Enhancement of verb retrieval

Neuromodulation, repetition priming, and aphasia rehabilitation

by

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To my beloved husband

CHAPTER 1

General introduction

There is an increasing interest in enhancement of cognitive functions. Cognitive enhancement can play a role in improving performance in young individuals, in the maintenance of cognitive functions in aging, and in the rehabilitation of impaired cognitive functions in various neurological conditions, such as stroke. Furthermore, data from studies of cognitive enhancement can be used to increase our understanding of the architecture of the cognitive system, and of the interactions between the building blocks of cognition.

This dissertation addresses the enhancement of verb retrieval. Verbs are central to the process of sentence construction, and play therefore a major role in communication. The process of verb retrieval is vulnerable to brain damage, being selectively disrupted in a high proportion of patients who present with aphasia after stroke. Nonetheless, there is relatively little research on the treatment of verb retrieval in aphasia in comparison to other types of impairment. This thesis has a specific focus on understanding the mechanisms of enhancement in verb retrieval, both in healthy individuals, and patients with aphasia. This enhancement is studied with behavioral techniques and transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique.

1.1 Theoretical background

Aphasia rehabilitation is reported to result in considerable improvement in communication (Brady, Kelly, Godwin, & Enderby, 2012; Cappa, Benke, Clarke, Rossi, Stemmer, & van Heugen, 2005). Nevertheless, 43% of patients still present with aphasia 18 months after stroke (Laska, Helblom, Murray, Kahan, & Von Arbin, 2001). There is a need to increase the effectiveness of therapy, in order to improve the quality of life of people with aphasia. Knowledge about the structure of the language system can be used to drive the design of treatment protocols that aim to rehabilitate specific processes that are impaired after stroke (Caramazza & Hillis, 1993). In addition, understanding how the language system can be changed by experience, and which other aspects of cognition can support this change, is crucial to fine-tune therapeutic approaches (Baddeley, 1993). In addition to refining behavioral treatment approaches, knowledge about the language processing system, its plasticity and the interactions between language and other cognitive functions may increase efficiency in using new technologies, such as neuromodulation techniques, in aphasia rehabilitation. This dissertation aims to increase our understanding of the mechanisms that support enhancement of verb retrieval, both in the intact language system, and in aphasia.

1.1.1 From verb retrieval to sentences

It is widely accepted that there are different levels of representation within the language system. These levels include a store of conceptual features (that is, the set of features that generate meaning -semantics), syntactic features (that is, grammatical features such as grammatical class), and representation of phonological features (that is, segmental and supra-segmental properties of the word's phonological form). Different models of language production structure the organization of information within each level differently, and also assume differences in the way

the levels interact (e.g., Bastiaanse & Van Zonneveld, 2004; Dell, 1986; Levelt, 1999; Miozzo & Caramazza, 1997; Patterson & Shewell, 1987). As an example, we present the model of Bastiaanse and Van Zonneveld (2004, adapted from Levelt, 1989; see Figure 1.1). In general, it is agreed that after a stimulus picture is presented (or, in natural language production, the intention to communicate a message is generated), related semantic (and, in some models, grammatical) features are activated. This level of information is termed the *lemma* in Figure 1.1. The *grammatical encoder* generates a sentence frame that suits the grammatical properties of the activated lemmas. Activation from the lemma level also spreads to phonological representations (the *lexeme* level). The phonological representations that reach threshold are selected for production, inserted in the sentence frame and encoded phonologically.

Words of different grammatical classes may differ in the nature of their representations at different levels. For instance, verbs have more grammatical detail than nouns (Conroy, Sage, & Ralph, 2006). The grammatical properties of verbs have motivated a wide body of research, due to the verb's central role in sentence production. Verb representations entail information about verb argument structure (that is, the necessary sentence components that should co-occur with a specific verb), and the thematic roles of these arguments. For instance, a grammatical sentence with the verb "to hike" only needs to include a subject who performs the action (the thematic agent) and the verb ('the man hikes'), whereas a sentence with the verb "to put" requires someone who does the action (the agent), some target for the action (the theme), a place (the location), and the verb ('the man puts the book on the table'). In addition, the verb meaning establishes selection restrictions for these arguments (for instance, the sentence "the man puts the philosophy on the table" may be grammatical, but it is odd under a literal reading).

Figure 1.1. Schematic representation of a language processing model

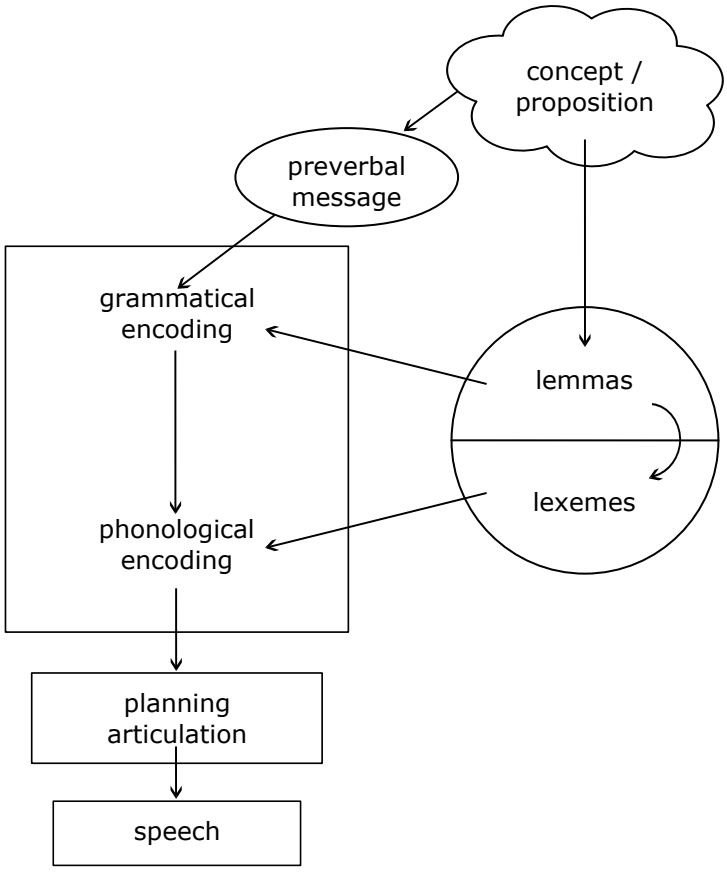

*Figure 1.1.*Based on Bastiaanse and Van Zonneveld (2004), and adapted from Levelt et al., (1998). Copyright: Roelien Bastiaanse, University of Groningen.

1.1.2 The facilitation of word production

Word retrieval can be facilitated by a prior occurrence of the same word (repetition priming) or by primes that are related phonologically or orthographically. In repetition priming (when the prime is the same word as the target), picture naming, word reading, and lexical decision are facilitated (Tenpenny, 1995; see Chapter 3 for a more detailed description of priming). Studies with healthy individuals using functional magnetic resonance imaging have shown that performance facilitation associated with repeated naming relies on two types of practice effects.

On the one hand, task practice is associated with neurofunctional changes in areas which are important for the language processes involved in naming. These are the implicit, task-specific computations that are activated irrespective of the specific words being produced by the subject. On the other hand, repeated exposure to the same items (item practice) is associated with changes in areas involved in other cognitive functions, such as episodic memory for the repeated items (e.g., Basso et al., 2013; Heath et al., 2015).

The repetition priming literature using Event-Related Potentials (ERPs) has also provided strong indications that facilitation induced by prior exposure to the same stimulus relies both on changes in implicit computations and explicit recall of the previous occurrence of these stimuli (e.g., Olichney et al., 2000). It has been argued that repetition priming reflects facilitation occurring at the level of lexical retrieval (e.g., Barry, Hirsh, Johnston, & Williams, 2001). With ERP data, it was suggested that repetition-related facilitation occurs both in implicit processes (indexed by changes in the N400) and explicit processes (episodic retrieval of the prior occurrence of the stimuli, indexed by the Late Positive Component; Olichney et al., 2013). Nevertheless, there are still no ERP data available regarding repeated overt naming, and the literature also shows that the electrophysiological characteristics of repetition priming vary across modalities and tasks (e.g., Friedman, 1990; Olichney et al., 2000). This type of data is relevant for identifying the level of language processing at which repeated naming facilitates performance, and to assess the potential contribution of other cognitive domains (e.g., episodic memory) in improving performance.

1.1.3 The rehabilitation of verb production in aphasia

In aphasia, it has been shown that phonemic, orthographic (Hickin, Best, Herbert, Howard, & Osborne, 2002), semantic (Baum, 1997), and repetition priming can facilitate word retrieval

(Nickels, 2002). When administered repeatedly, the same tasks can result in long-lasting improvement (Hickin et al., 2002; Nickels, 2002). A recent review suggests that, at the single word level, the same rehabilitation techniques can be used for the rehabilitation of the retrieval of verbs and nouns (Webster & Withworth, 2012). Nonetheless, the same review states that improvement in verb production is more difficult to achieve than improvement in noun production. Hence, although the same techniques can be used for the two categories, they may not be equally effective for verbs and nouns.

Considering that verb representations entail information relevant for grammatical sentence construction (Saffran, Schwartz, & Marin, 1980), it has been proposed that verb therapy is more productive if delivered at the sentence level (e.g., Links, Hurkmans, & Bastiaanse, 2010). Sentence-level therapies often require identification of the verb and its arguments, and production of a sentence including all elements. This type of treatment approach results in improved production of treated verbs, both at the single-word and sentence level (e.g., Fink, Martin, Schwartz, Saffran, & Myers, 1992; Webster, Morris, & Franklin, 2005). Hence, these kinds of verb production treatment may have the potential to improve communication more generally.

Another desirable outcome of aphasia rehabilitation is generalization. This may refer to improved production of treated verbs in untreated contexts (for example, from single words to sentences, as discussed above). Generalization may also mean improved use of some specific grammatical operation (e.g., present to past tense transformation) in untreated verbs. Finally, it may refer to improved retrieval of verbs that were not produced during therapy. This is the sense of generalization that will be used throughout this thesis.

Generalization to lexical retrieval of untreated verbs occurs infrequently, and its mechanisms are poorly understood. Nonetheless, it has been suggested that the occurrence of generalization may depend on the characteristics of treatment, and/or the characteristics of patients. Generalization was reported after a treatment involving semantic, gestural, and repetition cueing (Rose & Sussmilch, 2008), in treatments that engaged knowledge of verb argument structure (e.g., Thompson, Riley, Den Ouden, Meltzer-Asscher, & Lukic, 2013) and those in which finite verbs were produced in sentence context (Links et al., 2010). All these studies share the feature that explicit knowledge of verb's argument structure was engaged during treatment. In addition, in the latter two studies treatment was provided in a sentence context. It may then be the case that, for generalization in verb retrieval to occur, treatment has to engage knowledge of the grammatical features that are part of verb representations.

In addition to the content of therapy, generalization may depend on the nature of impaired representations (Miceli, Amitrano, Capasso, & Caramazza, 2006). Lexical-phonological representations are unique labels in the mental lexicon. Each lexeme specifies the phonological form that is associated with a concept (that is, a set of semantic features that constitute meaning). In contrast, semantic representations are thought of as sets of features which, depending on co-activation patterns, constitute different meanings (Levelt, 1999). Hence, when a unique lexical representation is restored through treatment, effects of treatment will be specific to retrieval of that specific lexeme. However, when a semantic feature is restored, all concepts that are built using that feature will be better specified, hence increasing the levels of activation of all related lexical-phonological forms. Accordingly, Miceli et al. (1996) found no generalization after therapy (even to semantically-related words) in two aphasic patients with lexical damage (see

also Fillingham, Sage, & Lambon Ralph, 2006; Hickin et al., 2002; Parkin, Hunkin, & Squires, 1998).

1.1.4 Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique. A weak electrical current is delivered through electrodes positioned over the scalp. Current flows from the negatively charged electrode (the cathode) to the positively charged one (the anode). Stimulation modulates sodium- and calcium-dependent channels and NMDA (N-methyl-D-aspartate)-receptor activity, modulating in turn the resting membrane potentials of neurons (Liebtanz, Nitsche, Tergau, & Paulus, 2002). This is a lasting (but reversible) effect, whose putative cellular mechanisms are shared with those occurring in Long-Term Potentiation and Long-Term Depression. These correspond to long-term increase (strengthening) and reduction (weakening) of signal transmission between neurons, respectively. Therefore, they may be relevant in learning, memory formation and neural plasticity, potentially contributing to functional recovery after brain damage (Nitsche et al., 2008).

Studies using tDCS to modulate language functions have been conducted both in healthy individuals and in aphasic patients. In studies with healthy individuals, tDCS has been shown to increase verbal speed (Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008), fluency (Cattaneo, Pisoni, & Papagno, 2011; Iyer et al., 2005) and accuracy in naming famous people (Ross, McCoy, Wolk, Coslett, & Olson, 2010). Though stimulation sites vary across studies (e.g., left frontal areas in Cattaneo et al., 2011, and left temporal areas in Sparing et al., 2008), enhanced language production with tDCS has been reported frequently. For example, anodal tDCS (that is, with the anode over the scalp and the cathode in an extra-cephalic position) to the left temporo-parietal junction increased the

speed and the number of learned items in a paradigm requiring learning a novel vocabulary (Meinzer et al., 2014). Similarly, anodal tDCS to Broca's area increased the priming effect elicited by the auditory presentation of target words during naming (Holland et al., 2011). However, crucially, no studies with healthy individuals have investigated whether changes in performance after training addressing overt word production is enhanced by tDCS over and above behavioral facilitation techniques alone.

In aphasia, improved production of treated nouns and verbs has been enhanced by tDCS. Just as with healthy individuals, studies with aphasic patients have varied greatly in methodology, patient characteristics, and treatment protocols (e.g., Baker, Rorden, & Fridriksson, 2010; Marangolo et al., 2013a, 2014; Monti et al., 2008). In contrast to the evidence supporting the efficacy of tDCS to increase recovery for treated verbs and nouns, there is little information available regarding generalization. Marangolo et al. (2013b, 2014) report transfer of improved retrieval of treated verbs to spontaneous speech, and Baker et al. (2010) report numerical (but non-significant) increases in producing untreated verbs after tDCS. Crucially, no study has yet addressed the issue of generalization of lexical retrieval of untreated verbs with tDCS, using a treatment protocol likely to result in generalized improvement (e.g., the approaches by Links et al., 2010; Thompson et al., 2013).

1.2 Thesis outline

In this dissertation, I address the issue of enhancement of verb retrieval from several perspectives. I aim to provide a better understanding of the mechanisms of change that support experience-related language facilitation in healthy individuals, and the mechanisms that underlie item-specific improvement and generalization in aphasia recovery. With regard to tDCS, this research had two main goals: first, I aim to increase the understanding of how tDCS may be used

to increase the effects of aphasia therapy; second, I aim to test the efficacy of tDCS to enhance language facilitation in healthy individuals and the effects of therapy in aphasia. In addition, in order to provide a direct clinical application for this knowledge, I develop a theory-driven treatment program that engages these mechanisms and test its efficacy.

Chapter 2 is a review of the literature concerning the use of tDCS in aphasia rehabilitation. This review examines differences across studies in stimulation parameters, in behavioral treatment techniques and in the characteristics of the patients who were included in the different studies. It also provides methodological recommendations for other studies aiming to test the potential of tDCS to enhance treatment effects.

In the third chapter, a repetition priming ERP study designed to assess the electrophysiological properties of the word repetition effect in repeated overt action naming is described. This study helps to pinpoint which aspects of language processing are facilitated by repeated naming, and which other aspects of cognition promote this facilitation. In the same study, the potential of tDCS to increase performance above and beyond behavioral priming in healthy individuals is assessed.

Chapter 4 is a meta-analysis of the literature on rehabilitation of verb retrieval, which focuses on improved retrieval of treated and untreated verbs. I examine the predictive value of demographic, clinical, and treatment-related factors for both types of outcome. The factors that predict recovery can reveal mechanisms of change that are necessary for each type of improvement. In particular, I address the question of whether the two treatment outcomes (item-specific improvement and generalization) occur though different mechanisms, as suggested in the literature.

In Chapter 5, the efficacy of a treatment protocol designed to improve verb retrieval and morphological processing in sentence context is tested (adapted from Links et al., 2010). I predicted that verb retrieval should improve for both treated and untreated verbs, given that treatment was provided at the sentence level, and engaged knowledge of verbs' argument structure and their morphological properties. I examined whether the results of Links et al., (2010) can be replicated in an Italian adaptation of their treatment protocol. In addition, I extended treatment to two phases, which allowed examination of the occurrence of item-specific improvement and generalization over time, and created an optimal context to test whether tDCS can increase therapy effects both for item-specific improvement and generalization.

The overall contribution of this research program to our understanding of the mechanisms of change responsible for item-specific improvement and generalization is discussed in detail in Chapter 6. Limitations of the studies herein, and suggestions for future research are also outlined in this final chapter.

CHAPTER 2

tDCS in post-stroke aphasia: The role of stimulation parameters, behavioral treatment and patient characteristics[1]

Neurostimulation techniques have been recently adopted in aphasia rehabilitation. In several studies transcranial direct current stimulation (tDCS) was used to enhance treatment effects. The methodology adopted in different studies is characterized by a large variability, as concerns stimulation parameters (e.g., montage type, current intensity, session duration, number and frequency of treatment sessions), participant inclusion criteria (subacute vs chronic, selected vs general aphasia types) and characteristics of associated behavioral treatments (online vs offline treatment, focused on different underlying deficits). Group analyses report on positive results for most of the adopted paradigms. We review the available literature focusing on tDCS in the rehabilitation of stroke-related aphasia, with reference to the current views on tDCS's action mechanisms and on the factors that may influence the effects of stimulation. Even though our understanding of the mechanisms activated by neurostimulation techniques is still limited, available evidence already allows to propose methodological recommendations for studies intending to use tDCS as a treatment adjuvant. Where several options for a specific stimulation parameter seem suitable, we provide information to reach a knowledgeable decision.

[1] This chapter was published as de Aguiar, V., Paolazzi, C. L., & Miceli, G. (2015). tDCS in post-stroke aphasia: the role of stimulation parameters, behavioral treatment and patient characteristics. *Cortex*, 63, 296-316. doi:10.1016/j.cortex.2014.08.015

2.1 Introduction

Delivering direct electric current over the scalp has been used to treat various ailments since the first century AC. Torpedo fish and electric catfish were applied over the scalp of patients suffering from epilepsy and headache by Scribonius Largus, Pliny the Elder, Galenus and Ibn-Sidah (Kellaway, 1946). These reports can be considered the birth of electrophysiology.

In less remote times, scientists employed electric currents in clinical medicine and applied them to a variety of mental disorders. In the 19th century, successful treatment of melancholia and depression was reported following the application of galvanic currents to the scalp (Aldini, 1804; Arndt, 1869). The same procedure produced insomnia and long-lasting activation in healthy individuals, and facial muscle contractions in cadavers (Aldini, 1804). These early studies were characterized by extremely variable procedures and results. Due to this variability, direct current (hereafter, DC) treatment was progressively abandoned in the 1930's, when electroconvulsive therapy (ECT) was introduced. Although ECT results in the treatment of mental disorders were consistent and successful, use of this technique was hindered by considerable side effects (e.g., memory disturbance, loss of consciousness), that had not been observed following the application of DC (Priori, 2003).

During the 60's and the 70's, studies correlated the effects of DC to the potential difference recorded by EEG electrodes (Dymond, Coger, & Serafetinides, 1975), indirectly showing the influence of DC on brain excitability (Lippold & Redfearn, 1964). After this short revival, DC was abandoned again, due to mixed results and to concurrent, increasing effectiveness of drug treatments. At the end of the 90's, the effects of DC on brain activity were directly investigated via Transcranial Magnetic Stimulation (TMS), a technique that allows measures of cerebral excitability (Priori, Berardelli, Rona, Accornero, & Manfredi, 1998). Direct Current administered

before TMS pulses yielded measurable effects on TMS-induced Motor Evoked Potentials (MEPs). Subsequent studies showed that small amounts of very weak current traversed the skull and influenced brain activity (Nitsche & Paulus, 2001; Priori et al., 1998). These early studies led to develop a novel approach to non-invasive stimulation, transcranial Direct Current Stimulation (tDCS).

More recent investigations tried to clarify the mechanisms underlying tDCS effects on cortical excitability. tDCS appears to be a neuromodulatory technique, that affects the resting membrane potentials of neurons through the modulation of sodium- and calcium-dependent channels and NMDA (Nmethyl-D-aspartate)-receptor activity (Liebtanz et al., 2002). Anodal tDCS (A-tDCS) increases the mean neuronal firing rate (Bindman, Lippold, & Redfearn, 1964), thus promoting mechanisms that underlie long-term potentiation and depression. The latter two phenomena correspond to long-term enhancement and reduction of signal transmission between two neurons, respectively. Given their capacity to strengthen or weaken neuronal connections, they might facilitate learning and memory formation, as well as neural plasticity that contributes to functional recovery (Nitsche et al., 2008). tDCS does not generate action potentials; moreover, it is site-specific but not site-limited, meaning that it affects not only the targeted site, but also brain areas related to it. Cathodal polarization is thought to decrease cortical excitability due to hyperpolarization of cortical neurons, whereas anodal polarization increases cortical excitability due to subthreshold depolarization (Schjetnan, Faraji, Metz, Tatsuno, & Luczak, 2013).

In the last fifteen years, tDCS has been used in a wide array of mental disorders, for several reasons. The first order of reasons pertains to considerations on safety: the technique seems to have no significant adverse side effects, provided that stimulation parameters are kept within safety limits (Nitsche et al., 2003; Palm et al., 2008). A recent review of studies in humans from

1998 to 2008 reported that tDCS did not produce side effects other than a sporadic tingling sensation under the electrodes (Nitsche et al., 2008: Table 2.1). Secondly, the technique has practical advantages. The apparatus is more portable, less expensive and easier to use than other technologies. Thirdly, as far as experimental protocols are concerned, tDCS allows to easily conduct placebo, control conditions: subjects cannot reliably distinguish between real and sham stimulation with low stimulation intensities (Gandiga, Hummel, & Cohen, 2006), even though conflicting results are reported for higher intensities (Brunoni, Schetatsky, Lotufo, Benseñor & Fregni, 2014; O'Connel et al., 2012). In addition, tDCS is well-suited for online experiments. Lastly and most importantly, it has been shown to be effective in a variety of medical conditions, ranging from mood disorders (Brunoni et al., 2013) to chronic pain (Antal, Terney, Kühnl, & Paulus, 2010) and neurological disorders such as Alzheimer's disease, Parkinson's disease, stroke related motor deficits and neglect (for a review see Flöel, 2014).

2.1.1 tDCS in language research

In the language domain, the effects of tDCS have been studied in healthy individuals, and in individuals with aphasia. Behavioral studies in healthy subjects have shown that anodal tDCS (A-tDCS) improves verbal speed (Fertonani et al., 2010; Sparing et al., 2008), fluency (Cattaneo et al., 2011; Iyer et al., 2005) and accuracy in naming famous people (Ross et al., 2010). Positive results have been found with different stimulation sites, ranging from left frontal areas (Cattaneo et al., 2011; Fertonani et al. 2010; Iyer et al. 2005), to left temporal (Sparing et al., 2008) and right temporal areas (Ross et al., 2010). In learning paradigms, left frontal A-tDCS resulted in improved grammaticality decision after artificial grammar learning (de Vries et al., 2010), and left frontal cathodal tDCS (C-tDCS) negatively affected an action and object learning paradigm (Liuzzi et al. 2010). A-tDCS to the left temporo-parietal junction increased both the speed and

amount of verbal learning (Meinzer et al., 2014). When administered over Wernicke's area, A-tDCS resulted in faster responses following an associative verbal learning task (Fiori et al., 2011). These results attest to the potential of A-tDCS as a tool to enhance verbal performance and learning in healthy individuals, and suggest that left frontal C-tDCS may disrupt learning processes.

Neuroimaging research has provided information on how tDCS may improve language abilities. Meinzer et al. (2012) showed that improvement in semantic word retrieval during A-tDCS was related to reduced activation in the left Inferior Frontal Gyrus (IFG), and increased connectivity between the IFG and other major language hubs. Holland et al. (2011) showed that BOLD signal decrease in Broca's area after A-tDCS correlated with increased naming speed. Meinzer, Lindenberg, Antonenko, Flaisch, and Flöel (2013) showed that under baseline conditions elderly subjects present with greater bilateral prefrontal activation than young controls, and that this correlates with poorer performance in semantic word generation. After left prefrontal A-tDCS, task-related hyperactivity in bilateral pre-frontal cortices, anterior cingulate and precuneus was reduced, and performance in the elderly improved to reach the levels obtained by younger controls. Resting state connectivity, which before A-tDCS was enhanced in anterior areas and reduced in posterior areas as compared to younger individuals, also reverted to a pattern similar to that of younger individuals (Meinzer et al., 2013). These results suggest that A-tDCS may improve language skills by increasing the specificity (e.g., decrease in bilateral activation reported by Meinzer et al., 2013) and efficiency of task-related activation in the stimulated area, and by enhancing the connectivity of the stimulated area with the language network.

These mechanisms may be particularly beneficial in the rehabilitation of stroke patients. The present review focuses on the use of tDCS in aphasia therapy. Studies included in this review

were selected after a web search including several search engines (MEDLINE, PubMed, Web of Science, and Google Scholar). The following key-words were used in the search: tDCS, transcranial Direct Current Stimulation, tDCS AND aphasia, tDCS AND aphasia rehabilitation. In addition, we searched the reference section of each study, in order to identify other relevant studies. We excluded studies in which tDCS was administered to treat other types of deficits, and studies conducted solely with healthy individuals or with animals. No studies were excluded based on methodological shortcomings (when present, these are addressed in the current review). Given the small number of investigations in the literature, all identified studies in which tDCS was used in the treatment of patients with aphasia were included.

In the following sections, the characteristics of aphasia recovery and some methodological issues to be considered in designing tDCS studies in aphasia rehabilitation are briefly discussed. Subsequently, literature reports on tDCS in aphasia treatment are reviewed, and some critical considerations prompted by the comparative analysis of these studies are introduced. The final section contrasts methodological aspects of the reviewed studies, and provides suggestions for the optimal use of tDCS in the context of aphasia rehabilitation, keeping account of current knowledge on its putative mechanisms of action and of factors that may influence its effectiveness.

2.2 Aphasia recovery: from neuroplasticity mechanisms to neuromodulation

A variety of factors has the potential to influence the outcome of aphasia therapy. In this section we mention some which are of interest in the context of neuromodulation. Relevant roles can be played by stroke severity (Pedersen, Vinter, & Olsen, 2004) and by lesion characteristics such as site, size (Kertesz, Harlock, & Coates, 1979; Maas et al., 2012) and type (with hemorrhagic strokes related to better outcome than cardioembolic strokes; Hachioui et al., 2013). As for the

role of language impairment, less severe overall aphasic deficits (Pedersen et al., 2004) and sparing of phonological skills (Hachioui et al., 2013) are significant predictors of recovery. Demographic characteristics such as age and educational level also seem to contribute to language improvement after stroke (Hachioui et al., 2013). These and other variables may constrain the potential extent of neuroplasticity, resulting in the involvement of perilesional left hemisphere (LH) regions in linguistic tasks, and/or the acquisition and/or enhancement of language processing abilities in the intact right hemisphere (RH), and/or the (possibly maladaptive) activation of the non-dominant hemisphere (Hamilton, Chrysikou, & Coslett, 2011).

