smoothed warped (normalised) corrected white matter (derived from T1).

APPENDIX I

Total treated errors in the three therapy conditions

Error category	ARTIC			RIPP			RIPPA			Total
	B	I	F	B	I	F	B	I	F	
'Not a' correct	0	0	0	0	0	0	0	0	0	0
Perseveration	2	1	3	0	1	3	0	0	1	11
'Not a' incorrect	1	2	0	4	0	2	2	0	2	13
Visual	3	0	1	2	2	2	2	0	1	13
Other	3	0	2	1	1	2	6	3	1	19
Mixed	5	1	4	4	2	1	9	2	7	35
Disfluency	8	5	4	2	5	5	4	0	3	36
Initial	5	0	7	4	3	6	8	2	2	37
Formal	5	4	3	5	4	0	7	6	9	43
Informative circomlocution	12	5	9	20	2	4	17	0	9	78
Morphological	19	8	13	26	14	9	19	6	16	130
Empty circomlocution	26	12	15	19	12	13	24	20	13	154
Unrelated	15	24	18	20	12	19	22	16	19	165
Correct eventually	27	21	39	17	21	28	24	21	24	222
Distant phonological	39	25	29	48	28	22	31	19	31	272
Omissions	55	24	29	55	26	37	38	13	20	297
Close phonological	45	44	49	49	36	39	40	47	40	389
Semantic	100	42	71	91	38	70	105	30	47	594

Abbreviations: B = baseline, I = immediate testing, F = follow-up testing; ARTIC = repetition in the presence of articulation but no picture, RIPP = repetition in the presence of a picture, RIPPA = repetition in the presence of a picture and articulation.