It has been suggested that unilateral LH lesions yield cortical disinhibition in perilesional structures, thus increasing activity in intact, language-specific areas (Lang, Nitsche, Paulus, Rothwell, & Lemon, 2004). There is large agreement that peri-lesional LH activation is associated with successful recovery (Cornelissen et al., 2003; Karbe et al., 1998; Meinzer, Harnish, Conway, & Crosson, 2011; Rosen et al., 2000). Stroke-induced lesions can also disrupt the balance of inter-hemispheric competition. In the healthy brain, there is a mutual inhibitory control between the two hemispheres, mediated by transcallosal connections – increased excitation in one hemisphere is often associated with increased inhibition in homologous contralateral areas (Bütefisch, Wessling, Netz, Seitz, & Hömberg, 2008). Thus, a unilateral left-sided lesion reduces transcallosal inhibition of the RH by the LH, and therefore increases activity in the intact RH. Since the RH can still send transcallosal inhibitory impulses to the LH, activation in the damaged LH is further reduced (Murase, Duque, Mazzocchio, & Cohen, 2004).

Whether increased RH activation is beneficial or maladaptive is controversial (for discussion see Hamilton et al., 2011). Several studies have argued for a beneficial role of the RH, thus

promoting the idea that the two hemispheres are functionally homologous (at least to some degree) (e.g., Crosson et al., 2009; Fridriksson, Baker, & Moser, 2009). The critical factors in the post-stroke acquisition of linguistic abilities by the RH would be lesion size and the time post onset. The RH might serve an adaptive function in the acute and post-acute stages and a maladaptive one in the chronic stage (Heiss & Thiel, 2006; Kaplan et al., 2010; Turkeltaub, Messing, Norise, & Hamilton, 2011; Winhuisen et al., 2005). This view has motivated the use in aphasia treatment of Melodic Intonation Therapy (MIT; Albert, Sparks, & Helm, 1973), a technique that aims at recruiting RH regions in order to facilitate speech production. Other studies on chronic aphasia suggested that non-dominant hemisphere activation can be detrimental, either because it causes transcallosal inhibition of the damaged hemisphere (Martin et al., 2004; Naeser et al., 2005, 2011) or because it induces maladaptive plastic changes during the reorganization of language functions (Belin et al., 1996). In a recent report, involvement of different RH areas facilitated recovery, or interfered with it in the same participant (Turkeltaub et al., 2012).

To date, knowledge of the mechanisms underlying spontaneous recovery and of those underlying the effects of tDCS is insufficient to constrain neurostimulation strategies in post stroke aphasic patients. Furthermore, the effects of stimulation are difficult to disentangle from those tied to patient characteristics (e.g., pre-treatment language skills; lesion site and size, etc.). Nevertheless, the consideration that these variables might facilitate or reduce the individual's potential for achieving more significant neuroplastic changes, has led researchers using tDCS in aphasia rehabilitation to adopt various strategies, based on the hypothesized mechanisms of neuroplasticity after stroke. In line with the diversity of opinions about these mechanisms, four approaches to neuromodulation have been adopted: modulation of perilesional activation via A-

tDCS or C-tDCS; facilitation of RH activation via A-tDCS; downregulation of RH areas homologous to the LH lesion via C-tDCS; simultaneous LH A-tDCS and RH C-tDCS. The studies that used these approaches are reviewed in the next section.

2.3 tDCS studies of aphasia recovery

tDCS studies of aphasia recovery have adopted a wide range of electrode montages (placement of the polarized and of the reference electrode) and polarities, depending on the net effect they intended to obtain (excitation or inhibition of specific brain areas). According to modelling studies, current density is largest in the cortical area directly beneath the stimulation site (Miranda, Lomarev, & Hallet, 2006). In order to increase activity in a brain region, the anode can be placed on potentially relevant areas of the LH, whereas the reference electrode (in this case, the cathode) is placed either in a non-cephalic or in a cephalic position. For C-tDCS, the reverse electrode placement is used: the cathode lies over the area of interest and the reference electrode (this time the anode) is positioned over a cephalic or non-cephalic position. When placed in a cephalic position, the second electrode acts like an active electrode (Nitsche et al., 2008). Consequently, to exploit a truly mono-cephalic montage, electrode size should be adjusted in such way that the reference electrode releases a minimal current density. Since the latter is the quotient of current strength (voltage) and electrode size, this goal can be achieved by using a large electrode for reference (e.g., Vines, Norton, & Schlaug, 2011). In bi-cephalic montages, both the anode and the cathode are placed over cephalic positions of interest, resulting in the simultaneous delivery of excitatory and inhibitory current to two different brain areas (Nitsche et al., 2007). A recently suggested alternative is the use of electrode pairs (Lee, Cheon, Yoon, Chang, & Kim, 2013), one consisting of an anode over LH areas and a cathode over the right shoulder, the other consisting of a cathode over RH areas and a cathode over the left shoulder.

In this section, studies are divided according to the type of montage used. It should be noted that some authors described their studies as using a mono-cephalic montage, because a single area was targeted by stimulation. Regardless of whether they declared to have used one or multiple target stimulation sites, all studies in which two electrodes of the same size were placed over cephalic areas are considered here as having used a bi-cephalic montage. This is motivated by the fact that, in the context of inter-hemispheric competition models (Bütefisch et al., 2008; Murase et al., 2004), benefit might accrue in principle from bilateral neuromodulation. According to these models, bilateral modulation of brain activity can be particularly beneficial in stroke patients, as the imbalance of interhemispheric interactions induced by the focal lesion can be influenced by stimulating both hemispheres – e.g., by administering A-tDCS to perilesional areas and C-tDCS to contra-lesional areas (Lindenberg, Renga, Zhu, Nair, & Schlaug, 2010). This distinction between mono-versus bi-cephalic stimulation studies is further justified because the possibility that a second electrode placed on a cephalic area also exerts an effect cannot be dismissed (Nitsche et al., 2008).

2.3.1 Uni-cephalic montages

We begin by describing studies designed to assess the effects of stimulation to peri-lesional areas. In one such study (Monti et al., 2008), 8 non-fluent Italian aphasics with vascular lesions (left frontal cortical/subcortical, frontoparietal cortical/subcortical, frontotemporoparietal cortical/subcortical, frontoparietal subcortical) participated in two experiments: one to assess the effects of A-tDCS and C-tDCS over the lesioned area, and one to verify the specificity of the findings from the first experiment. In both experiments, current was delivered at 2 mA for 10 min; the reference electrode was positioned over the right shoulder. In the first experiment, patients were divided in two groups. The anodal group received A-tDCS or sham tDCS (S-tDCS)

over Broca's area; the cathodal group received C-tDCS or S-tDCS over Broca's area. Stimulation was applied offline: patients were asked to name pictures of concrete entities before and after stimulation. Monti et al. (2008) found significantly greater naming accuracy after C-tDCS, but not after A-tDCS or S-tDCS. No changes were found in reaction times (RTs), suggesting that improvement did not result from an aspecific change of arousal or attention. In the second experiment, all participants received C-tDCS or S-tDCS over the occipital lobe (intact in all subjects), to rule out that the effects reported in the first experiment were not specific to the stimulated area. In this case, naming accuracy did not change, thus supporting the idea that results of the first experiment were due to the stimulation of a language related area, and confirming the usefulness of C-tDCS over LH areas.

Baker et al. (2010) tested 10 patients with anomic or Broca's aphasia with left temporoparietal, frontotemporal, frontotemporoparietal, temporoparietooccipital LH stroke. Subjects received A-tDCS (to upregulate left perilesional regions) or S-tDCS for 5 consecutive days, paired with an anomia treatment that targeted concrete nouns of low-, medium-, and high-frequency in a picture-word matching task. The placement of the anode in the LH was determined individually, on the basis of MRI (Magnetic Resonance Imaging) and fMRI images (functional MRI), acquired during an overt picture naming task. In each participant, stimulation was applied to the intact area showing higher activity during correct naming. Naming accuracy for treated and untreated items was measured before treatment, after the fifth tDCS session, and 1 week after the end of tDCS treatment. Accuracy after treatment increased for treated items after A-tDCS, but not after S-tDCS. Improvement persisted for at least 1 week after the end of the protocol.

In yet another study, homologous contra-lesional areas were stimulated in 6 subjects with Broca's aphasia and left frontal damage (Vines et al., 2011). All participants were more than 1

year post-onset. They completed two therapy phases of 3 sessions each, with an intervening 1-week washout period. Concurrently to A-tDCS and S-tDCS, they received MIT (Albert et al., 1973). Stimulation (1.2 mA, for 20 min) was applied over the intact right IFG, and a reference electrode was placed in the left supraorbital region. This montage was intended to upregulate activation of RH areas homologous to the left frontal lesions. Patients improved in verbal fluency after A-tDCS.

Flöel et al. (2011) tested the effects of up- and downregulating RH activity, using either A-tDCS, C-tDCS or sham over intact right temporoparietal areas in 12 patients with aphasia, and a larger electrode for reference, placed over the left frontopolar cortex. Stimulation with a current intensity of 1 mA was delivered during the first 20 min of each hour, in three 2-h sessions per treatment phase. The interphase interval was of three weeks. A computerized anomia treatment for object naming was administered. Both A-tDCS and C-tDCS over the right temporoparietal cortex improved performance more than sham, but A-tDCS had a larger and longer-lasting (2 weeks) effect. In these two studies, upregulating RH activity yielded improved performance. Considering that the recruitment of RH areas is frequently thought to be maladaptive in the chronic stage (Heiss et al., 2006; Kaplan et al., 2010; Naeser et al., 2005; Turkeltaub et al., 2011; Winhuisen et al., 2005), this study raises the question of whether RH activation in the chronic stage is always maladaptive, or it can be modulated so as to turn into a language-beneficial pattern (see Section 2). Nevertheless, Flöel et al. (2011) also showed improved performance after C-tDCS of the same areas, indicating that both stimulation and inhibition might be beneficial. Clearly, further research looking at the effects of different tasks associated with RH stimulation is needed to better understand this issue.

2.3.2 Bi-cephalic montages

In the studies that follow, authors aimed at downregulating RH activation (Jung, Lim, Kang, Sohn, & Paik, 2011; Kang, Kim, Sohn, Cohen, & Paik, 2011), at upregulating LH activation (Fiori et al., 2011; Fridriksson, Richardson, Baker, & Rorden, 2011; Marangolo et al., 2013a; Saidmanesh, Pouretemad, Amini, Nilipor, & Ekhtiari, 2012) or at reaching both goals (Lee et al., 2013). Since in these studies two electrodes of equal size were placed over cephalic areas, stimulation is likely to have simultaneously modulated task-relevant RH and LH areas. This is particularly important for studies using a symmetrical (or almost symmetrical) montage (Jung et al., 2011; Kang et al., 2011; Lee et al., 2013; Marangolo et al., 2013a; Saidmanesh et al., 2012), which we discuss first.

Lee et al. (2013) were to our knowledge the only researchers to use two pairs of electrodes when administering bi-cephalic stimulation. One pair consisted of an anode over the left IFG and a reference over the left buccinator muscle, the other of a cathode over the right IFG and a reference on the right buccinator muscle. This bi-cephalic montage was contrasted with a mono-cephalic montage (anode over the left IFG and reference over the right buccinator muscle). Stimulation was combined with speech therapy, in a single session per condition. Eleven subjects (6 non-fluent) were included in this study. Whereas both conditions increased object naming accuracy, only the bi-cephalic montage was associated to an additional decrease in response times.

In Jung et al. (2011) and Kang et al. (2011), the cathode was placed over the RH homologue of Broca's area and the anode over the left supra-orbital cortex. Jung et al. (2011) recruited 37 LH stroke patients (Broca's area, Wernicke's area, arcuate fasciculus and insula). Among them, 10 had fluent aphasia, and 27 had non-fluent aphasia. Stimulation was combined with speech

therapy, individually tailored on the basis of patients' impairments. Current was applied at 1 mA for 20 min. Baseline values for each subject were determined by the scores in the K-WAB (the Korean version of the Western Aphasia Battery) and by the AQ% (Aphasia Quotient percentage), as assessed before treatment. After ten sessions (5 days a week for 2 weeks) the AQ% improved significantly, albeit to different extents depending on type of aphasia, lesion type and time post-onset. Notwithstanding the high number of participants and the choice of different, individually tailored aphasia treatments (two highly positive characteristics of this work), results must be considered cautiously, as the study did not include a control (sham) condition nor a control site to ensure that results were unequivocally due to stimulation.

Kang et al. (2011) treated 10 Korean-speaking patients with a single ischemic LH lesion (frontal, frontotemporal, frontoparietotemporal, subcortical and temporoparietal), and different types of aphasia (Broca's, anomic, global). Stimulation was applied online (2 mA for 20 min), and patients received word-retrieval training on concrete nouns. Accuracy and response times were measured before treatment to determine baseline values, and were considered as outcome measures. S-tDCS was applied as a control condition. After 5 consecutive days of treatment, accuracy improved significantly, without significant reduction in response times. Kang et al. interpreted this latter result as an indication that the observed improvement was genuine, and did not simply correspond to a movement along a speed/accuracy trade-off curve.

The three studies considered so far (Jung et al., 2011; Kang et al., 2011; Lee et al., 2013) included patients with various aphasia syndromes. Even though language impairments varied substantially across and within samples, all studies report positive results. Taken at face value, these results suggest that the same stimulation parameters could be used in patients with various clinical forms of aphasia, in association with speech therapy. Without inspecting individual data,

however, it is not clear that all patients benefited to the same extent from the adopted methodology – an unlikely possibility, considering the variability observed in healthy individuals (Horvath, Carter, & Forte, 2014).

Saidmanesh et al. (2012) studied the effects of tDCS on 20 Persian-speaking non-fluent aphasics, presenting with antero-posterior and posterior lesions. Participants received tDCS or S-tDCS; the anode was placed over the left dorsolateral prefrontal cortex, and the cathode in a symmetrical, contralateral position. Current was delivered at 2 mA for 20 min. Concurrent with stimulation, patients performed a picture naming test (concrete nouns). After treatment, they completed the same picture naming task, together with an evaluation of working memory performance; their AQ was also measured. Significantly greater improvement was reported after A-tDCS than after S-tDCS in all measures: naming accuracy, working memory and AQ%. In this study, the same areas were stimulated in all participants, regardless of lesion site, and positive findings are reported. Also in this case, it would be crucial to analyze individual data in order to verify if and to what extent lesion size and site influenced the outcome of tDCS.

In the study by Marangolo et al. (2013a), verbs were targeted for treatment instead of nouns. Seven non-fluent aphasic patients with varying LH ischemic lesions (temporal, frontotemporal, insula, frontotemporoparietal, subcortical) were recruited. Anode placement was decided based on previous TMS studies showing a crucial role for frontal regions (Broca's area) in action naming, as opposed to temporal regions (Wernicke's area). The cathode was positioned over the contralesional frontopolar cortex, and current was delivered at 1mAfor 20 min. Each subject completed 3 stimulation protocols (tDCS with the anode over Broca's area, tDCS with the anode over Wernicke's area, S-tDCS, with the anode placed over Broca's area). The order of stimulation conditions was randomized across subjects. For each participant, 3 groups of video clips were

prepared, each representing actions that subjects had comprehended but failed to name in a pre-treatment evaluation. During each tDCS session, a different set of video clips was presented. Each treatment phase lasted for 5 consecutive sessions (one session per day) and was separated from the following by a washout period of 6 days. Naming accuracy was assessed four times: before treatment, after day 5 of each session block, 1 week and 4 weeks after the end of the entire experimental protocol. Sustained and greater improvement in accuracy was observed when the anode was placed over Broca's area than over Wernicke's area or during S-tDCS. This result was taken as support for the functional relevance of Broca's area in verb processing. It cannot be entirely ruled out, however, that A-tDCS over Broca's area was more effective simply because in this case the symmetrical montage allowed an optimal modulation of interhemispheric interactions which was not the case for the asymmetric montage resulting from anode placement over Wernicke's area.

Fiori et al. (2011) recruited both healthy and aphasic participants. Since the present review focuses on tDCS in aphasia recovery, only data from the latter are discussed. Three patients with non-fluent aphasia were included, with linguistic abilities characterized by intact semantic processing and damage to the phonological output lexicon. Lesions included the left frontoparietal subcortex, frontoparietal cortex/subcortex and frontotemporoparietal cortex/subcortex. Treatment was provided in 2 phases, each lasting 5 consecutive days: the anode was placed over Wernicke's area and the cathode over the contralateral fronto-polar cortex, rendering the montage asymmetrical. Current was delivered at 1 mA for 20 min. The order of stimulation procedures (tDCS, S-tDCS) was randomized. Stimulation was delivered during language therapy (object naming). Items to be treated were selected during a pre-treatment comprehension task, and consisted of concrete nouns that patients had to produce

during tDCS in a word-retrieval task. The dependent measures were accuracy and response times, assessed before and after stimulation, as well as 1 and 3 weeks after the end of tDCS. Fiori et al. reported significantly improved performance both after A-tDCS and after S-tDCS, even though larger effects were found with the former. Improvement associated with S-tDCS could be due to the intensive language therapy patients were exposed to. Faster response times were observed only in the tDCS condition. Both effects persisted for at least 3 weeks after the end of the protocol.

Fridriksson et al. (2011) also used an asymmetrical montage. They recruited 8 fluent aphasics with posterior cortical or subcortical lesions. As in Baker et al. (2010), the anode was placed over the perilesional regions that showed the greatest activation on a pre-treatment fMRI scan acquired during an overt picture-naming task. The cathode was placed over the right forehead. Patients participated in 5 consecutive sessions of A-tDCS (1 mA for 20 min) and 5 consecutive sessions of S-tDCS, in randomized blocks separated by 3 weeks. They were asked to perform a word-picture matching task (same items as in Baker et al., 2010). Response times were measured before treatment to assess baseline values, after 5 A-tDCS sessions and 3 weeks after the end of treatment. A significantly larger decrease of response times after A-tDCS than S-tDCS was found, persisting for at least 3 weeks after the final session. In this study, response times were chosen as the dependent measure instead of naming accuracy. This was because response accuracy at baseline was close to ceiling, and accuracy changes would not adequately measure treatment-related effects.

Overall, positive effects are reported after tDCS. In monocephalic montages, tDCS has been reported to be effective regardless of stimulation polarity (anodal/cathodal) and location (LH/RH), when associated with a relevant linguistic task. Bi-cephalic montages were also

systematically associated with positive findings, irrespective of aphasia type, lesion site, stimulation site within the LH and treatment task. Nevertheless, it is relevant to consider that responses to stimulation show a large individual variability, even in healthy individuals (Horvath et al., 2014 – see also below). Consequently, the lack of information on individual aphasic participants in these studies could mask effects due to different stimulation parameters, treatment tasks and patient characteristics (See Tables 2.1 and 2.2 for a detailed description of the parameters used across studies). A closer look at aphasia rehabilitation studies, in relation to the mechanisms that may be putatively affected by different methodologies is needed to derive recommendations for clinical and research tDCS use. This is the focus of the next section.

Table 2.1. Stimulation parameters in studies of aphasia rehabilitation using tDCS

Authors	Intensity	Montage and polarity	Design	Inter-phase interval	Duration	Nsession/ condition	Modality	Short-term results	Long-term results
Baker et al. (2010)	1 mA	A-tDCS or S-tDCS (LH, individually) Electrodes: 5x5cm Reference: right shoulder	Crossover, 2 phases	1 week	20 min	5	Online	Improved accuracy after A-tDCS	After 1 week
Monti et al. (2008)	2 mA	A-tDCS, C-tDCS, S-tDCS (Broca) Electrodes: 5x7cm Reference: right shoulder	Crossover, 2 phases	1 week	10 min	1	No behavioral treatment	Improved accuracy after C-tDCS	n.a.
Vines et al. (2011)	1.2mA	A-tDCS (right homologous to Broca's area). Electrodes: 16.3cm^2; reference = 30cm^2 Reference: left supraorbital	Crossover, 2 phases	1 week	20 min.	3	Partially online	Improved verbal fluency after A-tDCS	n.a.
Flöel et al. (2011)	1mA	A-tDCS, C-tDCS, S-tDCS (right temporo-parietal cortex) Electrodes: active=5x7cm; reference=10x10cm Reference: left supraorbital	Cross-over, 3 phases	3 weeks	20 min.	3	Partially online	Improvement after both A- and C-tDCS, with larger effect of A-tDCS	After 2 weeks, only for A-tDCS.
Lee et al. (2013)	2mA	Mono (A-tDCS to the left IFG) and bi-cephalic (A-tDCS to left IFG, C-tDCS to the right IFG) Electrodes: 5x5 cm Reference: right buccinators muscle	Cross-over, 2 phases	>24 hours	30 min.	1	Online	Improved accuracy in both conditions, and RTs in bi-cephalic montage.	n.a.
Jung et al. (2011)	1 mA	C-tDCS (LH, Broadmann area 45) Electrodes: 6x6 cm Reference/anode: contralateral supraorbital	ABA design (1 phase only)	-	20 min	5	Online	Increased aphasia quotient	n.a.
Kang et al. (2011)	2 mA	C-tDCS, S-tDCS (RH, F8 of 10-20 system) Electrodes: 5x5cm Reference/anode: left supraorbital	Crossover, 2 phases	1 week	20 min	5	Online	Improved accuracy after C-tDCS	n.a.
Saidmanesh et al. (2012)	2 mA	A-tDCS, S-tDCS (left DLPFC) Electrode:5x5cm Reference/cathode: right DLPFC	Between groups	-	20 min	10	Online	Improved naming and aphasia quotient after A-tDCS	n.a.
Marangolo et al. 2013a	1mA	A-tDCS (Wernicke and Broca), S-tDCS (Broca) Electrode: 5x7 cm Reference/cathode: contralateral frontopolar	Crossover, 2 phases	6 days	20 min	5	Online	Improved accuracy after A-tDCS	After 1 and 4 weeks
Fiori et al. (2011)	1 mA	A-tDCS, S-tDCS (left Wernicke) Electrodes: 5x7cm Reference/cathode: contralateral fronto-polar	Crossover, 2 phases	1 week	20 min	5	Online	Improved accuracy and RTs in A-tDCS	After 3 weeks in two subjects
Fridriksson et al. (2011)	1 mA	A-tDCS, S-tDCS (LH, individually determined) Electrode: n.a. Reference/cathode: right forehead	Crossover, 2 phases	3 weeks	20 min	5	Online	Improved RTs after A-tDCS	After 3 weeks

Table 2.2. Patient characteristics, tasks used during treatment and outcome measures

Study (language)	N° of subjects	Time post-onset	Lesion location	Aphasia type(s) / functional locus of impairment	Location(s) stimulated	Therapy task	Outcome measures
Baker et al. (2010) (English)	10	~1-20 years	Left temporoparietal (n = 4); frontotemporal (n = 3); frontotemporoparietal (n = 1); temporoparietooccipital (n = 1); MCA territory, medial frontal lobe, and basal ganglia (n = 1).	Anomic aphasia (n = 6), Broca's aphasia (n = 4)	Individually tailored, based on fMRI data: premotor cortex (n = 5), dorsolateral prefrontal cortex (n = 2), anterior prefrontal cortex (n=1), pars triangularis (n=1), pars opercularis (n=1).	Picture-word matching task (items = single words, nouns).	Accuracy of treated and untreated nouns, assessment before the treatment, after the 5th session, after 1 week.
Monti et al. (2008) (Italian)	8	2-8 years	Left frontal cortical/subcortical (n = 3); frontoparietal cortical/subcortical (n = 2); frontotemporoparietal cortical/subcortical (n = 2); frontoparietal subcortical (n=1)	Broca's aphasia (n=4); global aphasia (n=4)	Broca's area; occipital lobe used as control site.	No behavioral treatment.	Accuracy and response times, assessed before and after stimulation.
Vines et al. (2011) (English, one Russian-English)	6	>1 year	Left frontal lobe	Broca's Aphasia	Right posterior Inferior Frontal Gyrus (2.5cm posterior to electrode F8 of 10-20 EEG system).	Melodic Intonation Therapy (Albert et al. 1973) (level adjusted based on individual skills).	Verbal fluency tasks, picture description and picture naming. Assessed before and after each stimulation session.
Flöel et al. (2011)	12		Left frontal, temporal, parietal and occipital lesions. No lesions in right hemisphere.	n.a.	Right temporo-parietal cortex (Talairach coordinates 57/-30/3)	Computerized naming task (items = single words, nouns).	Naming trained objects across 4 consecutive probes (1 point per correct response).
Lee et al. (2013) (Korean)	11	8-180 months	Inferior left MCA (n=9); Left basal ganglia (n=2)	Broca's aphasia (n=4), Transcortical motor aphasia (n=2), Anomic aphasia (n=5)	Left IFG (in monocephalic condition), and left and right IFG (in bicephalic condition).	Picture naming and reading short paragraphs (items = single words and short paragraphs).	Response time and accuracy in a picture naming test and picture description. Assessed before and after each session.

Study (language)	N° of subjects	Time post-onset	Lesion location	Aphasia type(s) / functional locus of impairment	Location(s) stimulated	Therapy task	Outcome measures
Jung et al. (2011) (Korean)	37	<30 days - >90 days	Broca's area, Wernicke's area, arcuate fasciculus, insula.	Fluent (n=10), non-fluent (=26)	Brodmann area 45.	Individually tailored.	Aphasia quotient and Korean Western Aphasia Battery.
Fiori et al. (2011) (Italian)	3	~2-5 years	Left frontoparietal subcortical (n = 1); frontoparietal cortical/subcortical (n = 1); frontotemporoparietal cortical/subcortical (n = 1).	Non-fluent (mild to severe) aphasia. Impaired phonological output lexicon	Wernicke's area	Object naming (items = single words, nouns).	Naming accuracy and response times. Assessment before and after treatment (1 week and 3 weeks after) stimulation.
Kang et al. (2011) (Korean)	10	6-168 months	Frontoparietotemporal (n=2), frontotemporal (n=3), frontal (n=1), subcortical (n=3), temporoparietal (n=1)	Global (n=3), Broca's (n=4), anomic (=2), transcortical motor (n=1)	Right Broca's homologue area (F8).	Cued naming, word-picture matching and answering yes/no questions about target words (items = single words, nouns).	Response accuracy and RTs before treatment and after the 5th day of treatment.
Saidmanesh et al. (2012) (Persian)	20	≈60 months	Anteroposterior (n=9); posterior (n=11)	Non-fluent aphasia	Left dorsolateral prefrontal cortex.	Computerized naming task (items = single words, nouns).	Picture naming and evaluation of working memory and aphasia quotient. Assessed before and after treatment.
Marangolo et al. (2013a) (Italian)	7	7 months-7 years	Left temporal (n=1), left frontotemporal (n=2), left insula (n=1), left frontotemporoparietal (n=2), subcortical (n=1)	Non-fluent aphasia	Wernicke's area, Broca's area.	Action naming (items = single words, verbs).	Accuracy on an action naming task. Assessed before and after treatment, on the fifth day, 1 week and 4 weeks after treatment.
Fridriksson et al. (2011) (English)	8	10-150 months	Posterior cortical or subcortical	Fluent aphasia	Left posterior cortex (individually tailored based on fMRI data from an overt picture-naming task).	Spoken word-picture matching task (items = single words, nouns).	Response times. Assessment before, immediately after and 3 weeks after the stimulation.

2.4 Methodological issues

The main methodological issues that arise from a review of the studies involving the use of tDCS in aphasia rehabilitation concern stimulation parameters, the characteristics of the behavioral treatment associated to tDCS, and the characteristics of the participants. For each of these, a number of variables may significantly affect the outcome of stimulation. Some issues can be discussed with reasonable confidence, based on already available data from rehabilitation studies and from studies on healthy subjects. Discussion of other dimensions, such as polarization (A-tDCS vs C-tDCS) in relation to lesion type, montage, and models of current distribution in damaged brains, must be more tentative, as relatively few elements are available to discern merits and flaws.

2.4.1 Stimulation parameters

As noted in the previous section, studies vary in their choice of stimulation intensity (1 mA, 2 mA), electrode montage and polarity (ipsilateral anodal/cathodal, contralateral anodal/cathodal or bi-cephalic anodal and cathodal modulation), duration of each session (between 10 and 20 min) and frequency of stimulation sessions (intersession and interphase intervals).

2.4.1.1 Stimulation intensity

Stimulation intensities of 1 mA (Baker et al., 2010; Fiori et al., 2011; Fridriksson et al., 2011; Jung et al., 2011; Marangolo et al., 2013a) or 2 mA (Kang et al., 2011; Lee et al., 2013; Monti et al., 2008; Saidmanesh et al., 2012) were typically used, and in most cases current density varied between .029 and .08 mA/cm2. Higher current density might yield larger effects, but might also influence activity in regions deeper than those intended to be targeted by treatment. Beyond these considerations, the main limitation in applying larger currents is safety: a stimulation

intensity of 2mA is more likely to cause skin burns, especially in treatment protocols that include multiple sessions (Palm et al., 2008).

In addition, even though the evidence is contradictory, higher stimulation intensities may interfere with double blinding. O'Connell et al. (2012) reported that following 20 min of 2 mA stimulation, participants guessed with above chance accuracy at whether they had received real or sham stimulation, and assessors also gave above chance judgments, guessing based on skin redness. Brunoni et al. (2014) argued that above-chance judgments were associated with perception of clinical response and not with skin sensations or redness due to stimulation, and hypothesized that lower blinding accuracy in O'Connell et al. (2012) was due to the relatively shorter ramp-up period (5 sec, compared to 30 sec used in Brunoni et al., 2014). This issue needs to be resolved to inform the use of stimulation intensities above 1 mA. Given that this was the case in Monti et al. (2008), Kang et al. (2011), Vines et al. (2011), Saidmanesh et al. (2012) and Lee et al. (2013), the results of these studies should be considered carefully. As a short aside, none of the studies of aphasia rehabilitation using tDCS reports a particular procedure to guarantee successful blinding, such as questioning the patient after the end of the treatment or keeping a record of the reported sensations, as in Fertonani, et al. (2010). This procedure would be particularly relevant in within-subject studies, in which the same participant receives both tDCS and sham.

2.4.1.2 Electrode montage and polarity

Whereas perilesional A-tDCS was found to be effective in several studies (Baker et al., 2010; Fiori et al., 2011; Fridriksson et al., 2011; Lee et al., 2013; Marangolo et al., 2013a; Saidmanesh et al., 2012), another study failed to report increased performance accuracy after A-tDCS (Monti et al., 2008). This discrepancy may be due to a variety of factors: the number of tDCS sessions (1

vs 10 in Baker et al. 2010), the duration of stimulation (10 vs 20 min, respectively), the relationship between neuromodulation and speech therapy (offline vs online, respectively), or the anatomy of stimulated areas (lesioned in Monti et al. 2008 and intact in Baker et al., 2010).

C-tDCS over lesioned LH areas improved naming accuracy, whereas no effect was observed after C-tDCS over unimpaired LH areas remote from the lesion (Monti et al., 2008). Jung et al. (2011) also used C- tDCS over LH areas that were intact in some patients and lesioned in others. The unexpected facilitatory effect after C-tDCS (Monti et al., 2008) was attributed to a tDCS-induced release from ipsilesional cortical inhibition (Bütefisch, Kleiser, & Seitz, 2006; Lang et al., 2004; Shimizu et al., 2002), which may have increased activity in stimulated areas. Overall, current evidence supports the use of perilesional A-tDCS, but indicates that C-tDCS over lesioned (Monti et al., 2008) or peri-lesional areas (Jung et al., 2011) may also be effective. Findings are in line with the observation that restoring normal patterns of LH activation is associated with the best recovery (Saur et al., 2006), and with neuroimaging studies showing a positive correlation between perilesional activation and recovery (Heiss et al., 1997; Rosen et al., 2000). The data obtained with A-tDCS by Monti et al. (2008) and with C-tDCS by both Monti et al. (2008) and Jung et al. (2011) provide preliminary indication that decisions on polarity within the LH may have to take lesion site into account: A-tDCS might be less effective when administered directly over the lesion, and C-tDCS might yield a positive outcome even when administered over the lesion site. Further advances on this issue clearly depend on overcoming the limitations of the anodal-cathodal model, given that in fact, cathodal stimulation does not always yield inhibition and anodal stimulation does not always result in excitation (e.g., Monte-Silva et al., 2013).

Choosing between stimulation approaches may not be an all-or-none decision. Specifically, as regards the role of LH vs RH activation, it should be kept in mind that the functional effect of RH activity could differ across subjects – it might be compensatory in some cases, and maladaptive in others. Inhibiting the RH (as in the bi-cephalic montage) might be useless when the LH has recovered, harmful when RH activity is compensatory, and useful only when it is maladaptive. Among other factors, the role of RH activation may vary depending on lesion size (Kertesz et al., 1979): in the event of extensive LH damage, the RH might play some (albeit very partial) compensatory role, and increasing its activation may actually improve performance accuracy in language tasks (Vines et al., 2011).

A bi-cephalic approach (A-tDCS to perilesional LH areas together with C-tDCS to RH areas) can potentially stimulate the perilesional cortex while decreasing transcallosal inhibition. Four studies tested the effects of different montages on motor recovery in stroke patients (Fusco et al., 2013; Lee et al., 2013; Lindenberg et al., 2010) and healthy individuals (Vines, Cerruti, & Schlaug, 2008). Fusco et al. (2013) found that A-tDCS was the most effective, followed by C-tDCS, whereas bicephalic (anodal and cathodal) stimulation produced the least satisfactory results. Other authors report more positive outcomes from the bi-cephalic montage (Lee et al., 2013; Lindenberg et al., 2010; Vines et al., 2008), consistent with models of interhemispheric competition (Bütefisch et al., 2008; Murase et al., 2004). A disadvantage of this montage is that it does not allow to determine which electrode drives the detected effects, or if both electrodes do so. This issue should be considered in studies wishing to draw inferences on the role of a specific brain area, but is less relevant for studies whose main aim is to establish which approach ensures the largest effects.

Ideally, montage and polarity should be chosen on a single patient basis. Pioneering studies in this respect were conducted by Baker et al. (2010) and Fridriksson et al. (2011), who determined montages on an individual basis, with reference to preliminary fMRI naming sessions aimed at localizing in each patient the areas of greater LH activation associated to correct responses. Even though this is a promising research avenue, it is not yet possible to reliably establish a clear cut quantitative relation between the activation detected by fMRI and the underlying brain activity (Logothetis & Wandell, 2004). Until other techniques are available, which allow reliable testing of the optimal montage on an individual basis, decisions should be based on current evidence, suggesting that A-tDCS and perhaps C-tDCS (Monti et al., 2008) to the LH are both adequate choices, and that bi-cephalic montages may have an added advantage (e.g., Lee et al., 2013; Marangolo et al., 2013a). Furthermore, if treatment task aims specifically at recruiting RH areas, A-tDCS of the RH can be appropriate (Vines et al., 2011).

Finally, a practical consideration must be made regarding the choice of electrode placement, when targeting specific brain areas. Most studies rely on the correspondence between EEG scalp coordinates and cortical areas (Okamoto et al., 2004) or between the subject's MRI scan and magnetic tracking of the scalp (www.mricro.com/mrireg.html). However, it has been suggested that individual differences in head and brain topographies may result in different current distribution, despite similar electrode placement (Datta, Truong, Minhas, Parra, & Bikson, 2012). Individualized modelling of current distribution may be required to bypass this issue (Datta et al., 2012), which may be partially responsible for the inter-subject variability of the effects of stimulation.

2.4.1.3 Session duration, frequency and interphase interval

We now turn to time-related stimulation parameters. The ideal duration of stimulation is a matter of debate. In almost all studies reviewed here, tDCS lasted 20 min. Only Monti et al. (2008) applied A-tDCS for 10 min. The observation that they failed to find beneficial effects might indicate that in aphasia a 20-min A-tDCS is preferable to a shorter stimulation. Further studies have shown that protocols lasting more than 20 min are safe. Stimulating up to 50 min did not result in either cognitive or emotional disturbances in healthy subjects (E.M.W., as cited in Nitsche et al., 2008). However, such long stimulation should be applied cautiously, since it could engage neurophysiological homeostasis. If the physiological range of cortical activity is exceeded, neurons may adapt and therefore reduce their activation level (Miniussi, Harris, & Ruzzoli, 2013; Siebner et al., 2004). A long-term effect of prolonged stimulation sessions might be the unintended downregulation of the network involved in the task, and ultimately a decrease in performance. In the healthy brain, A-tDCS for 13 min increased motor excitability for up to 90 min (Nitsche & Paulus, 2001), but stimulation for 26 min decreased motor excitability (Monte-Silva et al., 2013). Motivated decisions on this issue will have to be based on a clearer understanding of how quickly neurophysiological homeostasis happens.

Previous research on C-tDCS in healthy participants (Monte-Silva, Kuo, Liebtanz, Paulus & Nitsche, 2010) has shown that the inter-stimulation interval influences outcome. In short-interval protocols (interval: up to 20 min), each stimulation is administered during the aftereffect period of the previous stimulation, potentiating its effects. In long interval protocols (intervals: 3 h and 24 h), stimulation is delivered when the aftereffect of previous stimulations has subsided. When two C-tDCS sessions are applied with a 24-h interval, the first produces the expected inhibitory effect, but the second produces no effect for the first 60 min after stimulation. The inhibitory

effect of the second session is observable only after 120 min. When A-tDCS is administered twice with a 24-h interval, its initial excitatory effect converts into inhibition (Monte-Silva et al., 2013). These timing constraints related to session duration and intersession interval are obviously at odds with the positive findings reported in the aphasia literature, where stimulation is typically applied for 20 min, on a daily basis. Perhaps, the timing of tDCS aftereffects differs between healthy and lesioned brains. This could be because the current propagates differently in intact versus damaged neural tissue (e.g., due to different biochemical environments in spared and lesioned areas). Also in this case, a better understanding of the mechanisms underlying observed differences will lead to establish the best frequency of tDCS sessions and to optimize treatment protocols.

The interphase interval is particularly relevant for studies using a crossover design (Table 2.1), in which the participant receives treatment under at least two stimulation conditions, separated by a "washout" period. This period should be long enough that the effects of the first treatment phase do not carry over to the second. Based on the duration of after-effects reported in earlier studies (Fregni et al., 2005; Nitsche et al., 2003; Nitsche & Paulus, 2000, 2001; Nitsche et al., 2005), Nitsche et al. (2008, p. 218) state that "For 4 sec of tDCS […] a break of 10 sec between each period of stimulation is sufficient. For tDCS durations that produce short-lasting (namely, for about 10 min) after-effects, a 1-h break between stimulation sessions is sufficient. For tDCS durations resulting in long-lasting after-effects (1 h or more), an intersession interval of 48 h to 1 week has been suggested". The duration of the after-effects of protocols based on daily sessions for 5-10 days (as is the case in most studies on aphasia) is still unclear. In aphasia rehabilitation there is evidence that treatment effects can be sustained up to four weeks after the end of treatment (Marangolo et al., 2013a). Needless to say, the goal of rehabilitation research is to

achieve long-lasting effects, and to understand the mechanisms that promote them. In this context, after each treatment phase it is necessary to distinguish gains that are stable during washout and therefore indicate that treatment was effective, from continued improvement during the washout phase, which might indicate that stimulation is still influencing brain excitability. In crossover designs, a stable behavioral baseline must be documented before a new treatment phase is started. Starting a second phase while the subject is still improving after the first phase would not allow to establish if the improvement at the end of the second phase corresponds to the continuing effects of the first phase, or to effects specifically induced by the second phase.

Findings on stimulation duration, frequency and interphase interval are difficult to manage, as in most cases they were obtained from healthy individuals, and therefore cannot be transposed as such to aphasia rehabilitation. Based on available reports, 20-min tDCS, over 5-10 sessions with a daily frequency and at least a 1-week washout period, seem suitable choices for an aphasic population. In crossover studies, the stability of behavioral parameters must be documented before starting a new treatment phase.

2.4.2 Characteristics of the behavioral treatment

Two characteristics of the behavioral treatment may interact with the effects of tDCS: the modality of concurrent speech therapy (online, offline) and the task used during therapy.

2.4.2.1 Online versus offline treatment

In aphasia recovery, tDCS seems to positively influence at least two parameters: amount and speed of learning. Greater ease of learning has been attributed to a tDCS-induced, increased secretion of BDNF (Brain-Derived Neurotrophic Factor, a protein essential for new learning), which mediates LTP (Long-Term Potentiation) via the activity of NMDA and tyrosine-kinase B

receptors (Fritsch et al., 2010). In humans, it has been hypothesized (Schjetnan et al., 2013; p.4) that "the production and release of neural growth factors after stroke generate a permissive environment for neuronal regeneration in the perilesional cortex. These proteins may be responsible for a large part of synaptic modifications that facilitate recovery after stroke". In other words, tDCS would reinstate a pre-morbid state of learning, by positively conditioning the state of activation of neurons recruited by therapeutic procedures, conducive to recovery. The success of a rehabilitation protocol would depend on the neuronal state induced by tDCS (Silvanto, Muggleton, & Walsh, 2008). Furthermore, the increases in synaptic activity induced by tDCS administered to mice outlast the duration of stimulation only when stimulation is paired with ongoing synaptic activation (Fritsch et al., 2010). At the behavioral level, this translates into the use of a behavioral training task, that can be administered concurrently with stimulation (online) or precede it (offline).

Online tDCS (i.e., during a speech therapy session) can potentially optimize the effects of language stimulation during speech/language therapy sessions, whereas offline tDCS (i.e., before speech therapy) may prime the language system in preparation for the task used during treatment. Most patient studies (e.g., Baker et al., 2010; Marangolo et al., 2013a) adopted the online approach. The study by Monti et al. (2008) and investigations on healthy subjects also included offline tDCS (Cattaneo et al., 2011; Jeon & Han, 2012). A comparative study of online versus offline stimulation on healthy participants showed that A-tDCS decreased vocal response times in young subjects in both conditions, but that only online tDCS reduced vocal response times in elderly participants (Fertonani, Brambilla, Cotelli, & Miniussi, 2013). Until a similar study is conducted with aphasic subjects, the absence of effects of offline peri-lesional A-tDCS in Monti et al. (2008) suggests that online tDCS is preferable in elderly persons with aphasia.

2.4.2.2 The selection of the task to be used during the behavioral treatment

In healthy subjects Antal et al. (2004) showed that the same stimulation condition (C-tDCS to the visual cortex) has opposing effects on the perception of coherent movement, depending on the characteristics of the stimuli presented during stimulation. In aphasic participants, Marangolo et al. (2013a) showed that action naming improved after A-tDCS to Broca's, but not Wernicke's area. These studies stress that selecting the correct pairing between stimulation site and treatment task may crucially constrain the outcome. The goals of aphasia therapy may be better achieved if tDCS is delivered to an area putatively involved in the task at hand, as this ensures that electrical stimulation is paired with ongoing synaptic activation, a seemingly necessary factor for lasting effects (Fritsch et al., 2010). Previous research on the effects of speech therapy supports the view that treatment tailored to address each individual's level of language impairment is more effective than therapy focused on language processing levels unrelated to the patient's difficulties (Jacquemot, Dupoux, Robotham, & Bachoud-Lévi, 2012). This should be taken into account also in neurostimulation research. Support for the relevance of the relation between task-dependent effects and stimulation site also comes from the observation that A-tDCS to the RH was effective when associated with MIT (Vines et al., 2011). As for the task to be used during treatment, researchers have privileged word recognition (e.g., Baker et al., 2010; Fridriksson et al., 2011) and word retrieval (e.g., Fiori et al., 2011; Kang et al., 2011), in the context of object-picture matching, object naming or action naming exercises.

A careful choice of the task to be administered during treatment is implicit in a recent hypothesis on the implications of tDCS's state dependency. Miniussi et al. (2013) hypothesize that tDCS effects may result from changes in the amount of noise and in the signal-to-noise ratio (i.e., relevant activation vs irrelevant activation) in the stimulated brain network. A-tDCS decreases

membrane potential both in neuronal populations that are relevant to the task and in neuronal assemblies that are not involved in it (see Figure 2.1). This will cause the firing of neurons that are already close to threshold, which are also likely to be relevant to the task at hand. These authors propose a model in which "easy" tasks (such as the "high coherence" condition in Figure 2.1) yield activation that is much closer to threshold in task-relevant than in task-irrelevant neural populations. In such cases the signal-to-noise ratio is high, because the task is likely to involve a consolidated neural network, and therefore A-tDCS is more likely to cause firing only in task-relevant neural populations. With increasing practice, the signal-to-noise ratio increases, and performance improves. This model is consistent with data showing decreased brain activation in relation to task practice (Basso et al., 2013; Petrini et al., 2011). Conversely, in a more difficult task (such as the "no coherence" condition in Figure 2.1) the level of noise is higher, as the network is not consolidated. In this case, A-tDCS might increase both noise and signal to a similar extent, thus preventing facilitation.

Decreases in firing rate due to C-tDCS will also have task-dependent behavioral consequences: in an easy task, no particular benefit accrues from decreasing general noise. Thus, performance accuracy may remain unchanged if the signal is still strong enough to reach threshold, or may even decrease, because in this case both task-relevant and task-irrelevant activation are pushed farther away from threshold. In a difficult task, C-tDCS may filter irrelevant activation and hence increase the signal-to-noise ratio, resulting in performance facilitation. Results consistent with this possibility were reported by Dockery, Hueckel-Weng, Birbaumer, and Plewnia (2009): C-tDCS facilitated early (and more difficult), and not later (and easier) stages of learning; whereas, A-tDCS facilitated later and not earlier stages of learning during a task that required planning ability.

Figure 2.1. Effects of neurostimulation in relation to the characteristics of the behavioral task

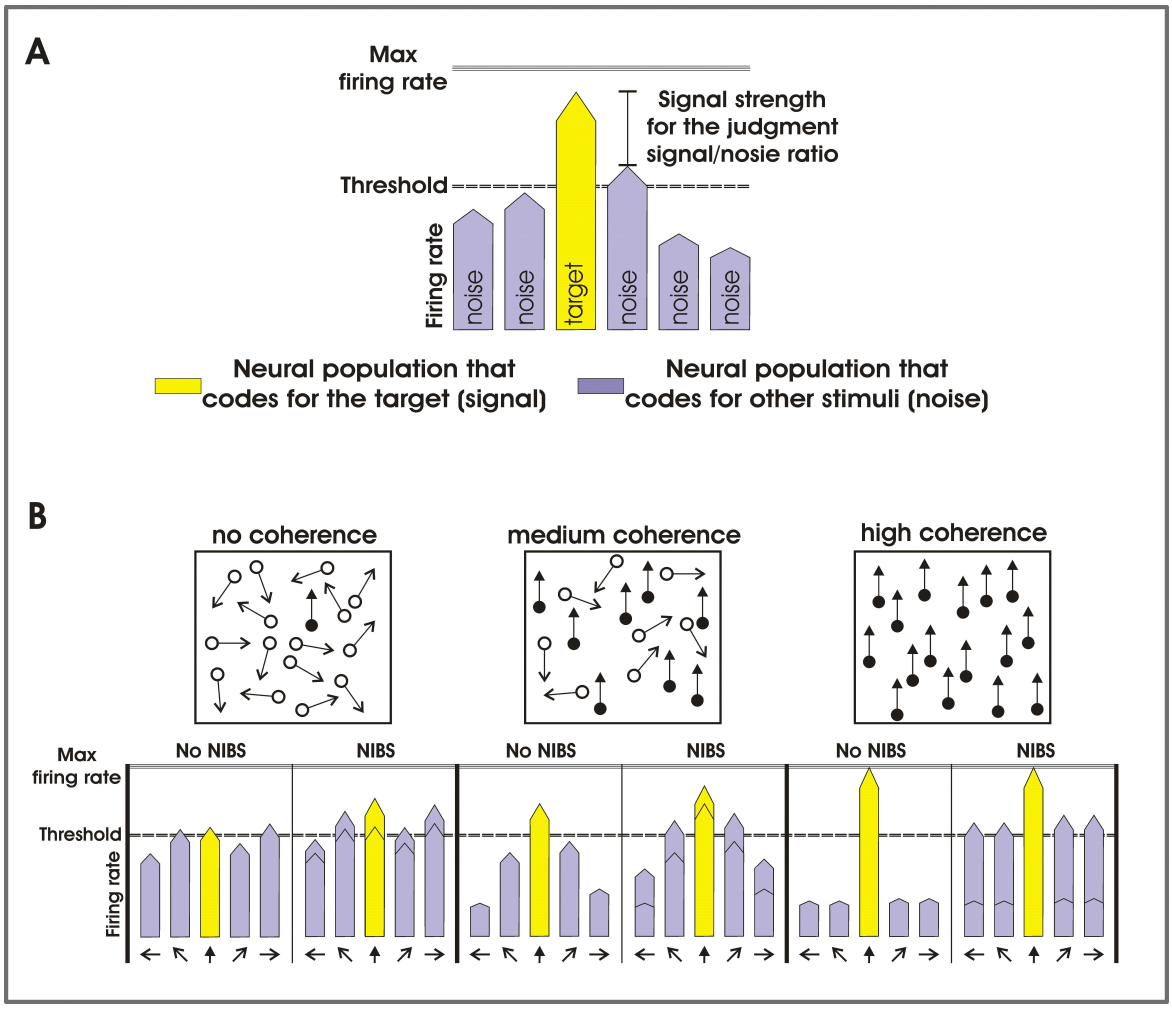

Figure 2.1. Vertical bars indicate the firing rate of neural populations affected by stimulation. Panel A illustrates the relation between target (in yellow) and non-target signals (in purple). Panel B illustrates how target and non-target signals change when non-invasive brain stimulation (NIBS) is administered with a difficult ("no coherence"), medium difficulty ("medium coherence") and easy task ("high coherence"). From Miniussi et al. (2013). Reprinted with permission.

In summary, A-tDCS may be more suitable if delivered concurrently to easy tasks, and C-tDCS may be more appropriate when the task is difficult. In speech therapy, task difficulty may be adjusted by defining a cueing strategy that provides greater or lesser support for naming. Increasing cues are used more frequently in aphasia literature. If the patient fails to name, s/he is

given incremental cues to facilitate target retrieval (e.g., initial sound, then initial syllable, then the first two syllables, then the entire word). In decreasing cue therapies, the cue is provided before the participant produces a response attempt, thus ensuring success in naming even at the early stages of treatment (Abel, Schultz, Radermacher, Wilmes & Huber, 2005). Both strategies seem to effectively improve naming of both nouns and verbs (Conroy, Sage, & Lambon Ralph, 2009a). Furthermore, task difficulty also depends on the severity of the language deficit, and increasing or decreasing cues may be more appropriate depending on aphasia severity and individual tolerance to frustration. Even though there is a lack of experimental studies to support the hypothesis that the mechanisms described by Miniussi et al. (2013) apply to the lesioned brain, it may be relevant to keep in mind this possibility (together with the severity of the language deficit and the polarity of stimulation) while defining cueing strategy.

Current knowledge on the effects of tDCS cannot yet significantly constrain the course of action during aphasia rehabilitation. For the time being, if extant views on the effects of tDCS are accepted, the best strategy is to use tDCS to create the neural prerequisites for change, and to do so by administering speech therapy online during a task that (a) engages the stimulated network and (b) has the appropriate difficulty level to optimize the nature of stimulation effects. In addition, the behavioral task should be designed so as to address the functional level of impairment responsible for the aphasic symptoms (see Section 4.3.3).

2.4.3 Patient characteristics

Patient inclusion criteria in tDCS research have been mainly informed by safety issues. General safety considerations in tDCS research have been discussed in detail by Nitsche et al. (2008). Here we focus on some specific characteristics of stroke patients, and discuss some implications of the most frequently adopted recruitment strategies for investigations on aphasia recovery.

2.4.3.1 Lesion size and location

Regarding the characteristics of the lesion, the most frequent inclusion criterion was the occurrence of a single LH stroke (Baker et al., 2010; Fiori et al., 2011; Kang et al., 2011; Lee et al., 2013; Marangolo et al., 2013a). In two studies, subjects with lesions encompassing the frontal lobe (Vines et al., 2011) or restricted to posterior regions (Fridriksson et al., 2011) were recruited.

The presence of vascular brain damage mostly constrains the choice of electrode montage, whose underlying criteria will have to be constantly revised in the context of models of disrupted current distribution (Datta, Baker, Bikson, & Fridriksson, 2011). According to Hamilton et al. (2011), polarization should be decided in relation to lesion type. As regards mono-cephalic montages, they propose a three-level hierarchy. In the case of small lesions sparing language areas, perilesional A-tDCS should facilitate recovery. When damage is severe and affects linguistic abilities, recruitment of perilesional areas by A-tDCS and concurrent speech language therapy should yield good recovery in most cases. Finally, if the LH is massively lesioned, the RH could take over language functions via the recruitment of homologous regions, or could further disrupt spared linguistic abilities via transcallosal inhibition. In this latter case, LH stimulation is not expected to be advantageous, as a large lesion might perturb the distribution of current density and result in unpredictable responses from damaged intracortical connections. Two options are open in these patients, both relying on RH stimulation: A-tDCS, if the RH appears to have taken up linguistic functions, or C-tDCS, if maladaptive synaptic changes emerge or if RH-driven inhibition of the LH seems to hinder spared linguistic processes in the damaged hemisphere.

Available evidence from aphasia treatment with tDCS does not allow to assess if the strategies defined by Hamilton et al. (2011) actually result in increased efficacy of tDCS, but they at least set the path for a potential additional strategy. In some studies (Jung et al., 2011; Monti et al. 2008) C-tDCS was administered over LH areas, which were at least partially (Jung et al., 2011) or mostly damaged (Monti et al., 2008), with positive results. Even though the mechanisms underlying improvement associated with C-tDCS over the LH are not well understood, further research may aim to address this issue. Detailed information about each participant's lesion was provided in four studies (Baker et al., 2010; Fiori et al., 2011; Kang et al., 2011; Marangolo et al., 2013a). However, the main difficulty in analyzing the relation between lesion characteristics and stimulation site is that individual outcomes (including statistical analysis) were not reported on, with the exception of Marangolo et al. (2013a). Future studies will have to address the relation between lesion size/location/site and polarity of stimulation. For the moment, in order to deliver the appropriate type of stimulation to brain areas active during adaptive and maladaptive function, individual pre-treatment fMRI naming data could be used (e.g., Fridriksson et al., 2011). This would allow to by-pass concerns related to lesion size and location, even though it would still leave open the meaning (excitatory vs inhibitory, adaptive vs maladaptive) of observed activations. At any rate, if fMRI is to be used as the sole determiner of electrode positioning, measures will have to be taken in order to ensure reliable results. This may be achieved by running multiple scans in each case, thereby ensuring that observed activations correspond to the network supporting correct language performance (Kurland et al., 2004), or by substantially increasing the number of items used in a single scan. It is likely that the choice between these two strategies will depend on the patient, given that not all aphasic speakers are able to complete long testing protocols.

Another issue related to the choice of stimulation site concerns the potential anatomical constraints of tDCS. At the moment there is no indication on whether certain brain areas are more responsive to neurostimulation than others. In addition to relying on the careful analysis of the efficacy of tDCS in subjects with lesions to various LH regions, answering this question will require an increase in spatial resolution of the technique. The electrodes most frequently used in aphasia rehabilitation research cover large areas (35 cm2). In order to better assess the effectiveness of stimulation to specific brain areas, high-density tDCS is required, which can be achieved by using smaller electrodes, in configurations that yield more focal stimulation (Datta et al., 2009). Furthermore, the model of current distribution used to predict which brain areas receive the current delivered at the scalp should be developed so as to take account of the presence of lesioned tissue (Datta et al., 2011).

2.4.3.2 Time post onset

There is general agreement that spontaneous recovery takes place in the first months post-onset (see Hamilton et al., 2011). A recent study on rats found greater improvement when tDCS was applied 1 week than 1 day after stroke onset (Yoon, Oh, & Kim, 2012). Even though there is no evidence in humans, this preliminary observation could indicate that A-tDCS in post-acute stroke enhances neural reorganization by inducing synaptic plasticity. Stimulating after this initial period (i.e., after damage has 'stabilized' and the linguistic system has been partially reorganized) would thus appear to be the optimal strategy. However, current knowledge does not allow clear predictions on the effects of tDCS with relation to time post-onset in humans. With the exception of Jung et al. (2011), whose subjects were treated at least 60 days after stroke onset, studies reviewed here enrolled patients who were at least 6 months post-onset.

This criterion for subject selection has two justifications: first, choosing participants in the sub-acute stage could hinder the discrimination between treatment effects and spontaneous recovery; second, since C-tDCS is considered as a potential treatment for post-stroke epilepsy (Fregni et al., 2006), it is not possible to exclude a priori that A-tDCS might increase the risk of epileptic seizures in these patients. Considering that seizure risk is higher in the first year post-onset and is influenced by stroke type, size, location and severity (it is higher following large, anterior, hemorrhagic lesions), and by the occurrence of post-stroke complications (Burn et al., 1997), it is wise to avoid using tDCS in this time window, and in patients showing these characteristics. The lack of strict safety criteria, especially with relation to the clinical populations that can be treated with tDCS, is the main limitation for extending its use to acute patients.

2.4.3.3 The functional level of impairment

Even in subjects with putatively homogeneous cognitive profiles, such as healthy individuals, stimulation effects show a large inter-subject variability (Horvath et al., 2014). In addition, whether there is also intra-subject variability in the effects of stimulation on healthy individuals is a matter of debate, and the few existing data are contradictory (Alonzo, Brassil, Taylor, Martin, & Loo, 2012; Monte-Silva et al., 2013). Be this as it may, the issue of inter-subject variability, particularly the variability linked to individual differences in language deficits, is extremely relevant in studies with aphasic speakers (see next paragraphs).

In many studies the only inclusion criterion was the presence of aphasia (Baker et al. 2010; Jung et al., 2011; Kang et al., 2011; Lee et al., 2013). In some cases, participants were recruited based on the presence of non-fluent (Fiori et al., 2011; Marangolo et al., 2013a; Monti et al., 2008; Saidmanesh et al., 2012; Vines et al., 2011) or fluent (Fridriksson et al., 2011) aphasia. Only two studies (Fiori et al., 2008; Marangolo et al., 2013a) focused treatment on items that patients had

comprehended but failed to name, therefore somewhat restricting enrolment to subjects whose main language deficit involved post-semantic processes. Regardless of recruitment criterion, in all studies tDCS-based treatment focused on anomia. This choice is fully understandable, considering that anomia is the most frequent aphasic sign (Williams & Canter, 1982), and that it occurs in chronic aphasias, irrespective of clinical type (Kertesz & McCabe, 1977). However, if one considers the level of detail reached by studies on language disorders, this approach is less than optimal.

It has been known for quite some time that in naming tasks a failure to produce the target word may result from disparate language deficits – the loss of the corresponding meaning; the unavailability of the target lexical form in the face of spared meaning; the retrieval of insufficient phonological or orthographic information to support spoken or written output (e.g., Gainotti, Silveri, Villa, & Miceli, 1986; Howard & Orchard-Lisle, 1984; Kay & Ellis, 1987). A similar variety of disorders underlies semantic errors (e.g., Caramazza & Hillis, 1990; Hillis, Rapp, Romani, & Caramazza, 1990). In addition, evidence has been provided that deficits arising at different functional levels are also associated with damage to distinct brain regions (Cloutman et al., 2009), and benefit from distinct behavioral treatments (Hillis, 1989). Failure to draw these basic distinctions when recruiting subjects for a tDCS study will inevitably lead to include in the same group subjects with heterogeneous language disorders, and therefore will prevent a fair evaluation and a better understanding of the limitations and merits of tDCS.

As a consequence of these considerations, the effects of tDCS in individuals with aphasia are better investigated in the context of within-subject (e.g., crossover) designs, as in these cases the same participant, whose language impairment can be accurately identified by reference to current models of speech processing, is involved in different stimulation conditions across several

treatment phases. Within-subject designs are preferable to between-subject (e.g., case-control) designs, in which different stimulation conditions are applied to distinct groups of participants. In this latter case, the substantial qualitative and quantitative variability of language impairments affecting participants in the two or more experimental groups would not ensure comparability of results across cognitively homogeneous samples. Obviously, procedures to ensure successful blinding would be critical in these studies (see Section 4.1.1.).

Ideally, within-subject studies should report on the outcome of each participant, together with detailed information on each patient's lesion site/size and time post-onset. This single-case series methodology is certainly more time consuming, but may unveil consistencies that would otherwise be obscured by inter-subject variability. If this information is available, questions on individual factors that may constrain the effects of tDCS, at the functional level (e.g., whether certain cognitive deficits are more responsive to tDCS) or at the anatomical level (e.g., whether certain brain areas are more responsive to tDCS) will begin to receive principled answers.

2.5 Conclusions

A critical reading of the literature suggests that tDCS is effective, in spite of the variety of stimulation parameters, patient characteristics and associated behavioral treatments used in various studies. In the last years, a number of neurostimulation techniques has obtained FDA (Food and Drug Administration) approval for the treatment of specific conditions (George & Aston-Jones, 2009), but this has not yet been the case for tDCS. The current limitations to the clinical use of tDCS stem from a number of unsolved issues (both theoretical and practical), that must be dealt with in order to give healthcare providers explicit recommendations on how and when to use the technique, and to recommend its large-scale clinical use.

Some questions will find answers from experimental clinical studies. They concern, for example, identifying the combination of current intensity (1 mA vs 2 mA), duration of tDCS session (10, 13 or 20 min) and number of sessions (5, 10 or 20) likely to yield the best results. The procedure has proven to be safe, but strict and explicit guidelines for the use of tDCS will be crucial to inform studies of the effects of tDCS resulting from different stimulation parameters. Further research is also needed to verify if long-term effects (beyond 1month) are present and to identify possible detrimental outcomes. Available data suggest that perilesional, online A-tDCS can reduce language disorders in chronic aphasia, but whether or not these two dimensions interact with intensity, duration and number of tDCS sessions deserves more systematic investigation. Obtaining increasing amounts of data from stroke patients is critical, as it is still unclear whether the results of methodological studies with healthy individuals can be generalized to stroke patients. The same is true for research aiming to understand the mechanisms underlying tDCS-induced changes (Meinzer et al., 2013). In short, upcoming research studying tDCS with advanced neuroimaging techniques should include individuals with aphasia. This will, for instance, help clarify the relation between lesion site, size and recommended stimulation montage and polarity, and evaluate the recommendations provided by Hamilton et al. (2011).

Other issues will find a solution in (or will be greatly helped by) technical and theoretical progress. A critical prerequisite for delivering the most appropriate stimulation is to be able to define and circumscribe the to-be-stimulated area. Dedicated functional neuroimaging exams, possibly including Diffusion Tensor Imaging (DTI), can be of value. However, selective stimulation of a specific target area requires using smaller electrodes, which allow higher-density tDCS. Additionally, more detailed models of current distribution in damaged tissue are necessary (Datta et al., 2011).

Clear answers to all these questions will need time. Other issues, however, could be tackled already, simply by adopting a methodologically careful approach. To mention but an example, at this stage of tDCS use in aphasia rehabilitation, an effort should be made to understand if the technique is equally effective when targeting damage to different language mechanisms – e.g., "semantic" versus "lexical" anomia. Lack of detailed individual information makes it impossible to answer questions of this type on the basis of published studies, largely due to the failure to consider and manage the across-subject variability inherent in the selection criteria typically adopted. Applying knowledge from the cognitive neuroscience of language to studies of tDCS in aphasia recovery could improve our use of the technique. It would lead to administer detailed, model-driven assessment batteries, to draw detailed inferences on the functional deficit in each participant, to select participants with homogeneous functional lesions, to clearly identify the functional target of tDCS associated speech therapy, and to design treatment protocols that are putatively specific for each type of language deficit. If made available in published reports, along with neuroanatomic and neurofunctional data, this information will improve the interpretation of treatment outcomes.

The single-case series design has additional advantages. It decreases the effects of inter-subject variability, thereby allowing to compare data across studies in a principled manner. It allows determining whether each individual improves significantly – if tDCS is to be used in clinical practice, functionally relevant improvements should be observed at the single-subject level. If only some participants benefit from the technique, extensive information on each individual helps to find commonalities among subjects who improve and those who fail to do so, thereby identifying factors that may constrain the efficacy of tDCS, both at the functional level (e.g., whether some cognitive deficits are more likely than others to be ameliorated by tDCS) and at

the neural level (e.g., whether the integrity of specific brain areas is critical for the success of treatment, or whether stimulation to specific areas is particularly fruitful). At the same time, even if emphasis is placed on individual cases, the single-case series approach still permits to study tDCS effects in larger samples of cognitively homogeneous patients, as participants can be legitimately grouped post-hoc, based on the demonstrable homogeneity of their language deficits. It can lead to establish whether tDCS is not only safe but also effective, and to more accurately identify the aphasic subjects who are most likely to benefit from it. In short, this approach can eventually provide the information necessary to recommend, based on empirical results and on safe ethical grounds (Walsh, 2013), the largescale clinical use of tDCS, even in settings in which sophisticated technologies (e.g., fMRI) are not available.

CHAPTER 3

ERP signatures of repetition priming in spoken word production and the absence of tDCS-related enhancement[2]

Naming performance can be enhanced by repeated naming (repetition priming) and by transcranial direct current stimulation (tDCS). We examine the neurophysiological properties of repetition priming during naming, and assess whether tDCS can enhance naming performance over and above the effects of repetition priming. Participants named pictures of actions before, during and after a facilitation phase that entailed receiving either anodal tDCS over Broca's area or Sham stimulation during repeated action naming. To examine the effects of repetition priming and tDCS, we compared pre- and post- facilitation response times, as well as resting state electroencephalography (EEG) and Event Related Potentials (ERPs). Repetition speeded responses and attenuated the N400 amplitude for facilitated but not unfacilitated items. The Late Positive Component (LPC) was modulated by repetition for both sets of items. The N400 and LPC were modulated by the repetition lag and/or the number of repetitions. ERPs correlated with response latencies during the time-windows of the N400 and LPC. tDCS did not influence behavioral measures or ERP amplitudes. We conclude that the word repetition effect in overt production shares neurophysiological characteristics described in other language tasks. These may reflect enhanced implicit, task related processing and the influence of explicit, episodic memory. In comparison to behavioral priming, tDCS did not change naming latency.

[2] This chapter is currently under review in *Neuropsychologia*.

3.1 Introduction

Performance on tasks such as picture naming, word reading, and lexical decision is enhanced by previous exposure to target words (Tenpenny, 1995): participants produce faster and more accurate responses to repeated items. This effect is known as repetition priming, and reflects the change in lexical accessibility of a word due to its recent occurrence (van Petten, Kutas, Kluender, Mitchiner, & McIsaac, 1991). Although repetition priming has been investigated across several tasks, no study has described the neurophysiological characteristics of the word repetition effect in overt word production. Performance enhancement in several language tasks has also been observed after transcranial direct current stimulation (tDCS). Nonetheless, there is surprisingly little research with healthy individuals addressing changes in language production before and after tDCS. This is particularly relevant when trying to ascertain whether tDCS could provide additional performance enhancement when compared to behavioral facilitation techniques alone. In this study we used Event Related Potentials (ERPs) to examine the neurophysiological nature and timing of repetition priming effects during repeated naming attempts. Additionally, we examined the potential of tDCS to enhance the effects of repetition priming.

3.1.1 Naming and behavioral priming of the naming process

The Levelt, Roelofs and Meyer model (Levelt, Roelofs, & Meyer, 1999) asserts that picture naming requires sequential processing of at least the following stages: conceptual preparation (from picture to concept), lasting around 200ms; lemma retrieval (grammatical information), which lasts around 75ms; and form encoding, which includes phonological code retrieval (80ms), syllabification (20ms per phoneme or 50-55ms per syllable) and phonetic encoding (145ms) (Indefrey, 2011). Lexical retrieval (form encoding) has been argued to be influenced by

age of acquisition (Carrol & White, 1973) and word frequency (Oldfield & Wingfield, 1965). Late-acquired and less frequent words have longer naming latencies. The word repetition effect is larger in late-acquired words (Barry et al., 2001) and attenuated for high frequency words (Forster & Davis, 1984). The modulation of repetition priming by these properties of words has led researchers to state that the word repetition effect reflects facilitation of processing at the level of lexical retrieval (Barry et al. 2001).

Two accounts on the mechanisms of word retrieval are also relevant in the context of repetition priming. In one account (e.g., Jackson & Morton, 1984), word retrieval is thought to depend exclusively on access to abstract word representations (*pure abstractionist account*); repetition priming may then reflect increased ease of access to these representations. In the other account (e.g., Logan, 1990) word retrieval is thought always to be mediated by recollection of previous events in which the same word occurred (*pure episodic account*). In this account, increased word accessibility in repetition priming is thought to depend on the strength of the episodic trace. Therefore, the episodic account predicts larger repetition priming effects when the prime shares perceptual, contextual and task-related similarities with the target (van Petten et al., 1991).

In fact, priming within the same modality has stronger effects than cross-modal priming (e.g., Barry et al., 2001). This finding supports episodic accounts of priming. Nonetheless, response times in picture naming have also been found to be decreased by primes presented in different modalities. Visual primes such as masked presentation of the target word (Ferrand, Grainger, & Segui, 1994; Maxfield, Morris, Frisch, Morphew, & Constantine, 2015), and the first syllable of the target (Ferrand, Segui, & Grainger, 1996) result in faster naming. Similarly, auditory priming decreases naming latencies in paradigms such as concurrent auditory presentation of the target

word (Holland et al., 2011) and auditory presentation of words that share the first syllables with the target (Meyer & Schriefers, 1991).

The priming effect observed when a word occurs twice or more during the same task (and consequently, the same modality) is usually called repetition priming, identity priming or the word repetition effect. Naming of previously named pictures is faster regardless of whether the two naming instances occur within or between sessions. This effect has been documented with 50-item lags within the same session (Durso & Johnson, 1979), and with inter-session intervals up to 48 weeks after the first naming session (Cave, 1997). Mitchell and Brown (1988) showed that the magnitude of the priming effect was stable in the period of one to six weeks after the first naming session. In contrast, recognition of which items had been previously named declined in this 6-week period, denoting a dissociation between implicit and explicit memory. The persistence of priming effects despite the decay in recognizing prior occurrences of the same primes provides evidence in favor of an abstractionist account for the mechanisms of priming. Behavioral results on episodic vs. abstractionist accounts for repetition priming are so far inconclusive. Research using neuroimaging methods has allowed the examination of potential contribution of different types of processes to repetition priming, as discussed in the next section.

3.1.2 Neurofunctional and neurophysiological effects of repetition priming

Neuroimaging research has described the phenomenon of repetition-related cortical plasticity. A pattern of decreased activation in response to repeated stimulus presentation has been reported across a range of paradigms, including repetition priming for auditory nonwords (Davis, Di Betta, Macdonald, & Gaskell, 2009) and written words (Kerr, Gusnard, Snyder, & Raichle, 2004). The deactivated areas vary across tasks depending on the cognitive processes engaged (Henson, 2003). Van Turennout, Ellmore, and Martin (2000) examined neurofunctional changes

during picture naming with short- (30 seconds) and long-lag (3 days) repetition. Decreased activation in the left inferior frontal gyrus and increased activation in the left insula were mainly observed for long-lag repetition, whereas deactivation in the bilateral occipital cortex was greatest in short-lag repetition. These results may reflect the work of two learning mechanisms. Changes in posterior regions may reflect the immediate formation of more specific object-form representations. Changes in anterior areas may reflect gradually emerging reorganization of the brain network involved in lexical retrieval based on experience.

After repeated object naming, Basso et al. (2013) found differential neurofunctional effects of task practice and item practice in their functional magnetic resonance imaging study with healthy individuals. Task practice resulted in decreased activation in extra-striate, pre-frontal and superior temporal gyri (bilaterally). These are areas involved in task-related computations (perceptual priming, articulatory planning and phonological lexical retrieval, respectively). Item practice resulted in increased post-training activity in the central precuneus and posterior cingulate, and decreased activity in the left posterior fusiform (related to structural object representations), anterior cingulate, and left insular/inferior frontal cortices (involved in processing low frequency words). The central precuneus and the posterior cingulate are involved in episodic memory retrieval (Henson, Rugg, Shallice, Josephs, & Dolan, 1999). Increased activation of the left precuneus was also found to underpin the behavioral facilitation observed after repeated naming attempts, both in healthy individuals and in individuals with aphasia (Heath et al., 2015). Hence, some neurofunctional changes that occur in repetition priming could reflect facilitation in implicit processes (processing of the experimental stimuli and of the requested response), while other neurofunctional changes could mark the contribution of episodic retrieval to that facilitation (e.g., van Turennout, Bielamowicz, & Martin, 2003).

In ERP (event related potential) research, the word repetition effect has been mostly studied in tasks that do not require spoken production/overt spoken responses tasks (e.g. visual word recognition: Van Strien, Verkoeijen, Van der Meer, & Franken, 2007). Given that there are no reports on the neurophysiological correlates of repetition priming arising from repeated naming, we rely on the literature regarding repetition priming in other tasks to help establish predictions about the possible effects of repeated naming on ERPs. ERPs to repeated words typically show attenuation of the N400 (that is, less negative ERPs between 300-500ms; e.g. Rugg, 1985). In addition, ERPs to repeated and new words differ in amplitude between 500-800ms (van Petten et al., 1991). This latter effect is typically larger at central and parietal sites (Friedman, 1990; Kayser et al., 1999; Rugg, 1990; Van Strien et al., 2007) and it has been inconsistently labelled the Late Positive Component/Complex (LPC), P3b, P300 and P600.

N400/LPC modulation by repetition has been reported in a variety of tasks, such as visual word recognition (Van Strien, et al., 2007; Kayser et al., 1999; Friedman, 1990; Rugg & Nieto-Vegas, 1999), auditory word recognition (Rugg & Nieto-Vegas, 1999), reading paragraphs (Van Petten et al., 1991), auditory lexical decision (Rugg, 1990; Joyce, Paller, Schwartz, & Kutas, 1999) and visual lexical decision (Rugg, 1985; Joyce et al., 1999). ERPs in the LPC time window are sometimes more negative (e.g., Olichney et al., 2000) and other times more positive following the second presentation of words (e.g., Friedman, 1990; Kayser et al., 1999; Rugg, 1985; Van Strien et al., 2007). With longer lags between prime and target (15 minutes, in Rugg, 1990), differences in the N400 time-window were attenuated and the LPC was found to be more positive for repeated words.

In a recent ERP experiment assessing priming effects in adults who stutter and typically fluent adults, overt picture naming was primed with a masked written presentation of either the target

or an unrelated word (Maxfield et al., 2015). ERPs were measured after the presentation of the masked prime, from the onset of picture presentation for naming. In comparison to priming with unrelated words, priming with the targets resulted in more negative ERPs around 200ms (in particular at frontal sites), less positive ERPs around 300ms (in particular in posterior sites) and more positive ERPs around 500ms (in particular in central sites) in the group without fluency disorders. The latter result overlapped with the N400 and was interpreted as an N400 attenuation for primed words. No significant effects of priming were observed in the LPC latency.

Maxfield et al. (2015) contrasts with the previously described reports in that it is the first study reporting priming effects in word production. As expected, there are similarities (N400 attenuation) and differences (no effects of priming in the LPC latency) to what was observed in other modalities. However, though performance was measured in production, the primes were written words. Considering that functional imaging studies propose that different loci of repetition suppression reflect the different neural substrates engaged in the task, (e.g., Davis et al., 2009; Basso et al., 2013), it is not clear whether the neurophysiological characteristics of repetition priming may differ depending on the modality in which the priming stimulus is presented and/or that in which the response must be produced.

3.1.3 ERP research in word production

In electrophysiological experiments, the time-course of language processing has been most-often studied using metalinguistic and covert paradigms, in an attempt to avoid signal contamination by speech gestures (Ganushchak, Christoffels, & Schiller, 2011). Though these tasks result in a better signal-to-noise ratio, it is well known that covert and overt naming paradigms are associated with different patterns of brain activity, and therefore are likely to engage different cognitive resources (e.g., Christoffels, Formisano, & Schiller, 2007). The use of overt production

in ERP research has increased in recent years (Aristei, Melinger, & Abdel Rahman, 2011; Etchell, Sowman, & Johnson, 2012; Laganaro et al., 2009; Strijkers, Costa, & Thierry, 2009), showing that it is possible to collect high quality data in overt paradigms.

ERP studies of word production identify markers of lexical access between 208 and 388ms after stimulus presentation (Costa, Strijkers, Martin and Thierry, 2009). Strijkers et al. (2009), have also shown that the P2 amplitude (160-240ms) is sensitive to the lexical frequency of named words. These latencies overlap only partially with the N400 effect and precede the LPC modulation observed in repetition priming. Examining the ERP effects of word repetition in overt production in the light of the literature that describes the stages and time-course of processes involved in picture naming (Indefrey, 2011; Indefrey & Levelt, 2004; Levelt et al., 1999), will allow the level of processing at which repetition facilitates naming to be identified.

3.1.4 tDCS and the facilitation of word production

tDCS is a neuromodulation technique. In studies of language, applying anodal tDCS has been found to increase the benefits of training in healthy individuals and in individuals with aphasia (e.g., de Aguiar et al., 2015a; de Aguiar, Paolazzi, & Miceli, 2015b; Monti et al., 2013). The effect of tDCS is shown to be task specific (Antal et al., 2004), to depend on task difficulty (Miniussi et al., 2013), and on appropriate pairings of task and stimulation site. For example, Marangolo et al. (2013a) found that stimulating Broca's area during verb retrieval treatment resulted in an increase in the response accuracy of people with aphasia in an action-naming task. However, response accuracy when the same treatment protocol was associated with stimulation to Wernicke's area did not differ from sham stimulation.

Few studies have examined the effects of tDCS in paradigms using behavioral priming or training techniques. The use of anodal tDCS during the training phase can enhance artificial grammar learning (stimulation to Broca's area: de Vries et al. 2010), and speed up learning of novel words (Wernicke's area: Flöel, Rösser, Michka, Knecht, & Breitenstein, 2008). In contrast, cathodal tDCS during the training phase disturbs learning of novel words (Liuzzi et al., 2010). Following learning, anodal tDCS enhances retrieval of previously learned novel words (Fiori et al., 2011).

Sparing et al. (2008) assessed the effects of tDCS on picture naming. Subjects named experimental items in a baseline phase (8 times), immediately before tDCS, during tDCS and immediately, five and 10 minutes after tDCS. Naming was faster immediately after anodal tDCS than after Sham, but the effect was very short-lived, as no differences could be detected at the longer post-stimulation measurement times. Given that the experimental procedure was preceded by 8 trials of naming (the baseline), during which response times would be speeded, the potential for additional behavioral facilitation as a result of stimulation may have been substantially reduced. However, another study more directly assessed priming of picture naming (Holland et al., 2011). During anodal tDCS to Broca's area, to-be-named pictures were paired with auditorily presented target names or noise controls (speech stimuli submitted to a noise-vocoding routine). This study found significantly larger priming (comparing auditory primes and control) in the tDCS condition in comparison to Sham (Holland et al., 2011).

Holland et al. (2011) used functional magnetic resonance imaging and found tDCS-induced decreases in activation in Broca's area. Studies using ERPs may also contribute to understanding the mechanisms of facilitation induced by tDCS. However, there are (to date) no language priming experiments with tDCS effects examined using ERPs. In language processing, Wirth et

al. (2011) reported that anodal tDCS over the left dorsal pre-frontal cortex yielded faster responses in object naming, increased the semantic interference effect in ERPs, and decreased delta power. This type of information can be used to understand the mechanisms of change induced by tDCS, which may inform treatment. For example, language recovery in aphasia is also associated with delta power decrease (Hensel, Rockstroh, Berg, Elbert, & Schönle, 2004). Effects of tDCS on delta power (Wirth et al., 2011) suggest that its administration may enhance recovery in aphasia.

In the current study we examine repetition priming during an action-naming task: naming as primed by prior naming. In addition to facilitating performance in healthy individuals, this strategy has been used successfully in aphasia rehabilitation (e.g., Heath et al., 2015) but, to the best of our knowledge, the electrophysiological correlates of repeated naming have not been previously described. As in other tasks, we expect repetition to result in N400 attenuation and changes in the LPC time-window. The exact polarity of these changes cannot be predicted based on previous research, due to the variability reported across tasks. Furthermore, a subset of our items is named in an intermediate facilitation phase, during which participants receive anodal transcranial direct current stimulation (tDCS) and Sham, in separate sessions. We expect the repetition priming effects to be larger in real tDCS, in comparison to Sham.

3.2 Method

3.2.1 Subjects

Twenty-four subjects, recruited via social networks, participated in this study. Of these, two failed to complete the experiment, two were excluded due to measurement errors and two due to poor data quality. The remaining 18 participants (10 female) are included in the analyses. The mean number of years of education was 15.2 (STD=2.8), and participant's ages ranged from 18

to 32 years (mean: 22.1, STD = 3.7). All participants were right-handed native speakers of English, with normal or corrected-to-normal vision, with no history of neurological or psychiatric disorders. The study was approved by the local ethics committee and participants provided informed written consent.

3.2.2 Design

A 2x2x2 repeated measures design was adopted for this experiment, with the within-subjects factors Time (PreFacilitation, PostFacilitation), Facilitation (Facilitated verbs, Unfacilitated verbs), and Stimulation (Sham, tDCS). All participants were assessed in two separate sessions, receiving real tDCS in one session, and Sham in the other session (the order of administration of tDCS or Sham was randomized across participants; see Figure 3.1). There was an inter-session interval of approximately one week. In order to exclude repetition effects across sessions, the participants were presented with different sets of stimuli in each session.

3.2.3 Materials

Stimuli consisted of 200 pictures of actions (critical items) and 100 pictures of objects (fillers). All images were 300x300 pixel, black-and-white line drawings. Pictures of objects and actions were retrieved from the International Picture Naming Project (Szekely et al., 2004), the Object and Action Naming Battery (Druks & Masterson, 2000) and a new version of the Verb and Sentence Test (Bastiaanse, unpublished). Items were included if the respective source reported name agreement above 70%. We created four sets of action pictures (critical items) and two sets of object pictures (fillers). Items across sets were matched for relevant linguistic variables, including picture-name agreement, picture-naming response latency[3], visual complexity of images, lexical frequency, age of acquisition, imageability, familiarity, number of items starting

[3] Reaction times to the target were only available for items from the International Picture Naming Project.

with a fricative, number of phonemes, number of syllables, and number of letters. Additionally, noun sets were matched for number of objects represented in the picture, word complexity (whether the noun was a compound), and semantic category, and verb sets were matched for the number of pictures coming from each of the sources[4], number of verb-noun homophones, instrumentality, face/arm/leg actions, manipulability, tense regularity, transitivity, and number of internal arguments.

Participants were distributed pseudo-randomly across four experimental lists (controlled for gender), in order to obtain a balanced number of participants for each stimulation order (Sham first or tDCS first) and for the set of verbs used in the facilitation phase of Day 1 and 2, hence avoiding list effects. On each testing day, participants were tested with the same set of items before and after facilitation, with experimental blocks presented in the same order (to balance order effects across sessions) and experimental items randomized within each block (to avoid predictability of the subsequent items). Across participants, the order of presentation of experimental blocks was randomized.

3.2.4 Procedure

In each session, the procedure included three main phases (also described in Figure 3.1). First, in the *Pre-facilitation phase*, we collected 5 minutes of eyes-closed, resting state electroencephalography (EEG), followed by ERPs during the naming paradigm and finally, 5 more minutes of eyes-closed, resting state EEG. In the second phase, *Facilitation phase*, participants received either Sham or real tDCS for 13 minutes. For the first 3 minutes subjects rested. During the last 10 minutes of stimulation, they named the subset of to-be-facilitated verbs. Participants named the set of items twice, in a randomized order, during this phase. The

[4] This was because the pictures from the different sources varied in drawing style.

third phase, *Post-facilitation phase*, included 5 minutes of eyes-closed, resting state EEG followed by ERPs during the naming task (all items named: facilitated, unfacilitated and fillers). This means that in each session, participants named facilitated verbs 4 times (PreFacilitation, First run of facilitation, Second run of facilitation, and PostFacilitation), and they named unfacilitated items twice only (PreFacilitation and PostFacilitation). The same drawings were used at all times, but the images were flipped horizontally for presentation at PostFacilitation. This manipulation aimed to decrease any effects of priming of low-level image processing, making our ERP and behavioral data more interpretable in terms of language-related processing. As shown in Figure 3.1, the same tasks were administered across the 2 experimental sessions, and the whole procedure lasted approximately 120 minutes for each session, including preparation time.

3.2.4.1 Naming task, training and behavioral data

Participants were tested in a dimly illuminated, electrically shielded room. They sat in a comfortable chair, approximately 100cm from the screen. Stimulus presentation for the action (n=100) and object (n=50) naming task was programmed using Presentation® software (version 16.3, www.neurobs.com). For each trial (see Figure 3.2), participants were shown a fixation cross (for 500 to 1000ms), followed by the word VERB or NOUN (1000ms), which informed the participant whether s/he should name the subsequent item using a verb or noun. A second fixation-cross then appeared (randomly lasting between 500 and 1000ms), followed immediately by the drawing of the item to be named which remained on the screen for a fixed duration of 2600ms). The next trial started immediately after the offset of the image. Long latency responses were followed by a "Too slow!" message. A slow response was defined as any response time more than 2 standard deviations above the mean of the response times given in Szekely et al.

(2004) for the items retrieved from the International Picture Naming Project. This threshold was used for all experimental items (also those from the Verb And Sentence Test and the Object and Action Naming Battery).

Figure 3.1. Experimental procedure

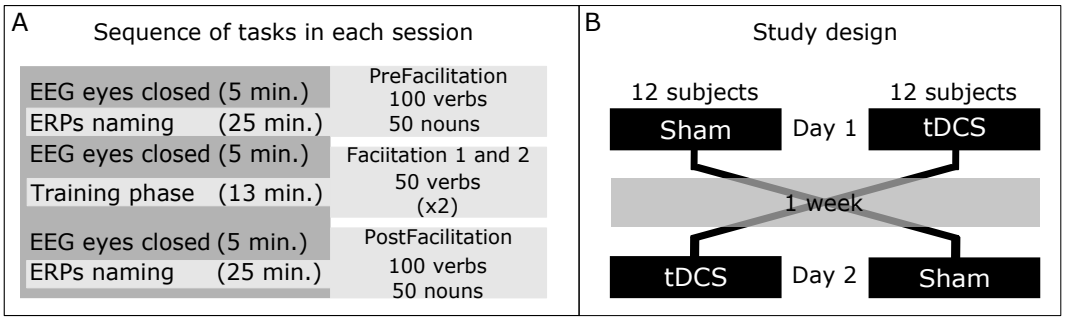

Figure 3.1. Participants were assessed over 2 sessions with a 1 week interval. The same protocol was used in both sessions, with a change in the stimulation condition. The sequence of tasks used in each session in presented in Panel A. Panel B shows the cross over design, with 12 participants allocated to each stimulation condition in each session.

Participants were instructed to name each item using a single word, which was a noun or a verb in the present continuous tense (e.g. walking), and to avoid hesitations. The naming task used during the facilitation phase was similar to that presented during the PreFacilitation and PostFacilitation phases, except that only action naming was required (as nouns were not present in the list). This task had a maximum duration of 9 minutes. Throughout all measurements, vocal responses were recorded and response latencies were measured from picture onset. Hesitations and self-corrections were scored post-hoc. Target accuracy was scored manually.

Figure 3.2. Trial structure during the naming tasks

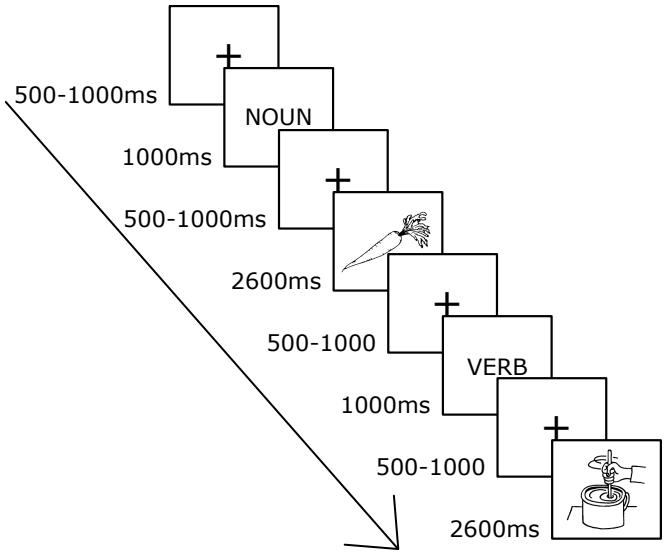

Figure 3.2. Naming during the facilitation phase included only verbs, but the word category was still shown, to keep the task as similar as possible, across experimental procedures. Duration of each stimulus is represented next to each frame. Each trial had a maximum duration of 5600ms.

3.2.4.2 EEG recording

EEG was recorded using a Biosemi system (Van Rijn, Peper, & Grimbergen, 1990; for a complete description, see www.biosemi.com). For compatibility with the tDCS equipment and in order to maximize the number of electrodes included in the analysis, 26 Biosemi electrodes were placed on a Neuroelectrics cap (Neuroelectrics, Barcelona, Spain, http://neuroelectrics.com/enobio; e.g., Kranczioch, Zich, Schierholz & Sterr, 2014), which was also used for the placement of the tDCS electrodes (see Figure 3.3). The 26 EEG electrodes were placed according to the international 10-20 system guidelines, in the positions Fp1 and 2, AF7 and 8, F7 and 8, F4, C1 and 2, C3 and 4, T7 and 8, P3 and 4, P7 and 8, O1 and 2, PO7 and 8, Oz, Pz, Cz, Fz, and Fpz. F3 was not recorded because part of the tDCS electrode covered this position. External flat-type electrodes were positioned on the outer canthus and below the left eye, aligned to the center of

the pupils (in order to measure EOG signals) and over the right and left mastoids (for offline referencing). The data was digitized with 24-bit accuracy at 2048Hz and recorded using the Biosemi Active Two software.

Figure 3.3. EEG and tDCS electrode montage

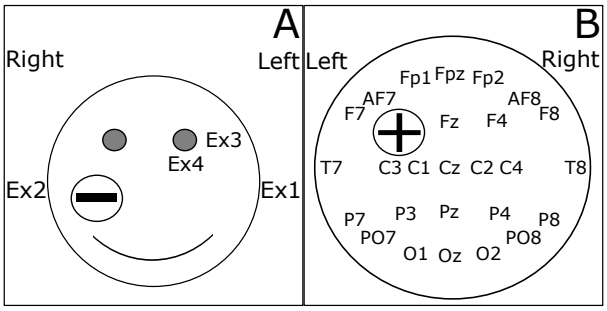

Figure 3.3. Twenty-six Biosemi electrodes were mounted on a Neuroelectrics cap. The anode (represented with a '+' sign) was placed over Broca's area and the cathode (represented with a '-' sign) over the right zygomatic bone.

3.2.4.3 tDCS

tDCS was administered using the Neuroelectrics StarStim equipment (Neuroelectrics, Barcelona, Spain, http://neuroelectrics.com/starstim; e.g., Dutta & Nitsche, 2013). Two electrodes were placed in the 25cm^2 sponges, and current intensity was set to 1mA, resulting in a current density of 0.04mA/cm^2. Stimulation was delivered for 13 minutes and the two sessions were spaced by approximately 1 week (6-8 days). Stimulation was administered online (during the facilitation phase of naming), but started 3 minutes before the beginning of the naming task. A monocephalic montage was used, with the anode placed over Broca's area and the cathode placed over the right zygomatic bone. Broca's area was identified as the crossing point between T3-Fz and F7-Cz (Friederici, Hahne & Cramon, 1998).

3.2.5 Analyses

3.2.5.1 Behavioral data analysis

Participant's responses were scored for accuracy of the first response. Trials containing self-corrections were excluded to avoid interference from error related negativity (e.g., Yeung, Cohen, & Botvinick, 2004), an ERP effect present in responses perceived as incorrect by the subject. Trials in which different acceptable responses were produced in pre- and post-facilitation measurements were also scored as incorrect and excluded from further analyses to ensure that the same words were used across experimental conditions (pre-, and post-measurements). Finally, trials with a reaction time greater than 2 standard deviations from the individual's naming latency (calculated separately for pre- and post-facilitation measurements and for each session) were marked as reaction time outliers and excluded from further analyses. Altogether, these procedures resulted in the exclusion of 24% of trials. This proportion was expected, given that some items had as low as 70% name-agreement (as reported in the source). Reaction time data was furthermore transformed, using a log10 transformation.

To examine the offline effects of tDCS, and to assess the effect of facilitation on response latency, a repeated-measures ANOVA including the factors Time (PreFacilitation, PostFacilitation), Stimulation (tDCS, Sham) and Set (Facilitated Verbs, Unfacilitated Verbs) was computed. To examine word repetition effects over the four naming attempts, and the potential role of tDCS in modulating changes across these four measurements, we computed a repeated-measures ANOVA on the RTs for facilitated verbs including the factors Time (PreFacilitation, Facilitation1, Facilitation2, PostFacilitation) and Stimulation (Sham, tDCS). In both analyses, when the sphericity assumption was not met in the data, a Greenhouse-Geisser correction was applied.

3.2.5.2 EEG and ERP data analysis

EEG and ERP data were analyzed using Statistic Parametric Mapping (SPM8; Litvak et al., 2011; http://www.fil.ion.ucl.ac.uk/spm). ERP data were down-sampled to 250Hz. ERPs were calculated for a window of 1400ms, corresponding to a 200ms baseline before the onset of the to-be-named picture and a 1200ms interval for word retrieval during picture presentation. EEG channels were re-referenced to the mastoid average. Data were band-pass filtered between 0.2 and 40Hz and an additional stop band filter between 49 and 51 Hz was applied to suppress line noise. Trials excluded from the behavioral data analyses (incorrect responses and RT outliers) were also excluded from ERP data. Trials containing eye movement artifacts were detected and corrected using SPM8 routines. Correction was made using a signal space projection algorithm. Furthermore, trials likely to contain other types of artifacts (e.g., movement related to coughing) were rejected using a threshold of 2 for the trial's accumulated z-score. Data were corrected by electrode and by condition using a 200ms baseline. Trials were averaged by condition using a robust averaging procedure which computes the mean while down-weighting outliers.

The 26 electrodes were distributed over 3 regions of interest (ROIs): anterior (Fp1, AF7, F7, Fp2, AF8, F4, F8, Fpz and Fz), central (C1, C3, T7, C2, C4, T8 and Cz) and posterior (P3, P7, P07, O1, P4, P8, PO8, O2, Pz and Oz). Two time windows were selected for analysis: 300-500 (for the N400) and 500-800 (for the LPC), following van Petten et al. (1991). We anticipated that response times would largely overlap with the time windows of interest, but also extend beyond these time-windows. Instead of rejecting trials with overlapping response times, we opted to analyze a control time window (800-1000ms), in which the largest proportion of reaction times was expected to fall. If effects observed in the earlier time-windows were due to the vocal response onset, they should remain significant during this control time-window. This allowed for

the maintenance of data processing similar to previous investigations of the word repetition effect.

A repeated measures ANOVA including the factors Time (PreFacilitation, PostFacilitation), Condition (tDCS, Sham), Set (Facilitated Verbs, Unfacilitated Verbs), and ROI (Anterior, Central, Posterior) was computed, to examine effects of repetition, stimulation and facilitation in ERP data. In order to ensure test-retest reliability in a paradigm with a long latency between the two measurement points, the same analyses were performed with epochs time-locked to the onset of the screens with word category information (ACTION, OBJECT). This analysis was computed for three time-windows, and therefore the p-values were adjusted using a Bonferroni correction. When the sphericity assumption was not met in the data, a Greenhouse-Geisser correction was applied. Follow-up tests were pursued when relevant interactions were identified. We calculated point-to-point Spearman correlations for all conditions, between naming latencies and the ERP amplitudes for each sample (that is, every 4ms for a 250Hz sampling rate), along the 1200ms epoch. Correlations were considered reliable when they were significant for at least 15 consecutive samples (Costa et al., 2009).

For resting state EEG data, the signal was down-sampled to 250Hz. Re-referencing and filtering proceeded as for ERP data. The data from 5 minutes of rest were segmented into epochs of 2000ms, resulting in 300 trials for each resting state measurement. Trials and channels containing artifacts were rejected based on peak-to-peak amplitude, with a threshold of 400μV for trials. Channels were excluded from further analyses if more than 3% of trials recorded from a given channel had artifacts. For conversion to the frequency domain, we used the Fieldtrip multi-taper frequency transform routine (*Hanning taper* for frequencies below 30, and discrete prolate spheroidal sequences – *DPSS* – for Gamma) implemented in SPM8, with a frequency

resolution of 0.741Hz, for a time-window of 1400ms (300ms of EEG was cropped from both ends of the 2000ms time-window, to avoid edge artifacts). Though the main focus was on the Delta band (1–4 Hz), we performed exploratory analyses also for Theta (4.5–7.5 Hz), Alpha (8–12 Hz), Beta (12.5–30 Hz) and Gamma (35–40 Hz) frequency bands. Repeated measures ANOVAs including the factors Time (Pre 1, Pre 2, Post) and Condition (Sham, tDCS) were computed, for the absolute power (μV^2) in each frequency band.

3.3 Results

3.3.1 Behavioral data

3.3.1.1 Effects for facilitated and unfacilitated verbs: PreFacilitation vs. PostFacilitation

The main effect of Facilitation ($F(1)= 26.603$, $p<0.001$) and Time ($F(1)= 14.366$, $p=0.001$) and the interaction of Facilitation*Time ($F(1)=57.479$, $p<0.001$) were significant. Follow-up t-tests contrasting PreFacilitation and PostFacilitation response times revealed a significant decrease in response times for both Facilitated and Unfacilitated verbs (Facilitated verbs: $t(17)=4.199$, $p=0.001$; Unfacilitated verbs: ($t(17)=3.299$, $p=0.004$). Furthermore, the two sets of verbs did not differ significantly at PreFacilitation ($t(17)=-0.162$, $p=0.873$), but there were significant differences between the two sets after facilitation ($t(17)=-6.683$, $p<0.001$), indicating that the facilitated verbs showed a greater reduction in response latency. There was no significant main effect of stimulation ($F(1)=1.696$, $p=0.210$) nor significant interactions involving Stimulation (Facilitation*Stimulation: $F(1)=0.150$, $p=0.704$; Time*Stimulation: $F(1)=1.174$, $p=0.294$; Facilitation*Time*Stimulation: $F(1)=1.728$, $p=0.206$; Figure 3.4, panels A to C).

Figure 3.4. Behavioral effects of word repetition in word production.

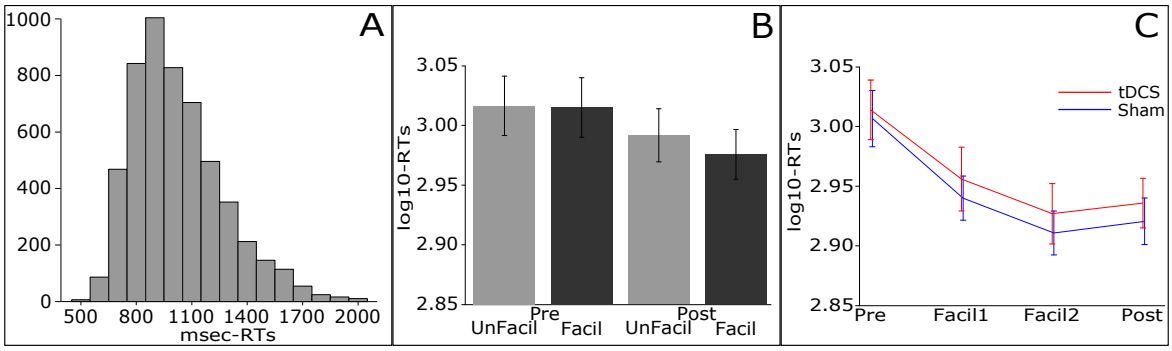

Figure 3.4. Panel A: distribution of naming latencies. Panel B: latencies for facilitated and unfacilitated verbs (Pre vs. PostFacilitation). Panel C: change in latencies for facilitated verbs across four naming attempts. Error bars represent the 95% confidence interval of the mean.

3.3.1.2 Effects for facilitated verbs across four naming attempts

The repeated measures ANOVA revealed a significant effect of Time (F(1.051)=13.041, p=0.002). Compared to PreFacilitation, Responses were faster at all other time points (Facilitation1: t(17)=14.823, p<0.001; Facilitation2: t(17)=23.818, p<0.001; PostFacilitation: t(17)=8.050, p<0.001), in Facilitation2 in comparison to Facilitation1 (t(17)=10.721, p<0.001), and in PostFacilitation in comparison to Facilitation1 (t(17)=2.678, p=0.016). Differences between Facilitation2 and PostFacilitation were not significant (t(17)=0.301, p=0.767). Once again there was no main effect of Stimulation (F(3)=2.257, p=0.151) nor an interaction between Time and Stimulation (F(3)=1.012, p=0.331).

In summary, response times were faster after the facilitation phase than before. This effect was larger for facilitated verbs. In addition, throughout the four naming occasions, response times for facilitated verbs decreased on the second and third occasion (but not in the fourth) in relation to the first. tDCS did not have a significant effect on response times.

3.3.2 ERP data

In the N400 time window (300-500ms) the main effect of ROI ($F(1.856)=54.969$, $p<0.001$) and the interaction of ROI*Time*Facilitation ($F(1.456)=7.939$, $p=0.015$) were significant. Follow-up tests at each ROI (anterior, central, and posterior sites) revealed a significant interaction of Time*Facilitation at posterior sites ($F(1)=19.616$, $p=0.018$), denoting that after the facilitation phase, ERPs to facilitated verbs were less negative in posterior sites during the N400 time-window. Analyses of ERPs to the control condition revealed a main effect of ROI ($F(1.541)=14.298$, $p<0.001$), but no main effects or interactions involving our critical factors (Time, Stimulation, Facilitation). The main effect of ROI marks differences in ERP amplitudes across the scalp (in relation to the mastoid reference) between the pre- and post-facilitation phases. Without interaction with other experimental factors, the effect of ROI is not meaningful. Therefore, the only meaningful effects observed between the two measurements are those related to our experimental manipulation. Hence, the significant effects observed in the N400 time-window can be reliably attributed to Time and Facilitation, and not to non-specific changes occurring during the 26-minute interval between the two measurements.

In the second time window analyzed (500-800ms), the main effects of ROI ($F(1.560)=65.19$, $p<0.001$) and Time ($F(1)=9.026$, $p=0.024$), as well as the interactions ROI*Time ($F(1.376)=16.979$, $p<0.001$), ROI*Facilitation ($F(2)=4.923$, $p=0.039$), Time*Facilitation ($F(1)=13.043$, $p=0.006$) and ROI*Time*Facilitation ($F(1.742)=15.083$, $p<0.001$) were significant. Follow-up tests at each ROI (anterior, central and posterior sites) characterized the effects of Time and Facilitation. The main effect of Facilitation (difference between facilitated and non-facilitated verbs) was significant over posterior sites ($F(1)=7.365$, $p=0.045$), with ERPs more positive to facilitated verbs. Furthermore, the main effect of Time (differences between

pre- and post-facilitation measurements) was observed at all sites (anterior: $F(1)=13.142$, $p=0.006$; central: $F(1)=11.287$, $p=0.012$; posterior: $F(1)=12.258$, $p=0.006$), revealing a relative positivity over posterior sites in the Post measurement, with reversed polarity at anterior sites. The interaction Time*Facilitation was significant over all sites (anterior: $F(1)=9.681$, $p=0.018$; central: $F(1)=8.834$, $p=0.027$; posterior: $F(1)=18.578$, $p<0.001$), denoting larger effect of Time for Facilitated verbs. In addition, the ERPs to the control condition in this time window showed a main effect of ROI ($F(2)=13.667$, $p<0.001$). Crucially, no main effects nor interactions involved the factors Time, Facilitation, or Stimulation (Figure 3.5, panels A to C).

Figure 3.5. ERP results and correlations between electrophysiological and behavioral data

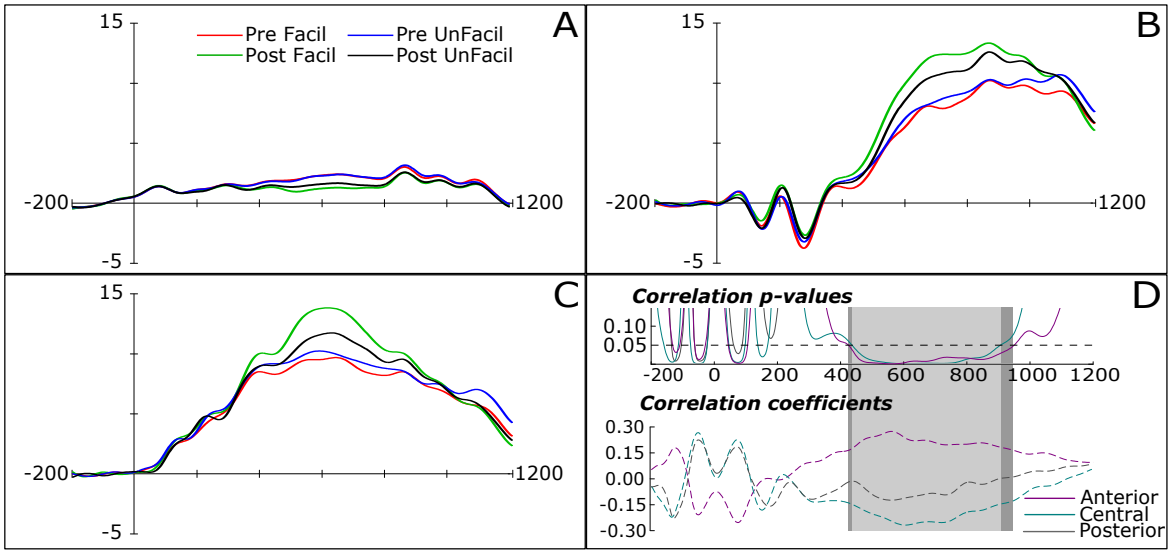

Figure 3.5. Panels A, B and C: grand average ERP waveforms for anterior, central and posterior channels, respectively. Panel D: correlation between ERP amplitude and log reaction times; significant correlations were found in the highlighted latencies.

In the control time-window (between 800 and 1100ms) the main effect of ROI ($F(1.396)=29.583$, $p<0.001$) was significant, but there were no main effects nor interactions involving Time, Facilitation, or Stimulation were observed. The same result was found for ERPs to the control condition in this time window (main effect of ROI: $F(1.592)=7.297$, $p=0.015$). Therefore, ERPs in the control time-window were not sensitive to our experimental manipulations (Time, Facilitation, or Stimulation).

3.3.3 Correlational analyses between ERPs and response times

For anterior channels, reliable correlations between response times and ERPs were observed between 428 and 948ms, with a mean correlation coefficient of 0.215 (SD=0.028). For central channels, correlations were reliable between 460 and 880ms (mean coefficient=-0.224, SD=0.032). For posterior channels, no correlations met the criteria defined (Figure 3.5, panel D). This correlation between behavioral data and ERPs indicates that the observed changes in ERPs (in particular at anterior and central sites) are likely to reflect cognitive processes that influence behavioral performance.

3.3.3.1 Frequency data

Resting state EEG was recorded twice before the facilitation phase, and once after the facilitation phase. The repeated measures ANOVA with the factors Time (PreFacilitation1, PreFacilitation2, and PostFacilitation) and Condition (Sham, tDCS) revealed no significant main effects or interactions, for any of the frequencies analyzed.

3.4 Discussion

In this study, we aimed to describe the neurophysiological characteristics of the repetition priming effect, in order to better understand the mechanisms underlying improved performance

following repeated naming. Facilitated verbs were named on four occasions and we found that participants performed faster over each subsequent occasion, except for the fourth. Unfacilitated verbs were named twice, and participants were faster on the second presentation of these items (PostFacilitation), despite a 26-minute interval[5] between these two naming attempts. ERP data revealed an attenuation of the N400 effect in posterior sites for facilitated verbs. In addition, Late Positive Component (LPC) modulations by repetition were observed for all verbs (both facilitated and unfacilitated), with ERPs being more negative in anterior sites and more positive in central and posterior sites at PostFacilitation in comparison to PreFacilitation. The LPC modulation was significantly larger for facilitated verbs (named 4 times), in comparison to unfacilitated verbs (named only at PreFacilitation and PostFacilitation). Significant correlations between reaction times and ERPs were observed from 428 to 948ms, at central and posterior sites, validating the relevance of cognitive processes indexed by the N400/LPC complex on behavioral performance. In addition, we aimed to assess whether tDCS could provide additional performance enhancement, when compared to repetition priming alone. In contrast to the large effects observed for repetition of naming attempts, we did not find significant effects of stimulation either in the behavioral or in the electrophysiological data.

Measuring ERPs following the control condition was important to establish the test-retest reliability of the paradigm, given that the two ERP measurements take place at an approximately 26-minute interval. In this comparison the main effects of region of interest (ROI) were significant but there were no significant differences between the two time points, for the control condition, supporting the reliability of our results over testing points. In addition, we used a

[5] This included: 5 minutes of resting state, a technical pause of 1 minute, 13 minutes of the facilitation phase, another technical pause of 1 minute, 5 minutes of resting state, and one more 1-minute technical pause prior to beginning the PostFacilitation ERP measurement.

control time-window (800-1100ms) which was after any predicted effects of our conditions would be expected to occur. As predicted, ERP analyses comparing our critical experimental conditions showed no statistically significant effects between 800 and 1100ms, though a large portion of verbal responses had an onset during this interval (see Figure 3.4, panel A). This also supports the claim that our effects are not the product of motion-related artifacts. We will start by discussing the effects of repetition, and then provide possible explanations for the absence of stimulation effects.

3.4.1 Effects of repetition priming in action naming

We found a significant decrease in vocal reaction times in PostFacilitation naming compared to PreFacilitation naming. This was significant for both facilitated and unfacilitated verbs. The fact that this effect was significant for unfacilitated verbs indicates that priming was sustained during the 26-minute interval that corresponded to the facilitation phase and resting state measurements. This was expected, given that naming of previously named pictures has previously been found to show long-lasting priming (up to 48 weeks; Cave, 1997). However, facilitated verbs showed a significantly larger effect, reflecting the extra priming obtained with two additional naming occasions during the facilitation phase. Moreover, there was significant priming even though the pictures used in the facilitation were flipped horizontally. By changing the orientation of the presented stimuli, the visual input and hence the picture recognition process, was not identical at the different time points, even if other visual features were unchanged (e.g., contrast, size). Importantly, the concept associated with the picture and the word to be retrieved were the same across time points. This means the priming effect that we observe in action naming is better explained by a facilitation in word retrieval than in early visual processing.

For facilitated verbs, each naming event had significantly faster reaction times than the previous one, except the fourth. One explanation for the lack of facilitation between the third and fourth testing points is related to differences in the task: the third time point is during the facilitation phase when participants named only 50 verbs, whereas at the final test point (PostFacilitation), participants named 100 verbs and 50 nouns. Consequently, task switching from naming nouns to verbs may have slowed responses and masked further facilitation. An alternative explanation is a saturation of the word repetition effect. Hauptmann and Karni (2002) have showed that repetition priming saturates after a limited number of repetitions.

Comparing PreFacilitation and PostFacilitation time points, there were significant modulations of ERPs by repetition priming in the time window from 300 to 800ms. From 300 to 500ms, an attenuation of the N400 in posterior sites was observed for facilitated items only. In contrast, no repetition effect was detected for unfacilitated verbs, even though these had also been produced once before. In our study, facilitated verbs differed from unfacilitated verbs in that they were repeated not only more often, but also closer in time to PostFacilitation naming. All things considered, these results are in line with observations of repetition priming in other modalities that show that modulations in the N400 by repetition are reduced or absent in long-lag paradigms, and are more pronounced with increasing numbers of repetitions (Rugg, 1990; van Petten et al., 1991). In addition, we have replicated the N400 attenuation found for cross-modal priming of word production (Maxfield et al., 2015).

A modulation of ERPs by repetition was also found in the LPC (500 to 800ms) at all sites, which was more pronounced for facilitated verbs. The neurophysiological characteristics of the LPC modulation were similar to those reported in other tasks: ERPs were more positive during PostFacilitation than PreFacilitation at central and posterior sites, as has been reported in

previous research with long lags between prime and target (Rugg, 1990), and in repetition priming studies of visual word recognition (Friedman, 1990; Kayser et al., 1999; Van Strien et al., 2007). At anterior sites, the repetition effect was characterized by a relative negativity in the LPC, like that observed in lexical decision and in semantic congruency tasks (Olichney et al., 2000; Rugg, 1985). Presence of this modulation for both facilitated and unfacilitated verbs (though larger for facilitated), reflects the previously reported robustness of the LPC to long intervals between two occurrences of a word (Rugg, 1990; van Petten et al., 1991).

LPC amplitude has already been shown to correlate with word recall accuracy (Olichney et al., 2000) and with verbal memory (Olichney et al., 2002). In our study, modest point-to-point correlations between ERP amplitudes and response times were significant for anterior and central electrode sites. In both regions, these correlations were significant at latencies of the overlapping partially with the N400 time window, and with the entire LPC time window. Even though the polarities were inverted in these sites, in both cases the correlations indicated that the faster the response, the larger the ERP modulation by repeated verb naming. Previous correlations between ERP and behavioral measures (Costa et al., 2009; Strijkers et al., 2009) have been interpreted as reflecting computations occurring at the corresponding latencies, as discussed in the next paragraph.

Word form encoding is thought to occur until around 600ms after stimulus onset and includes processes estimated to last around 350ms (Indefrey, 2011). This overlaps with the latency of N400 effects reported in this study and in other repetition priming paradigms (Mitchell & Brown, 1988). In fact, other studies have argued that the word repetition effect reflects facilitation specifically at the word form level (Barry et al., 2001). The LPC clearly outlasts the time course thought to be related to form encoding, but, in studies of reading aloud, it has been

related to the explicit (episodic) memory of the occurrence of the repeated words (Olichney et al., 2013). The fact that this episodic trace is correlated with reaction times indicates that recollection of prior events contributes, at least indirectly, to word production. Altogether, our results are in line with literature that suggests that repetition priming reflects changes in implicit (stimuli processing) as well as explicit (episodic memory) processes (Basso et al., 2013; van Turennout et al., 2003).

Repeated picture naming is a procedure used in aphasia rehabilitation (for a review see Nickels & Best, 1996). Priming effects in aphasia have been identified in tasks such as picture-word matching (Howard, Patterson, Franklin, Orchard-Lisle, & Morton, 1985), repetition (Barry & McHattie, 1991; Miceli et al., 1996; Nickels, 2002), and phonemic cueing (e.g. Best, Herbert, Hickin, Osborne, & Howard, 2002). Recent evidence suggests that similar mechanisms of repetition priming underlie the facilitation of language production both in healthy individuals and individuals with aphasia (Heath et al., 2015). As pointed out by Nickels (2002), the tasks used in priming paradigms can result in long-lasting improvement when administered repeatedly in the context of language therapy (Hickin et al., 2002). Markers of this facilitation (such as the N400 and LPC effects reported here) may denote the potential of the system to be enhanced by repetition. Further research may then test the value of these markers as predictors of aphasia recovery.

3.4.2 tDCS

While we found clear effects of repetition and facilitation on response latencies and ERPs, there were no effects of tDCS on response latencies, ERPs or resting state EEG. There are several possible explanations for this fact. First, we consider task difficulty. Miniussi et al. (2013) have proposed that stimulation effects may result from changes in signal-to-noise ratio (that is, the

ratio between relevant and irrelevant activation) in the stimulated network. If a task is easy, task-relevant activation will be much higher than task-irrelevant activation in areas involved in task-related processing. Anodal tDCS to those areas, may then raise task-relevant activation closer to threshold, and hence facilitate performance. If the task is difficult or novel, task-irrelevant activation is present simultaneously and to a similar level as task-relevant activation. In this case, anodal tDCS may increase both noise and signal to a similar extent and therefore prevent facilitation. As our task (action naming) was fairly easy for young, healthy participants, task difficulty is unlikely to account for the lack of stimulation effects.

Another account relies on stimulation site, and on its relation to action naming and the mechanisms of repetition priming. We chose to enhance activity in Broca's area because tDCS to this area has been shown to improve action naming in individuals with aphasia (Marangolo et al., 2013a). Lesion studies, data from intra-operative mapping of language functions and neuro-imaging studies have shown that pre-frontal structures, in particular the inferior frontal gyrus, are critical for verb processing (Rofes & Miceli, 2014). However, if the repetition priming effect observed in our study resulted mostly from the recollection of prior naming of the same items, then perhaps it would have been more fruitful to stimulate temporoparietal areas, which are involved in episodic memory (Ferrucci et al., 2008). Accordingly, Sparing et al. (2008) found enhanced performance in naming after anodal tDCS to the posterior peri-sylvian cortex, including temporoparietal areas.

A final possible explanation is a floor effect. As reported, the decrease in response latencies was larger than 100ms for unfacilitated verbs and 150ms for facilitated verbs. Perhaps it simply was not possible to decrease reaction times beyond that level. Considering the literature, this is unlikely. Sparing et al. (2008) administered tDCS after 9 trials of picture naming (nouns;

including 8 pre-experimental trials, and the pre-stimulation measurement) and found differences between tDCS and Sham in the 11th naming attempt, after stimulation had been delivered during the 10th naming attempt. Our study differs from that of Sparing and colleagues in multiple aspects (stimulation montage, site, grammatical category of words used during naming), but one crucial point is that while we aimed to assess whether tDCS enhances repetition priming, Sparing et al. (2008) assessed the effects of tDCS after exhausting the repetition priming effect. Their data indicated that anodal tDCS to the posterior peri-sylvian area after extensive repetition priming yielded a short-lived decrease (less than 5 minutes) in object naming latencies. Our data extends these findings, suggesting that while repetition priming is still actively reducing naming latencies (that is, in the first few attempts) tDCS does not have a measurable contribution to the enhanced performance. It is possible that the contribution of tDCS to performance in this task is so small that only near-ceiling performance (which is potentially less variable) may be enhanced. Together, these two studies indicate that tDCS has a limited effect in reducing picture naming latencies, when compared to behavioral priming alone. In contrast, the effect of repetition priming is more robust.

3.5 Conclusion

We report for the first time the electrophysiological characteristics of the word repetition effect in overt picture naming. This effect has similar characteristics to the word repetition effects identified in other tasks. We observe faster response times, as well as modulations of the N400 and LPC in repeated action naming. The N400 effect was found to be sensitive to lag between repetitions and/or number of presentations, as reported in previous literature arguing that these modulations reflect facilitation in implicit, task-related processing. LPC amplitude was less influenced by number of repetitions and/or lag, though the modulation was larger for facilitated

verbs. Significant correlations between vocal reaction times and ERP amplitudes which overlapped with both N400 and LPC latencies support claims that both implicit and explicit processes contribute to repetition priming. In accordance, similarities between our results and studies reporting repetition effects in other tasks (e.g., word reading) support the claim that these electrophysiological effects mark facilitation, not only in task-related processing, but also in other cognitive processes that may contribute to facilitation (e.g., episodic retrieval). These processes may be relevant for the treatment of individuals with language disorders. The repetition effect was not enhanced by tDCS.

CHAPTER 4

Item specific improvement and generalization in verb retrieval: Predictors and mechanisms of aphasia recovery

Demographic and clinical predictors of aphasia recovery were identified in the literature. Their contribution was not systematically examined when investigating treatment techniques and outcomes. For example, little attention was devoted to identifying and distinguishing predictors of item-specific vs. generalized improvement. These predictors may rely on different mechanisms, and therefore be predicted by different variables. Here, we reviewed the literature on predictors of aphasia recovery, and conducted a meta-analysis of single-case treatment studies designed to assess the efficacy of treatments for verb production. The contribution of demographic and clinical variables, and of some treatment features was assessed, by means of Random Forests (a machine-learning technique used in classification and regression). Improved production of treated verbs was predicted by an interaction of pre-treatment scores in verb comprehension and in word repetition, and of the frequency of treatment. Generalization to untreated verbs was predicted by an interaction including the use of morphological cues, presence of grammatical impairment, pre-treatment scores in noun comprehension and frequency of treatment. We conclude that item-specific improvement occurs frequently. It may depend on restoring access to and/or knowledge of lexeme representations, and requires semantic knowledge (as measured by verb comprehension) and phonological output abilities (including working memory, as measured by word repetition), to be relatively spared. Generalization occurs infrequently. It may depend on the nature of impaired language representations, and the type of knowledge engaged by treatment: generalization is more likely to occur where abstract features (semantic and/or grammatical) are damaged or treated.

4.1 Introduction

Aphasia recovery proceeds at a relatively fast pace in the first days after stroke, resolving in 38% of patients. Nonetheless, 43% of patients still present with aphasia 18 months post onset (Laska et al., 2001). Efforts were made to identify factors that determine the course, the pattern(s) and the potential for language improvement. Though behavioral treatment can substantially change the course of recovery (Pickersgill & Lincoln, 1983), few studies addressed in depth the role played by the deficit targeted by therapy, and the method and content of behavioral treatment. In this article we study treatment-related changes in verb retrieval, and identify potential predictors of improvement. We focus this meta-analysis on two specific outcomes: item-specific improvement and generalization in verb retrieval. By including only treatments that required overt verb production, we are able to discuss the role of each potential predictor in relation to the cognitive mechanisms that may be at play during language recovery, for treated and untreated verbs.

4.1.1 Predictors of aphasia recovery

In a prospective study, Pedersen, Stig Jørgensen, Nakayama, Raaschou, and Olsen (1995) found that the time course of aphasia recovery may depend on severity at onset. Stationary performance can be reached as early as 2 weeks post-onset by individuals with mild aphasia, at 6 weeks by those with moderate aphasia, and at 10 weeks by those with severe aphasia. Pickersgill and Lincoln (1983) suggested that recovery follows a specific pattern, in which language comprehension precedes language production. Accordingly, different courses of recovery were reported for patients with intact and with impaired comprehension, the former improving in speech production and the latter in comprehension and word repetition (Lomas & Kertesz, 1978).

Several studies identified demographic, clinical and treatment-related variables that may have a predictive value on long-term aphasia severity or functional communication disability. Research on demographic factors indicates that better language recovery is observed in younger subjects (Laska et al., 2001; Plowman, Hentz, & Ellis, 2012), in males, and in individuals with high levels of education, socio-economic status, and intelligence (Plowman et al., 2012).

Clinical predictors may extend to the pre-stroke period, as higher pre-stroke ability to perform everyday activities and duties correlates to better recovery (Maas et al., 2012). Improvement may also be influenced by initial stroke severity (Pedersen et al., 2004; Godecke et al., 2013), lesion site (Plowman et al., 2012) and size (Kertesz et al., 1979; Plowman et al., 2012; Maas et al., 2012). Recently, it was suggested that lesion size does affect recovery, but only to the extent in which larger lesions are more likely to encompass critical anatomical areas (Price, Seghier, & Leff, 2010).

Lesion size is inversely related to the role of intact peri-lesional and contra-lesional brain areas. In neuroimaging studies, increased activation in post- vs. pre-treatment comparisons is observed in left frontal and posterior temporo-parietal areas, in association with improved language performance (Fridriksson, Richardson, Fillmore, & Cai, 2012). In addition, while some right-hemisphere areas may have a disruptive influence on left hemisphere functions, others may contribute to better language processing (Turkeltaub et al., 2012). For example, a larger volume of the long segment of the right arcuate fasciculus predicts the amelioration of the aphasia quotient (Forkel et al., 2014).

Cognitive variables relate to the patient's cognitive profile after stroke. Across studies, initial aphasia severity was consistently identified as a predictor of language improvement (Plowman et

al., 2012; Pedersen et al., 1995, 2004; Godecke et al., 2013). More specifically, studies report on the predictive roles of the functional communication abilities at onset (Laska et al., 2001) and the initial severity of phonological impairment (as measured by tasks such as repetition, reading aloud, judging same/different spoken word pairs, and matching the first phoneme of a spoken word with a grapheme; El Hachioui et al., 2012). Initial aphasia severity, communicative ability, visuo-motor speed and attention predict return to work (Ramsing, Blomstrand, & Sullivan, 1991).

There is evidence that aphasia rehabilitation is effective both in the acute and in the chronic stages (Brady et al., 2012; De Jong-Hagelstein et al., 2011). In fact, treatment may substantially change the course of recovery. Patients who undergo Speech-Language Therapy improve more rapidly than those who do not. This difference is particularly evident in the first four months after stroke (Pickersgill & Lincoln, 1983). Nonetheless, few studies have addressed the characteristics of treatment that predict better recovery. In these investigations, better outcomes were associated with more intense aphasia therapy and with a higher number of total treatment hours (Bhogal, Teasell, & Speechley, 2003; Godecke et al., 2013).

In few studies, researchers investigated the predictive value of cognitive factors in recovery while taking into account the tasks used during treatment. Hickin et al. (2002) found that the effects of facilitation (the degree of priming obtained from a single exposure to a cue) correlate with effects of treatment (improvement observed with the repeated administration of the same cue). In aphasia, effects of semantic priming (Baum, 1997) and repetition priming in lexical retrieval have been reported (Nickels, 2002). The data by Hickin et al. (2002) indicate that the degree of priming predicts the potential for recovery if the same task is used in treatment.

Other authors carried out meta-analyses of single-case treatment outcomes to identify the features of treatment that are relevant for improvement. Jacquemot et al. (2012) reported that only tasks that engaged output phonology contributed significantly to improve naming. In addition, Jacquemot et al. (2012) showed that treatment is more effective when addressing the impaired level of language processing. These results highlight the specificity of improvement in relation to the levels of language processing engaged by treatment, and those affected by neurocognitive damage (Jacquemot et al., 2012).

Another meta-analysis (Dickey & Yoo, 2010) studied inter-individual differences in response to linguistically motivated aphasia therapy. Treatment protocols of this type promote explicit, meta-linguistic knowledge of language structure, which can generalize to untreated materials, and therefore promote more widespread language improvement (Thompson & Shapiro, 2005). In the study by Dickey and Yoo (2010), auditory comprehension scores predicted item-specific improvement, but none of the examined variables predicted generalization. These results suggest that item-specific and generalized improvement may rely on different neurofunctional mechanisms (Dickey and Yoo, 2010) and may, therefore, be predicted by different variables.

4.1.2 The process of verb production

While a detailed description of the language processing system is beyond the scope of this report (we refer the reader to Bastiaanse & Van Zonneveld, 2004; Levelt, 1999; Miozzo & Caramazza, 1997; Patterson & Shewell, 1987; Dell, 1988; Foygel & Dell, 2000; Gagnon, Schwartz, Martin, Dell, & Saffran, 1997; Rapp & Goldrick, 2000), a schematic summary of the mechanisms involved in language production is important to understand the functional effects of therapy for verb retrieval. Different language models acknowledge the existence of conceptual features (that is, the set of features that generate meaning), syntactic features (that is, a set of grammatical

features such as grammatical class, noun gender, verb argument structure, etc.), and phonological representations (that is, the segmental and supra-segmental properties of the word's phonology). They differ in whether phonological and grammatical features are thought to be accessed sequentially (e.g., Bastiaanse & Van Zonneveld, 2004; Levelt, 1999) or in parallel (e.g., Patterson & Shewell, 1987; Miozzo & Caramazza, 1997), and in whether the interaction between different levels of representation is considered unidirectional (Bastiaanse & Van Zonneveld, 2004; Miozzo & Caramazza; Patterson & Shewell, 1987; Levelt, 1999) or bidirectional (Dell, 1988; Rapp & Goldrick, 2000).

As an example, we present the model introduced by Bastiaanse and Van Zonneveld (2004, adapted from Levelt et al. 1998), illustrated in Figure 4.1. According to this model, when a concept is triggered, it will activate a *lemma* (that is, the lexical-semantic and grammatical representation). The lemma contains information about the meaning of a word, but also information about word class and, in case of verbs, information about argument structure, thematic roles and subcategorization. For example, for a verb like 'to bike', the lemma contains the information that it is a verb with one argument, an agent, that is subcategorized for a simple 'subject – verb' sentence.

Figure 4.1. Schematic representation of a language processing

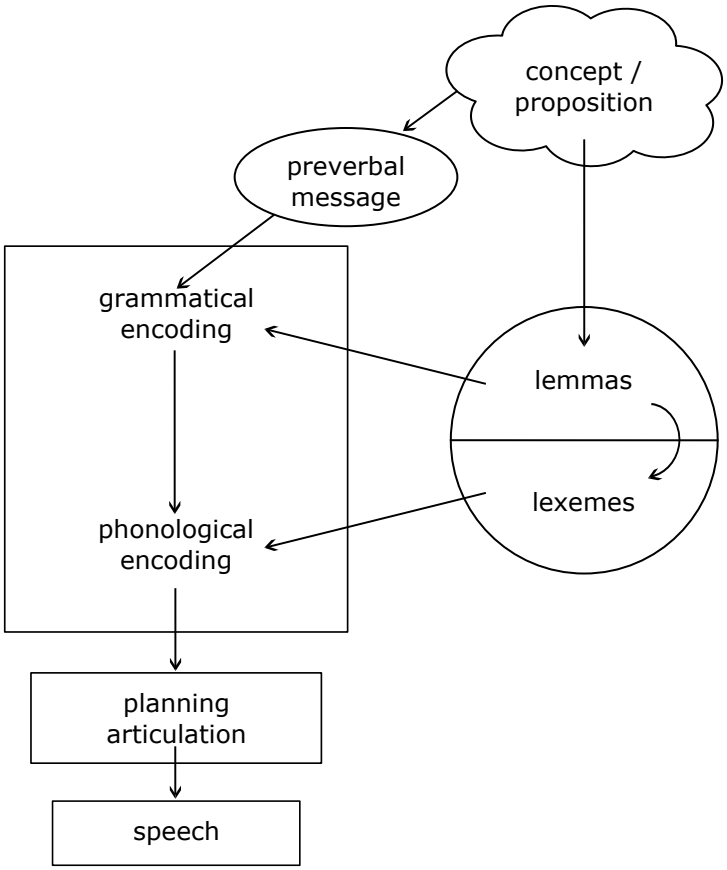

Figure 4.1. Based on Bastiaanse and Van Zonneveld (2004), and adapted from Levelt et al., (1998). Copyright: Roelien Bastiaanse, University of Groningen.

The *grammatical encoder* receives input from two sources (preverbal message and lemma level) and uses this information to form a sentence frame. The idea that a speaker wants to express (which may be the name of an object or action, but also a complete proposition) is formulated in a preverbal message. The grammatical encoder uses the verb-argument structure that is represented in the verb lemma to generate a sentence frame that suits the grammatical properties of the verb and the intention of the speaker (the concept / proposition). Therefore, it also specifies which grammatical information should be filled in the sentence frame, for example, 3rd

person singular / plural; past / present tense etc. The lemma activates the *lexeme* (that is, lexical-phonological representation or phonological word form), which is inserted in the sentence frame constructed by the grammatical encoder. This is the process of phonological encoding: phonemes are inserted and phonological rules are applied to plan and execute the articulation process. Verb production deficits may reflect impairment at each of these levels.

4.1.3 Recovery of verb production

The grammatical information associated with verbs is necessary for the production of grammatically well-formed sentences (Saffran et al., 1980). Accordingly, verb production scores are better predictors of communication in daily living than noun production scores, when both word classes are produced in sentence context (Rofes, Capasso, & Miceli, 2015a). Though relevant for everyday communication, and selectively impaired in a considerable number of patients (e.g., Luzzatti, Raggi, Zonca, Pistarini, Contardi, & Pinna, 2002; Miceli, Silveri, Villa, & Caramazza, 1984; Shapiro & Caramazza, 2003), verb production has been less often targeted in treatment studies than noun production.

A recent review shows that at the single-word level, verb retrieval disorders can be treated using the same Speech-Language Therapy techniques used for the treatment of noun retrieval (Webster & Whitworth, 2012), but suggests that verb recovery is more difficult to achieve. With verbs and nouns differing in the levels of semantic and grammatical detail that are entailed in their representations (see Conroy et al., 2006; Maguire et al., 2015), it is possible that the difference in treatment efficacy means that verb recovery and noun recovery rely on different mechanisms. A full investigation of factors that determine verb recovery is yet to be carried out. In examining these factors, the nature of the outcome (e.g., improvement in treated vs. untreated verbs) must be considered.

As suggested by Dickey and Yoo (2010) it is possible that item-specific improvement and generalized improvement rely on different mechanisms. When discussing the effects of a treatment protocol, the term *generalization* may refer to improved lexical retrieval of untreated items (e.g., the training of *walking* enhances the retrieval of *running*) or to the increased use of treated morphological and syntactic processes, in contexts different to those presented with treated items. For example, training the production of regular past tense morphology by using the verb *to walk* results in improved production of regular past tense morphology of other, untrained regular verbs. Generalization may also refer to improved retrieval of treated items in an untreated task (e.g., improved retrieval of *walking* in a sentence production task after treatment of *walking* in an action naming task). Throughout the present manuscript, we use *generalization* to denote improved lexical retrieval of untreated items.

Generalization is seldom reported in the aphasia rehabilitation literature, though it was observed after treatment of argument structure (Thompson et al., 2013), and of tense production in sentences (de Aguiar et al., 2015a; Links et al., 2010). It has been proposed that its occurrence is constrained by the underlying cognitive impairment (more likely in the event of semantic impairment (that is, impairment to lexical-semantic representations stored in lemmas), unlikely in the event of lexeme-level damage; Miceli et al., 1996) and/or by characteristics of the therapy task (more likely when abstract conceptual or grammatical features are treated; e.g., Boyle & Coelho, 1995; Thompson & Shapiro, 2005). In addition, it has been proposed that generalization is also influenced by an interaction of linguistic and extra-linguistic computations: with practice, the treatment task becomes easier and the cognitive load of task-specific computations is reduced. Consequently, more processing resources can be allocated to lexical retrieval when treated and untreated items are presented in the same task (de Aguiar et al., 2015a).

Though there are some accounts for the cognitive mechanisms of improvement in aphasia (e.g., Boyle & Coelho, 1995; Miceli et al., 1996; Thompson & Shapiro, 2005), treatment outcome may be influenced by demographic, clinical, anatomical and treatment-related variables. A systematic evaluation of such variables is lacking. We report on the meta-analysis of single-case studies and single-case series in which the treatment task required overt verb production. We examine the predictive value of demographic, clinical and treatment-related factors in determining treatment outcome, weighing the relative contribution of each variable while taking into account all the others. The potential contribution of these factors to treatment outcome is assessed for both item-specific improvement and generalization to untreated verbs. We discuss the potential cognitive mechanisms of change in response to treatment that each variable may reflect.

4.2 Method

4.2.1 Data extraction from the literature

We conducted a web search using the main search engines (Pubmed, Web of Science, and Google Scholar). We searched for articles including the key words Aphasia rehabilitation/treatment AND verbs OR Aphasia rehabilitation/treatment AND actions OR Aphasia rehabilitation/treatment AND sentences. We excluded literature reviews, neuromodulation studies, and articles in which (1) the aphasia rehabilitation technique did not entail overt verb production, (2) pre- and post-treatment performance was only measured in terms of morphosyntactic accuracy (rather than accuracy in lexical retrieval of verbs), and (3) no statistical analysis was reported on the outcomes of treatment for each individual. We considered only post-stroke aphasia, and excluded cases with other neurological conditions (e.g., head

traumas, tumors, primary progressive aphasias, etc.). The final database included 166 individual treatment outcomes, obtained from 30 articles[6].

From each study, we extracted the outcome of each treatment for each patient. The analyzed outcomes include improvement in retrieval of treated verbs (presence/absence of significant improvement), improvement in retrieval of untreated verbs (presence/absence of significant improvement). For each patient, we extracted three types of predictors from the article: demographic, clinical, and treatment-related. Demographic variables included Age, Gender, and Education. Clinical variables were Months Post-Onset, pre-treatment assessment scores (Noun Production, Verb Production, Noun Comprehension, Verb Comprehension, Word Repetition, Nonword Repetition), and variables relating to pre-treatment diagnosis (Fluency, Semantic Impairment, Lexeme Impairment, Sublexical Processing Impairment, and Grammatical Impairment). The pre-treatment assessment scores were obtained from a variety of standardized language batteries (e.g., Object and Action Naming Battery: Druks & Masterson, 2000; Verb And Sentence Test: Bastiaanse, Edwards, Maas, & Rispens, 2002), and from experimental tasks designed for the specific purposes of each study (e.g., Weinrich, Shelton, Cox, & McCall, 1997; Maul, Conner, Kempler, Radvanski, & Goral, 2014). Variables related to pre-treatment diagnosis (e.g., presence of semantic impairment) were inserted in our data as described in the article when available. When diagnostic information was not explicitly reported, but available data allowed reasonable hypotheses about the potential loci of language impairment, such information was

[6] Boo and Rose (2011); Carragher et al. (2013); Conroy, Sage, and Ralph (2009a, b, c); Edwards and Tucker (2006); Faroqi-Shah and Graham (2011); Fink et al. (1992); Harris, Olson, and Humpfreys (2012); Kim, Adingono, and Revoir (2007); Links, Hurkmans, and Bastiaanse (2010); Marshall, Chiat, and Pring (1997); Marshall, Pring, and Chiat (1998); Maul, Conner, Kempler, Radvanski, and Goral (2014); McCann and Doleman (2011); Park, Goral, Verkuilen, and Kempler (2013); Raymer and Ellsworth (2002); Raymer and Kohen (2006); Raymer et al. (2006); Raymer et al. (2007); Rodriguez, Raymer, and Rothi (2006); Rose and Sussmilch (2008); Wambaugh and Ferguson (2007); Wambaugh, Cameron, Kalinyak-Fliszar, Nessler, and Wright (2004); Wambaugh, Doyle, Martinez, and Kalinyak-Fliszar (2002); Wambaugh, Mauszycki, and Wright (2013); Webster and Gordon (2009); Webster, Morris, and Franklin (2005); Weinrich et al. (1997); Weinrich, Boser, and McCall (1999).

produced by the authors using the methodology outlined in Whitworth, Webster, and Howard (2005).

In relation to the characteristics of treatment, the following dimensions were included: Level of Output (patient required to single words, sentences, or both), Level of Input provided by the therapist (single words, sentences, or both), Cue Direction (increasing or decreasing cues), Finite Verbs (present or absent in patient's output), Semantic Cues (present/absent), Phonemic Cues (present/absent), Repetition Cues (present/absent), Written Cues (present/absent), Morphological Cues (therapy technique including specific training of tense production; present/absent), knowledge of verb Argument Structure (required/not required), Gestural Cues (present/absent). Other features included in the analyses were: Number of Treatment Sessions, Number of Treatment Days (the period across which treatment was delivered), Total Number of Treatment Hours (collapsed across all treatment sessions), Session Duration (in minutes), Treatment Frequency (number of sessions per week), and Treatment Intensity (number of hours per week).

4.2.2 Statistical analyses

Results were analyzed by means of the Random forests algorithm. Random forests is a machine-learning algorithm used for classification and regression. This methodology is particularly suitable for the analysis of data with many variables of different types (both continuous and categorical) and relatively few cases (Liaw & Wiener, 2002; Breiman, 2003). This method was selected because other advanced statistical treatment methodologies, such as logistic mixed regression models, could not compute models that account for complex interactions with many variables and few cases with the same reliability (for a demonstration of the superiority of random forests in modelling linguistic data, see Tagliamonte & Baayen, 2002). An additional reason for using Random forests is that it allows to extract variable importance. This dimension

reflects the average reduction of a model's accuracy when a given variable is left out (Breiman, 2003).

Data preparation and statistical analysis followed these steps, for each outcome variable:

(1) Missing values were imputed (that is, estimated) using Random Forests with the function rfImpute (Liaw & Wiener, 2002; Breiman, 2003). For factors, missing values are initially replaced by the most frequent level (breaking ties at random), and then adjusted based on a proximity matrix (that is, a measure of similarities across cases, that considers information available from other variables). Estimates were based on 100 iterations of growing 2000 trees. For additional quality check, this procedure was repeated twenty times, hence creating twenty different databases. The quality of estimated data was ensured by examining the consistency of the results obtained with different imputations. This procedure has been reported to produce accurate predictions in samples with a missingness of up to 56% (Shah, Bartlett, Carpenter, Nicholas, & Hemingway, 2014). Therefore, we excluded variables with proportions of missingness above this value.

(2) For each database, a random forest was computed by using the cforest function (Hothorn, Bühlmann, Dudoit, Molinaro, & Van Der Laan, 2006). We then extracted the importance of each potential predictor in determining outcome (varImp function: Strobl, Hothorn, & Zeileis, 2009). A conditional permutation importance was used to maintain the accuracy of predictions in the presence of correlations between variables (Strobl et al., 2009).

(3) The importance attributed to each potential predictor was averaged across the twenty data imputations, and the z-value of the importance of each variable was calculated in each of the 20 data sets. The dataset and the random forest that produced variable importance

measurements closest to the mean of the twenty imputations were selected for further analyses.

(4) Following the procedures in Tagliamonte and Baayen (2002), the accuracy (index of concordance *C*) of the selected random forest was calculated by using treeresponse (Hothorn, Hornik, Strobl, Zeileis, & Hothorn, 2015). A C-value above 0.80 indicates good classification performance (Chatterjee & Hadi, 2006).

(5) Finally, the ctree function (Hothorn, Hornik, & Zeileis, 2006) was used to construct conditional inference trees. Variables were introduced into the conditional inference tree iteratively (by order of importance), until the tree's accuracy, as measured with tree response did not improve further. The best conditional inference tree is reported in Figures 2 and 4. Example R code is available in Appendix A.

4.3 Results

4.3.1 Improvement of lexical retrieval for treated verbs

We extracted from the literature 142 cases in which treatment outcomes were reported for treated verbs. Significant improvement in verb retrieval was reported for 108 cases (76.1%), and 34 cases (23.9%) showed no treatment effect. The variable Nonword Repetition was not included in the Random Forest for treated verbs, due to a large proportion of missing data. After selecting the most representative imputed dataset using procedures (1) to (3) (see Method section), we obtained a random forest with an index of concordance C=0.94, and an Out-Of-Bag error (that is, classification error rate) of 0.18. The variable importance is represented in Figure 4.2.

Figure 4.2. Variable importance for item-specific improvement in verb treatment.

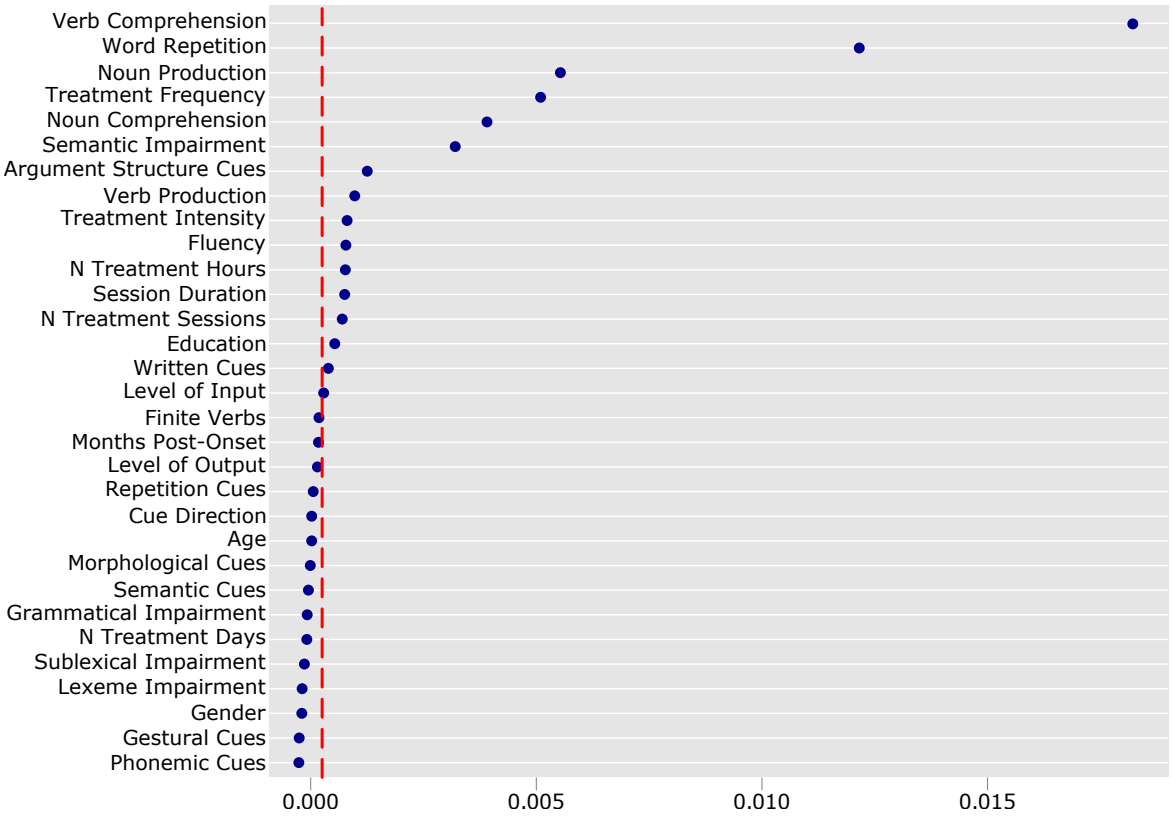

Figure 4.2. Predictors to the right of the dashed vertical line were significant. Variable importance is presented in the x axis.

The nodes of the tree in Figure 4.3 split automatically, based on differences in the probability of improvement observed for the different levels of a factor (e.g., the 'Frequency' node, numbered 5 in Figure 4.3). For continuous variables, the values that determine the split of the node are estimated on the basis of two-sample standardized statistics (Hothorn et al., 2006). The bars at the bottom of the tree represent the proportion of patients who improve and who do not improve, at each node of the tree. The split in verb comprehension around 67% accuracy indicates that patients with very poor verb comprehension (<67% correct on a comprehension test) were less likely to show item-specific improvement than those with verb comprehension accuracy above

67% (note the low proportion of patients who showed item-specific improvement, in the left-most branch of the tree). As for patients with comprehension above 67% accuracy, the subgroup with very poor repetition (<49% in word repetition test) was less likely to improve than the one with repetition accuracy above 49%. Among the latter, the subgroup that received fewer than three therapy sessions per week was more likely to improve than the subgroup receiving more than three sessions per week.

Figure 4.3. Conditional inference tree for treatment outcome for treated verbs.

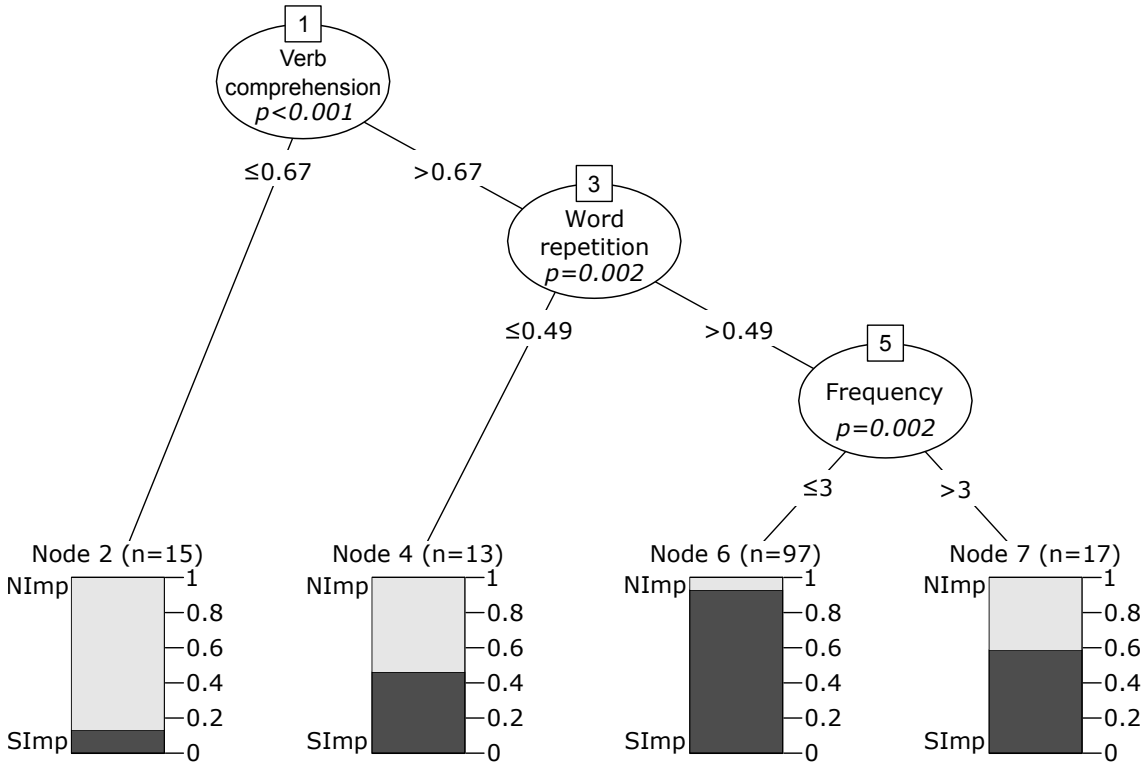

Figure 4.3. Nodes 1, 3 and 5 represent significant variables, with p-values presented within the node. Below each of these nodes, the values represent the points at which the node splits, therefore separating patients in groups with different predictions of outcome. Each of these groups is represented by a box, and the colors in the box represent the proportion of patients within each group that showed significant improvement after treatment (SImp, in dark grey) and the proportion that did not (NImp, in light grey).

4.3.2 Improvement of lexical retrieval for untreated verbs

The binary outcome for untreated verbs was extracted for 166 patients. Significant generalization was observed in 24 cases (14.5%), whereas no generalization occurred in 142 (85.5%). The most representative imputed dataset produced a random forest with an index of concordance C=0.96, and an Out-Of-Bag error rate of 0.14. The variable importance for predicting improvement in untreated verbs is represented in Figure 4.4. The best conditional inference tree was produced with the variables Grammatical Impairment (p=0.004), Noun Comprehension (p<0.001), Morphological Cue (p<0.001), and Frequency (p<0.001), reaching C=0.88 (Figure 4.5). No other variables met the established criteria.

Figure 4.4. Variable importance for generalization in verb treatment.

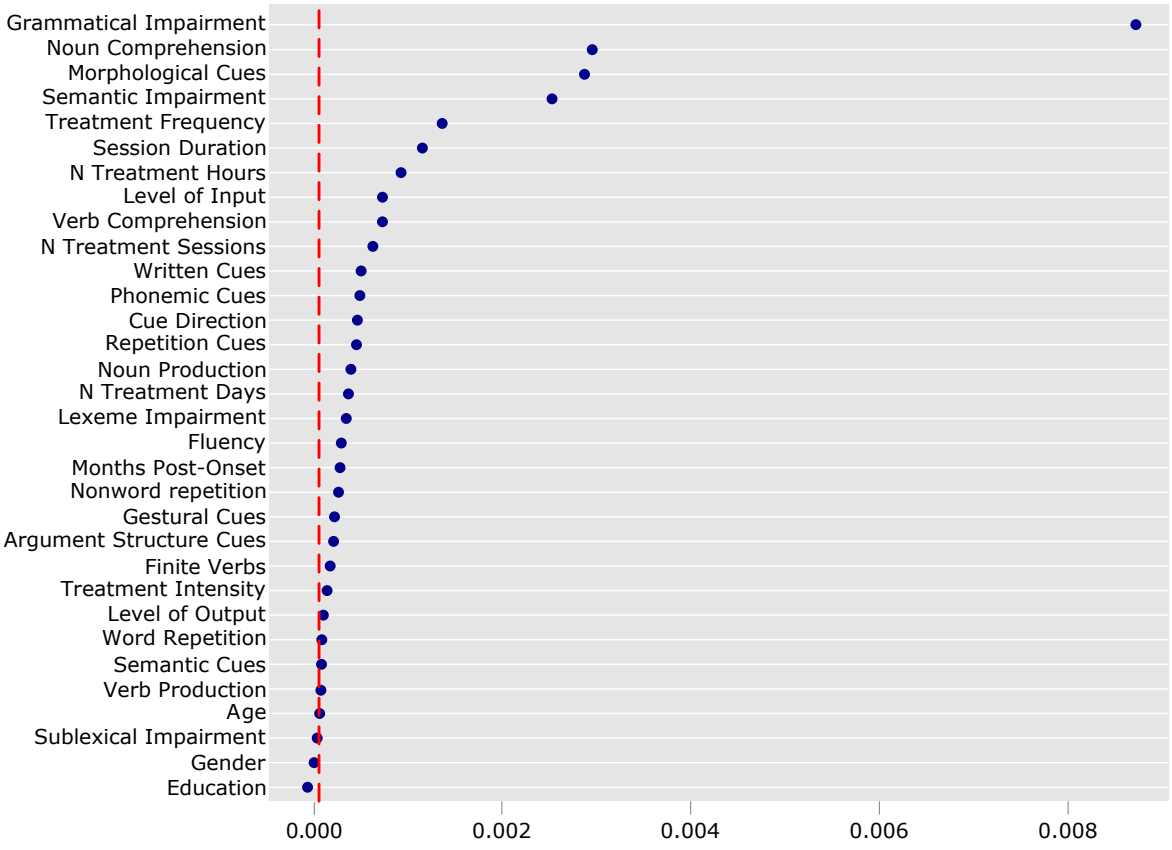

Figure 4.4. Predictors to the right of the dashed vertical line were significant. Variable importance is presented in the x axis.

Figure 4.5. Conditional inference tree for treatment outcome for untreated verbs

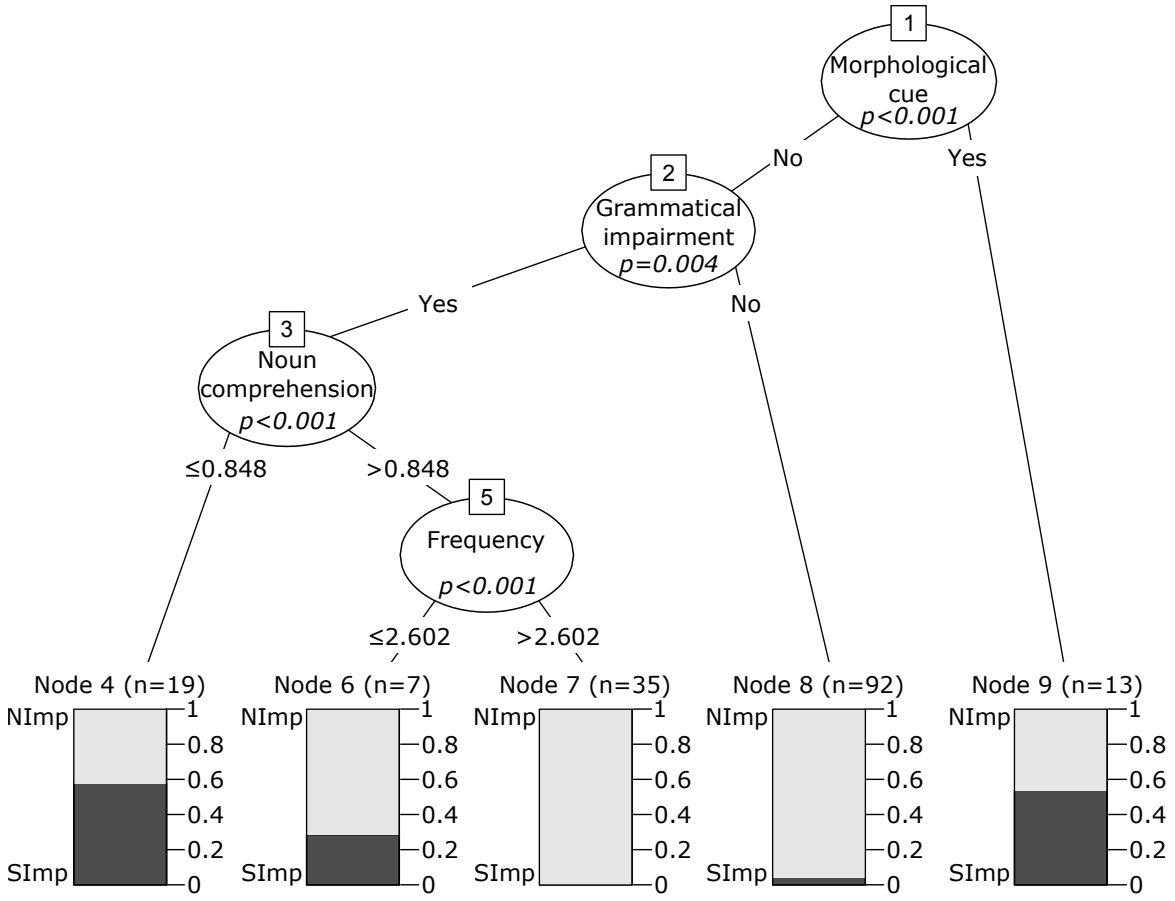

Figure 4.5. Nodes 1, 2, 3 and 5 represent significant variables, with p-values presented within the node. Below each of these nodes, the values represent the points at which the node splits, therefore separating patients in groups with different predictions of outcome. Each of these groups is represented by a box, and the colors in the box represent the proportion of patients within each group that showed significant improvement after treatment (SImp, in dark grey) and the proportion that did not (NImp, in light grey).

The two branches of the Morphological Cue node show that patients whose treatment protocol included morphological cues (consisting in all cases of therapy for tense production) were more likely to show generalized improvement. Among those who did not receive morphological cues during treatment, greater chances of generalization were observed in patients with grammatical impairment. In this subgroup of patients, those with poorer noun comprehension were more

likely to improve than those with higher scores (<84.8% accuracy in a noun comprehension test). Finally, patients with relatively spared comprehension were more likely to improve when they received fewer than 2.6 therapy sessions per week. A closer examination of the data shows that all patients who received morphological cues had been diagnosed with grammatical impairment. We compared improvement in patients with grammatical impairment who received (node 9 of the tree in Figure 4.5; n=13) and who did not receive morphological cues (node 3; n=61). Patients who did not receive morphological cues were less likely to improve (X^2 (1, N = 74) = 4.22, p = 0.039).

4.4 Discussion

Our meta-analysis of the literature on verb rehabilitation highlights differences between the predictors of item-specific improvement and generalization. Item-specific improvement was observed in 76.1% of the cases. It occurred more often in patients with higher verb comprehension scores. Among them, those with word repetition accuracy above 49% improved more often than those with poorer repetition. In patients with relatively high verb comprehension and word repetition scores, improvement was more likely when they received fewer than 3 therapy sessions per week. Generalization was uncommon (14.5% of the sample). It was observed more frequently in patients whose treatment included morphological cues. A specific pattern was observed in patients who did not receive morphological cues: generalization was more frequent in individuals with grammatical impairment and poor noun comprehension (<85%). Patients with grammatical impairment and relatively high noun comprehension were more likely to improve if they received fewer than 2.6 treatment sessions per week.

In the next sections we discuss the nature of recovery processes that may explain the role of these predictors. We start by discussing variables that are specifically relevant for either item-

specific improvement or for generalization, and then discuss Frequency, which is common to both types of outcome.

4.4.1 Item-specific improvement

Patients who perform well on standardized language tests show a higher potential for improvement. This has frequently has been reported in studies showing that severity plays a role in predicting recovery (e.g., Pedersen et al., 2004; Godecke et al., 2013). Dickey and Yoo (2010) report that auditory comprehension predicts item-specific improvement. So does the initial degree of phonological impairment, in a composite measure including word repetition, among other tasks (reading aloud, judging same/different spoken word pairs, and matching the first phoneme of a spoken word with a grapheme; El Hachioui et al., 2012). Pre-treatment severity of impairment as demonstrated by diagnostic tests of verb production is not a crucial predictor. This may mean that the observed predictive value of verb comprehension and word repetition should not be reduced to an effect of severity, but may rather reflect aspects of cognition that participate in item-specific recovery.

Both in response to treatment (Pickersgill & Lincolnn, 1983), and in spontaneous recovery (Lomas & Kertesz, 1978), the improvement of comprehension has been reported to precede that of production. Lomas and Kertesz (1978) propose that due to the broader representation of receptive language in relation to production, severe comprehension impairment may be associated with larger lesions and greater overall stroke severity. However, they also report that severity of the comprehension impairment determines not only the amount, but also the type of improvement: patients with low comprehension improve mainly in repetition and comprehension whereas improvement in language production occurs mostly in those with good comprehension.

This suggests that different mechanisms of change may be at work in patients with different levels of comprehension.

In the extracted data, verb comprehension was typically measured by testing the ability to match an auditorily-presented word to a picture, presented in an array that includes the target and one or more distractors (e.g., unrelated or semantic foils such as 'rowing' for the target 'sailing'; Bastiaanse et al., 2002; Druks & Masterson, 2000). Accurate performance on this task requires a complex set of processes. The input string of sounds/letters must be analyzed and recognized as a word in the appropriate input lexicon, and must activate the corresponding meaning (Patterson & Shewell, 1987). At the same time, the action pictures must activate abstract visuoperceptual representations and, subsequently, their corresponding meaning. Typically, pictures are selected so as to share many semantic features. The correct response is then contingent upon the ability to select the picture whose meaning fully matches that of the stimulus word. Poor performance on this task can therefore reflect deficits that arise at each of these levels of processing.

The predictive value of comprehension may reflect both a generic and a specific influence on verb retrieval. At a very general level, a comprehension deficit may significantly disrupt the therapeutic process by hampering participation in treatment tasks and successful implementation of compensatory strategies. The predictive effect of comprehension can be more specific, however. Semantic knowledge is involved both in word-picture matching and in action naming. Therefore, a severe impairment of semantic knowledge will inevitably yield deficits of both verb comprehension and production in the same individual. In agreement with this possibility, prior research showed that lexical processing can be facilitated by semantic priming in individuals with aphasia, and that the priming effect is reduced or absent in patients with poor comprehension (Baum, 1997). According to models that assume that activation proceeds in a

unidirectional fashion from the lemma level to the lexeme level (e.g., Bastiaanse & Van Zonneveld, 2004; Levelt, 1999), activation of the lexeme is inversely proportional to the extent of damage to the lemma. Consequently, relatively preserved semantic knowledge at the lemma level may yield above-threshold activation of the target lexeme. This way, in individuals with spared semantic knowledge, verb retrieval training can rely on activation of lexemes through the lemma level and therefore is more likely to succeed.

In patients with relatively better verb comprehension (above 67% accuracy), those with word repetition scores >49% had an increased chance of improvement. Also in this case, the relationships between verb retrieval, verb comprehension and word repetition can be complex. An obvious possibility is to attribute the predictive value of repetition to the fact that tasks of this type rely on short-term memory (Baldo, Klostermann, & Dronkers, 2008). In this framework, it should be stressed that influential models of memory, e.g., Atkinson and Shiffrin (1968), posit a crucial role for short-term memory in long-term learning. In agreement with this view, Papagno, Valentine, and Baddeley (1991) showed that healthy individuals use the phonological loop (in particular, subvocal rehearsal) when learning a foreign language vocabulary. In addition, a patient with impaired short-term memory phonological store (disrupting phonological recoding and phonological rehearsal) could not acquire new vocabulary in a foreign language, despite otherwise normal long-term learning abilities (Baddeley, Papagno, & Vallar, 1988). Considering the relation between word repetition and phonological short-term memory, and the support that short-term memory provides to vocabulary learning, our results suggest that short-term memory processes/abilities indexed by word repetition may facilitate the restoration of (or access to) lexemes. The exact nature of these processes cannot be established based on word repetition

only. Future research should address the relation between short-term memory and aphasia recovery using more direct measures of working memory.

Interestingly, short-term memory (as measured by repetition scores) affects performance only in a subset of patients with relatively good verb comprehension (see Figure 4.3). If poor comprehension disrupts the therapeutic process (as discussed in the previous paragraph), it is possible that the mechanisms of improvement mediated by short-term memory are only effective if patient's level of comprehension allows therapy to proceed efficiently. In addition, we should consider that regardless of short-term memory skills, picture-elicited verb retrieval requires patients to access lexemes from the lemma level. Perhaps short term memory/repetition can only facilitate recovery in the presence of good comprehension because, in this case, intact access to the lexicon through semantics can be strengthened to facilitate lexical selection (Baum, 1997). Supporting evidence comes from the repetition priming literature: priming effects are stronger (that is, they last longer) for words than for nonwords (Dannenbring & Briand, 1982; Kirsner & Smith, 1974; Scarborough, Cortese, & Scarborough, 1977), and with nonwords priming occurs only on items that were included in a study phase (Sereno, 1991). Finally, Lomas and Kertesz (1978) reported that aphasic patients with poor comprehension improve in repetition, while their production skills remain unchanged after therapy. This reinforces the hypothesis that repetition and its correlated cognitive processes only serve as a resource to facilitate recovery when access to the lexeme is at least partly spared. If it is not, rehabilitation of comprehension should be a priority.

Importantly, the study of Lomas and Kertesz (1978) does not specify the levels of language processing that were impaired before treatment and those that were modified after therapy and could therefore be responsible for improvement in repetition. The predictive value of repetition

scores may accrue from damage to mechanisms other than short-term memory, such as segmental disorders (the inability to retrieve the target phonemes, or to produce them in the correct order), or apraxia of speech (the inability to convert an abstract phonological representation into a correct speech plan). Protocols aiming at the recovery of verb retrieval deficits and focusing on overt language production (such as those selected for the present meta-analysis) have a greater chance of success when post-lexical damage is absent or mild, as in this case restoring activation of the lexemes targeted by treatment suffices to allow correct responses to occur. By contrast, damage to segmental (phonological) information or apraxia of speech will interfere with speech output. If sufficiently severe, post-lexical impairments may reduce effectiveness of verb retrieval remediation protocols by preventing the production of interpretable responses, thus resulting both in poor verb production and in pathological repetition scores.

4.4.2 Generalization

The first notable result regarding the factors that influence improvement in lexical retrieval of untreated verbs is that they differ from those associated with item-specific improvement. Prior studies had already suggested that item practice and task practice may rely on different neurocognitive mechanisms (Basso et al., 2013). The factors that significantly predict generalization are diverse. Two of them relate to treatment characteristics (morphological cues, frequency) and two to features of the subject's language impairment (noun comprehension, frequency). In the next paragraphs, we discuss treatment-related cognitive changes that may account for the predictive value of these variables.

Generalization in verb retrieval occurs infrequently (Webster and Whitworth, 2012), even following treatment techniques shown to result in generalization for noun production, such as

Semantic Feature Analysis (Wambaugh & Fergusson, 2007; Wambaugh et al., 2014). It is more likely when treatment addresses abstract properties or rules (e.g., argument structure or inflectional paradigm) that apply to more than one word or sentence. In the intact language system, different verbs share information about the syntactic structures in which they occur (Pickering & Branigan, 1998), and this facilitates production of shared constructions (structural priming: e.g., Bock, 1986). In aphasia, generalization is reported in the lexical retrieval of verbs after treatment of argument structure (Thompson et al., 2013), and of tense production in sentences (de Aguiar et al., 2015a; Links et al., 2010). Our finding that patients with grammatical impairment who do not receive morphological training are less likely to generalize than those who do is well in line with these studies. Training of these abstract properties, and in particular morphological training, may facilitate verb retrieval by alleviating the cognitive load associated with encoding grammatical information, thus allowing more resources to be allocated to verb retrieval. Data in line with this account were reported by Bastiaanse and Jonkers (1998) for agrammatic and Bastiaanse (2011) for fluent aphasic speakers. In spontaneous speech of both aphasic subgroups there is a relation between morphosyntactic complexity and verb retrieval.

Miceli et al. (1996) propose that generalization may or may not occur depending on the nature of the cognitive processes and representations that are impaired. For instance, lexemes are unique labels in an individual's mental lexicon, each specifying the phonological form associated with a concept (e.g., Roelofs, Meyer, & Levelt, 1998, 1998). If a patient has a deficit specific to lexical representations, treating a word is unlikely to improve retrieval of a different word, and item-specific improvement without (or with minimal) generalization is expected. In agreement with the prediction, Miceli et al. (1996) found no generalization (even to semantically-related words) in two patients with anomia due to lexical damage. Similar results were obtained by Fillingham

et al. (2006), Hickin et al. (2002), and Parkin et al. (1998).

A different outcome can be expected when information shared by many items in unavailable. As discussed above, shared information on sentence structure across verbs (Pickering & Branigan, 1998) can result in syntactic priming (Bock, 1986). If impaired, such knowledge can be restored through treatment of some verbs and become available also for untreated verbs (Thompson et al., 2013; Links et al., 2010; de Aguiar et al., 2015a). As reflected by our sample, morphosyntactic cues are typically presented to patients with "agrammatic" aphasia. These patients are more likely to show generalization following verb therapies than patients without grammatical impairment. This is observed in the subgroup of patients who did not receive morphological cueing, and supports the claim that generalization depends on the nature of the impaired language processes (Miceli et al., 1996).

Even when morphological cues were not presented, treatment may have engaged other types of grammatical knowledge. In fact, theories of speech processing share the claim that grammatical information (e.g., grammatical class, agreement and case assignment, etc.) is stored in the lemmas (Bastiaanse & Van Zonneveld, 2004; Miozzo & Caramazza, 1997; Roelofs et al., 1998), and it is retrieved even when verbs are produced at the single-word level. Hence, even when treatment does not require explicit access to grammatical information, such information is accessed implicitly. Patients with grammatical impairment may be more prone to generalization, due an impairment of generalizable (that is, shared) grammatical features, which are implicitly engaged in treatment, and can be at least partially restored by treatment.

Just like verb comprehension, poor noun comprehension may reflect damage to different levels of processing. But while patients with low verb comprehension scores improved less often on

treated verbs, patients with grammatical impairment and low scores in noun comprehension were more likely to improve on untreated verbs. In short, the data cannot be accounted for by a widespread comprehension impairment. Alternatively, we note that noun representations, in comparison to verb representations, are thought to have particularly high semantic detail (Conroy et al., 2006; Maguire et al., 2015). Therefore, tests that use nouns may be particularly sensitive to lemma-level impairment. Why this impairment was reflected by comprehension scores for nouns, rather than verbs may be confusing, and therefore it is relevant to highlight that the importance ratings show that both variables (verb and noun comprehension) are relevant for predicting generalization, but when considered simultaneously one surfaces as more important, potentially because both variables account for similar dimensions (Ishwaran et al., 2008).

Semantic representations are thought of as sets of features (e.g., a pen is elongated, used to write, has ink inside, etc.), which are shared by several words (pencils are also elongated and used to write, but do not have ink inside). In word retrieval, these features activate several, meaning-related word forms ("used to write" will activate both /pen/ and /pencil/). The lexeme with the largest semantic overlap is selected eventually (Bastiaanse & Van Zonneveld, 2004; Patterson & Shewell, 1987). In the event of a partial semantic deficit, naming errors may occur due to insufficient activation of features that are key to distinguish between related words (such as "has bristles", in our example), often resulting in semantically related words (Caramazza & Hillis, 1990).

Semantic features disrupted by brain damage, if restored by treatment, become available for the retrieval of all the words that share them. This will decrease the occurrence of errors to both treated words and untreated words with shared features. Semantic Feature Analysis (SFA; Boyle & Coelho, 1995) was designed based on this reasoning. The treatment techniques reported in our

database to produce generalization in subjects with grammatical impairment who did not receive morphological cues include discussion of verb's semantic features (Rose & Sussmilch, 2008; Carragher, Sage & Conroy, 2013), simultaneous semantic and gestural treatment (Rose and Sussmilch, 2008), gesture-only treatment (Rose & Sussmilch, 2008), repetition treatment (Rose & Sussmilch, 2008), and modified Constrained Induced Language Therapy (Maul et al., 2014). When reported, noun comprehension was below 84% in all subjects showing generalization. Not all of these treatment techniques required explicit discussion of semantic features. Nonetheless, the occurrence of semantic priming provides evidence that activation of semantic features occurs even if these are not explicitly discussed. Altogether, the effects of morphological cueing, semantic impairment (indexed by noun comprehension) and grammatical impairment in determining generalization after verb therapies point to the specificity of treatment outcomes in relation to the levels of language processing engaged by the treatment task (Jacquemot et al., 2012), and the levels of language impairment (Miceli et al., 1996).

4.4.3 Treatment frequency effect on item-specific improvement and generalization

The finding that patients who received fewer therapy sessions per week were more likely to show both item-specific and generalized improvement contrasts with previous reports (e.g., Boghal et al., 2003). At this stage, any attempt at an explanation is speculative, especially in the absence of many relevant details for each study (e.g., which treatment approach was selected, whether treatment was customized to each patient's needs or based on a "standard" protocol, etc.). For treated verbs, the apparently paradoxical effect of frequency is observed only in subjects with relatively high scores in verb comprehension and word repetition. In the light of the discussion in Section 4.1., this could mean that patients with mild semantic damage, and in whom phonological processes, short-term memory and articulatory planning are relatively

spared, have a greater potential for recovery and do not need frequent sessions (perhaps because they can learn the strategies applied during treatment sessions and apply them to more ecological circumstances of everyday life). However, it is not clear why the same (or a better) result cannot be obtained by increasing session frequency.

Similarly, we have no reasonable account for why patients with grammatical impairment who did not receive morphological cues and had severe noun comprehension problems were less likely to show generalization if they received more than 2.6 sessions per week. In any case, we note that patients who generalized received treatment on average for more days than those who did not show generalization (39.38 and 33.82, respectively), and that the two groups had a similar number of therapy sessions during that period (12.96 and 12.45, respectively). We took the conservative choice of disregarding variables that did not meet both of our criteria: improving model accuracy and being significant in our conditional inference trees. Nonetheless, the number of treatment days was also a significant predictor and therefore it is possible that this inverse frequency effect reflects the overall duration of treatment. In fact, Dickey and Yoo (2010) report that item-specific improvement occurs earlier in the course of treatment with a rapid and linear improvement, and generalization tends to appear later, and to show a slowly accelerating learning curve. It is then possible that these patients did not have enough therapy time. The relation of frequency, intensity, duration and amount of sessions with response to treatment (item-specific and generalized) should be systematically examined in future studies.

Data on the "reverse" effect of session frequency are clearly counterintuitive and difficult to interpret. However, regardless of the mechanisms underlying it, the finding that item-specific and generalized improvement is more likely in subjects who receive fewer therapy sessions challenges the general idea that more intensive treatment is more efficacious *per se* (Bhogal et

al., 2003). Reasons can be complex. For example, Brady et al. (2012) reported that patients tend to withdraw more often from intensive than non-intensive therapy. Further research should examine the complex nature of the relation between the frequency of weekly therapy and other treatment and patient-related variables.

4.4.4 Future directions

We provide tentative accounts for each of the identified predictors, in terms of cognitive mechanisms that potentially support improvement. Our interpretations are limited by theoretical and pragmatic issues. For example, even though we mentioned the potential role of cognitive, non-linguistic functions (e.g., short-term memory) in determining treatment outcome, few studies reported results of cognitive screenings. Collecting this information is critical for future meta-analyses. A similar consideration applies to lesion site, that was unspecified (or too vague to be used) in most studies. It is to be hoped that the diffusion of structural and functional neuroimaging techniques will help characterize brain structures and dynamics that contribute to specific types of recovery. In addition, we observed that pre-treatment scores in several tasks predicted item-specific or generalized improvement. Tracking changes in these dimensions after treatment is crucial to confirm the role of the underlying cognitive processes in constraining improvement. For example, if high levels of verb comprehension are tied to item-specific improvement in verb retrieval, changes in verb comprehension and production tasks should show a systematic correlation.

With respect to item-specific improvement, much of the literature used to support our interpretations comes from research with non-aphasic participants. The role of specific working memory processes in aphasia recovery should be independently established, in studies similar to

Papagno et al. (1991)[7]. The same applies to episodic memory skills, that might help build up the effects of treatment. Auditory verb/noun comprehension may be disrupted by damage to distinct levels of processing, each of which may contribute to its predictive value, and should be examined in future studies. Finally, the relation between the degree of preservation of semantic knowledge, sensitivity to priming, and potential for item-specific recovery must be confirmed empirically.

Similar considerations apply to generalization. A finer-grained study of the effects of structural and morphological priming in aphasic individuals is a prerequisite for clearer interpretations. This issue may be examined in patients with different types of language impairment, in order to disentangle the roles of conceptual and grammatical features. Furthermore, the patients included in this meta-analysis suffer from heterogeneous and often underspecified grammatical difficulties – some may have specific morphosyntactic difficulties, while others may have complex damage to one or more other processes involved in sentence production (e.g., Webster, Franklin, & Howard, 2004). Our data shows that generalization is partially accounted for by the characteristics of language impairment presented by the patient (semantic and grammatical impairment). The heterogeneity and/or under-specification of the levels of language impairment in the literature may account for some of the unexpected results (e.g., Rose & Sussmilch, 2008 vs Wambaugh et al., 2014), and should be explored in further research.

In addition, studies similar to this one may seek to identify predictors of other types of outcome. Improved communication in daily living is the final goal of aphasia therapy, and has been shown to improve after treatment of verb production in sentences (e.g., Links et al., 2010). Further

[7] Though PV (Baddeley, Papagno, & Vallar, 1988) had been previously diagnosed with aphasia (Basso et al., 1982), by the time she was studied there were no identifiable language deficits.

meta-analytic studies may help identify the predictors of transfer of treatment benefits to communication in daily life. Potentially, this will allow inferences about the mechanisms of change that underlie improved communication in daily living, and will help improve current treatment techniques and develop new ones which engage those mechanisms.

Finally, we are not able to account for the inverse relation between frequency of treatment and language improvement. Considering the high impact that this variable has in provision of healthcare, it is crucial to assess its role in relation to other patient-related and treatment-related variables.

4.5 Conclusion

Improved lexical retrieval of treated and untreated verbs occurs through different mechanisms. Item-specific improvement is observed in 76.1% of the patients. It may depend on restoring access to and/or rebuilding specific knowledge of lexemes. Success is determined by the availability of at least partial access to these representations (dependent on the activation of semantic features at the lemma level, indexed by verb comprehension scores), and by at least some ability to practice the labels to be restored or re-accessed (with short-term memory skills indexed by word repetition scores). The results on generalization are less clear. Generalization is infrequent (14.5%), and likely signifies that treatment-related changes occurred in these cases at the level of processing abstract features (e.g., semantic features, morphosyntactic processes, inflectional paradigms, argument structures, etc.), shared by different verbs. These features can be trained during therapy sessions by using few lexical items and contexts. If recovered, they become available for a larger number of items after treatment, thereby facilitating encoding of grammatical information and access to lexemes. Treatment techniques that engage processing of these features are associated with greater chances of generalization.

The present report should not be taken as an exhaustive list of all the factors and mechanisms that may be at play in item-specific recovery and generalization. Our description of prognostic factors and their interactions is inevitably incomplete and preliminary. However, it already challenges a simplistic interpretation of some well-established predictors of recovery (e.g., treatment frequency, intensity and aphasia severity). It invites to consider in detail the role of linguistic and language-related processes in subjects enrolled in treatment protocols. Our meta-analysis sheds some light on the mechanisms involved in different types of recovery, and can be used to inform theories and practices of therapy.

CHAPTER 5

Can tDCS enhance item-specific effects and generalization after linguistically motivated aphasia therapy for verbs?[8]

Aphasia therapy focusing on abstract properties of language promotes both item-specific effects and generalization to untreated materials. Neuromodulation with transcranial Direct Current Stimulation (tDCS) has been shown to enhance item-specific improvement, but its potential to enhance generalization has not been systematically investigated. Here, we test the efficacy of ACTION (a linguistically motivated protocol) and tDCS in producing item-specific and generalized improvement in aphasia. Nine individuals with post-stroke aphasia participated in this study. Participants were pre-tested with a diagnostic language battery and a cognitive screening. Experimental tasks were administered over multiple baselines. Production of infinitives, of finite verbs and of full sentences were assessed before and after each treatment phase. Nonword repetition was used as a control measure. Each subject was treated in two phases. Ten daily 1-h treatment sessions were provided per phase, in a double-blind, cross-over design. Linguistically-motivated language therapy focusing on verb inflection and sentence construction was provided in both phases. Each session began with 20 min of real or sham tDCS. Stimulation site was determined individually, based on MRI scans. Group data showed improved production of treated and untreated verbs, attesting the efficacy of behavioral treatment, and its potential to yield generalization. Each individual showed significant item-specific improvement. Generalization occurred in the first phase of treatment for all subjects, and in the second phase for two subjects. Stimulation effects at the group level were significant for treated and untreated verbs altogether, but a ceiling effect for Sham cannot be excluded, as scores between real tDCS and Sham differed only before treatment. Our data demonstrate the efficacy of ACTION and suggest that tDCS may enhance both item-specific effects and generalization.

[8] This chapter was published as de Aguiar, V., Bastiaanse, R., Capasso, R., Gandolfi, M., Smania, N., Rossi, G., & Miceli, G. (2015). Can tDCS enhance item-specific effects and generalization after linguistically motivated aphasia therapy for verbs? *Frontiers in Behavioral Neuroscience, 9*, 190. doi:10.3389/fnbeh.2015.00190

5.1 Introduction

Aphasia is an acquired language disorder that occurs following brain damage, frequently caused by stroke, traumatic brain injury or brain tumors. Though different rehabilitation strategies have been used in aphasia, they all share the general aim of improving communication. Currently available evidence indicates that aphasia therapy is effective (Brady et al., 2012). Nevertheless, 43% of the individuals with aphasia who suffer from language disorders due to a first-ever stroke are still aphasic 18 months post-onset (Laska et al., 2001). While most research on aphasia therapy focuses on the recovery of nouns, there is an increasing interest in the rehabilitation of verb and sentence production (Webster & Whitworth, 2012). Research addressing how to optimize verb and sentence rehabilitation programs to produce larger item-specific effects and generalization is needed. A recent addition to treatment tools for aphasia rehabilitation is tDCS—a neuromodulation technique introduced to increase treatment efficacy, in combination with Speech-Language Therapy. tDCS may enhance item-specific improvement, and it seems to be effective across a variety of tasks (de Aguiar et al., 2015b).

The current study has three main goals. First, to test the efficacy of the Italian version of ACTION, a treatment protocol shown to result in generalization (Bastiaanse et al., 2006; Links et al., 2010). We focus specifically on verb retrieval and inflection in sentence production, and assess the effects of treatment on both treated and untreated verbs. Second, to test the potential of tDCS in enhancing both item-specific improvement and generalization, when paired with ACTION. Third, to discuss individual outcomes in relation to group results, in order to better understand the effects of a treatment combining tDCS and ACTION. In this introduction, we describe the cognitive processes involved in verb and sentence production, and we provide an

overview of studies focusing on the treatment of verb and sentence production, and of studies using tDCS.

5.1.1 Verb and sentence production

A unique feature of lexical representations of verbs is that, contrary to most nouns, they contain information about argument structure that is necessary for sentence production (Saffran et al., 1980). This means that deficits in verb processing may contribute to deficits in sentence processing (e.g., patient HW, Caramazza and Hillis, 1991), though sentence-level deficits may also arise from other types of impairment. The speech-error model (Garrett, 1980) defines 3 processing levels involved in producing sentences. The message level entails the speaker's communicative goal and is a non-linguistic representation of the idea to be conveyed by the speaker. This idea becomes semantically and thematically specified at the functional level. Here, semantic word representations are retrieved, the predicate-argument structure of the main verb specifies the number of arguments and the thematic roles required by the verb, and thematic roles are assigned to semantic representations (Schwartz, 2013). Inflectional affixes are included in this syntactic frame (Garrett, 1980). Finally, sentence constituents are ordered, and phonologically specified representations (lexemes) are retrieved from the phonological output lexicon, at the positional level. With languages having a limited amount of possible predicate argument structures, there is evidence that different verbs share combinatorial nodes (i.e., the stored information about the syntactic structures in which they occur; Pickering and Branigan, 1998) and that recent exposure to a sentence structure may facilitate the production of the same structure with a different verb (a phenomenon known as structural priming; Bock, 1986).

Even though these levels are conceived of as distinct processing stages, interactions between them are also assumed. For instance, after a syntactic frame is specified, some lexemes are more

likely to be activated, due to their relation to appropriate semantic features (Bock, 1986). In addition, evidence for a relation between verb inflection and retrieval was reported by Bastiaanse (2011): individuals with fluent aphasia performed below norm in verb retrieval when producing finite verbs, but they were unimpaired when producing infinitives. Hence, syntax can influence lexical verb retrieval, due to both introduced lexical selection biases, and increased task complexity.

The neural correlates of these processes have been investigated in neuro-imaging research. Verb naming has been associated with activity in dorsolateral frontal and lateral temporal cortex (Perani et al., 1999), left frontal operculum and posterior middle temporal gyrus (Tranel et al., 2005). The processing of argument structure recruits left IFG (Inferior Frontal Gyrus) including BA47 and BA9, but also the superior temporal (Shetreet et al., 2007), angular and supra-marginal gyri and precuneus, which are more active in processing transitives than intransitives (Den Ouden et al., 2009). Thematic role assignment involves posterior peri-sylvian areas (Thompson et al., 2007). Tense inflection activates Broca's area, for both regular (e.g., Tyler et al., 2005) and irregular verbs (e.g., de Diego Balaguer et al., 2006). Kielar et al. (2011) report additional involvement of motor, premotor and posterior parietal regions in (overt and covert) present and past tense production. Each of these processes may be selectively impaired when the corresponding neural substrate is damaged, resulting in different sentence production deficits.

5.1.2 Rehabilitation of verb and sentence production

The interest in the rehabilitation of verb production has increased over the last decades. At the single-word level, verbs can be treated with the same techniques used for nouns, even though improvement in verb production seems more difficult to achieve (Webster and Whitworth, 2012). At the sentence level, treatment techniques typically include identifying the agent and

theme of each verb and then producing a sentence including all elements, thereby engaging predicate-argument structure retrieval and thematic role assignment. Aphasic individuals who underwent this type of treatment improved in retrieving treated, but not untreated verbs and showed improvement also in spontaneous speech (Fink et al., 1992; Webster et al., 2005). This suggests that verb production in sentence context may be a more productive treatment strategy than the production of verbs as isolated words. Research with sentence-level treatment has also led to the hypothesis that training complex syntactic structures results in generalization to untrained, linguistically-related, less complex structures (Complexity Account for Treatment Efficacy, Thompson et al., 2003). In line with this hypothesis, treating three-argument verbs in sentence production improved retrieval of untreated one- and two-argument verbs (Thompson et al., 2013).

A linguistically-motivated treatment protocol has been designed to address both lexical-semantic (argument structure) and syntactic (movement) properties of verbs (Treatment of Underlying Forms; Thompson and Shapiro, 2005). This treatment starts by addressing knowledge of/access to the thematic information of verbs. Aphasia patients are subsequently made aware of the properties of movement operations, in an explicit way. The benefits of treatment were shown to generalize to (less complex) constructions requiring the same type of movement as those treated explicitly, and to spontaneous speech (e.g., Thompson et al., 1996), in line with the Complexity Account for Treatment Efficacy (Thompson et al., 2003).

Two studies report on the treatment of verbal morphology by means of a Computerized Visual Communication protocol (Weinrich et al., 1997, 1999). This treatment was used to elicit past, present and future tense forms of regular and irregular verbs in sentences. In both studies, the

production of inflected verbs in sentences improved, and generalization was observed in the use of morphological transformations, but not in verb retrieval.

Notably, generalization to lexical retrieval of untreated verbs occurs infrequently (Webster and Whitworth, 2012). The occurrence of generalization may depend on patient characteristics and treatment characteristics. Individuals with semantic damage may be more likely to generalize if treatment restores semantic features that are shared across semantic representations of words. Lexical representations, however, are item-specific and patients with lexical damage are therefore less likely to generalize (Miceli et al., 1996). In what concerns treatment tasks, for nouns, treatments for semantic processing is thought to have greater potential to induce generalization, due to the large overlap of semantic features across words of the same semantic category (e.g., Boyle and Coelho, 1995). However, the same strategy produces only item-specific improvement in verb retrieval (Wambaugh and Ferguson, 2007; Wambaugh et al., 2014).

ACTION is a treatment protocol for aphasia rehabilitation developed for Dutch (Bastiaanse, Jonkers, Quak, & Varela Put, 1997). It includes four steps that address the different levels of processing necessary for producing verbs in simple, declarative sentences:

(1) Step 1, lexical level: action naming
(2) Step 2, syntactic level: sentence completion with a verb in the infinitive
(3) Step 3, morphosyntactic level: sentence completion with finite verb
(4) Step 4, sentence construction

In Bastiaanse et al. (2006), treating infinitives did not result in generalization, but treating finite verbs did. Links et al. (2010) found that, when infinitives were treated, untrained infinitives improved only marginally, and untrained finite verbs did not improve. By contrast, when finite verbs were treated, generalization was present for untreated finite verbs, but not for infinitives.

Notably, improvement extended to spontaneous speech and to a task tapping communication in daily living, and was sustained after 3 months.

Altogether, the literature shows that when verbs are treated as isolated words, item-specific improvement can be achieved using similar techniques to those used for noun rehabilitation. Generalization to untreated verbs was reported following semantic, gestural and repetition cueing (Rose & Sussmilch, 2008), when treatment was centered at the sentence level and the grammatical properties of verbs were taken into account in designing the treatment task (Bastiaanse et al., 2006; Links et al., 2010; Thompson et al., 2013). These studies share two features—treatment addressed grammatical properties of verbs (e.g., argument structure, inflection, movement) and focused on the sentence level. Engaging knowledge of these abstract properties may be an important ingredient to achieving generalization.

5.1.3 tDCS in aphasia rehabilitation

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique. A weak electrical current is delivered through electrodes positioned over the scalp (e.g., Nitsche et al., 2008). In language research, studies with healthy individuals show that anodal tDCS can increase speed (Fertonani et al., 2010) and amount of verbal learning (Meinzer et al., 2014). Cathodal tDCS, on the other hand, negatively affected learning in an action and object learning paradigm (Liuzzi et al., 2010). In aphasia rehabilitation, methodology varies substantially across studies. Positive effects were reported in spite of variations in current intensity (1–2 mA), stimulation polarity and montage (perilesional cathodal tDCS in Monti et al., 2008; perilesional anodal in Baker et al., 2010; contralesional cathodal tDCS in Flöel et al., 2011 and contralesional anodal tDCS in Vines et al., 2011) (for reviews, see Hamilton et al., 2011; Monti et al., 2013; de Aguiar et al., 2015b).

Models of inter-hemispheric competition (Murase et al., 2004) predict bicephalic montages (a perilesional anode and a contralesional cathode) to modulate interhemispheric interactions more efficiently than monocephalic montages (a perilesional anode and a reference electrode). Recently, it has been suggested that the optimal montage should be determined individually, based on lesion site and size (Hamilton et al., 2011) and the individuals' pattern of activation during correct language production (Baker et al., 2010).

Effective tDCS-related treatment enhancement may depend on appropriately pairing stimulation site and treatment task. Marangolo et al. (2013a, 2014) found that action naming and discourse cohesion were enhanced after stimulation to Broca's but not Wernicke's area[9]. Given that ongoing computations may depend on the pattern of cognitive impairments and brain damage, different patients may respond differently to tDCS. Currently, the lack of data on individual outcomes in many studies (except Marangolo et al., 2013a, 2014), and lack of detailed information about the linguistic deficits of participants do not allow establishing whether some treatments were more effective than others, as a function of lesion site and of cognitive impairment. Supporting the need to report individual outcomes, recent research with healthy participants identified a large variability in individual responses to stimulation (Horvath et al., 2014).

There is little information about the role of tDCS in promoting generalization. Some studies report a transfer to spontaneous speech (Marangolo et al., 2013b, 2014), and statistically insignificant increase of accuracy for untreated nouns (Baker et al., 2010). Nevertheless, in these studies pre-treatment performance was not measured in multiple baselines gathered in a time

[9] Given that electrodes of the same size were used over left and right hemisphere areas, the studies of Marangolo et al. (2013a, 2014) provide evidence for the efficacy of a bi-cephalic montage with anode over peri-lesional and cathode over contro-lesional areas. For a more detailed discussion see de Aguiar et al. (2015b).

window similar to that of treatment. In addition, no control task was administered to ensure that behavioral improvement was specific to treatment-related tasks. Therefore, it is not possible to measure the potential effect of task practice nor to rule out spontaneous recovery (Howard et al., 2015). It is relevant to note that generalization could be expected to occur in conversational therapy (Marangolo et al., 2013b,2014) due to the functional scope of treatment, but it was unlikely in picture-word matching (Baker et al., 2010). To assess the potential of tDCS in enhancing generalization, it is important to pair it with a treatment task likely to yield generalization (e.g., semantic feature analysis for nouns, or linguistically motivated therapies for verbs, such as Treatment of Underlying Forms or ACTION).

As mentioned earlier (Section Rehabilitation of Verb and Sentence Production), generalization in verb production has been observed infrequently. Treatment at the sentence level engaging knowledge of morphosyntactic properties of verbs appears to be effective with this regard, but studies reporting on generalized effects of verb treatment usually focus either on tense training or on argument structure training. In this study, we test the efficacy of the Italian adaptation of the ACTION protocol that combines training of lexical verb retrieval and of verbal morphology, in sentence context. This training should improve lexical retrieval of both treated and untreated verbs. In addition, here we test for the first time whether tDCS, in combination with speech/language therapy, can enhance both item-specific improvement and generalization.

5.2 Method

5.2.1 Recruitment and participants

The main inclusion criterion was a difficulty in verb retrieval and sentence construction. Eligible participants were nine right-handed[10] individuals with chronic aphasia after a left hemisphere stroke, aged between 18 and 80 years and with at least 5 years of education. Seven participants presented with their first-ever stroke. The two participants who had had prior lesions were assigned to distinct treatment groups (sham-first and tDCS first). Exclusion criteria were sensitive skin, epileptic seizures in the 6 months preceding enrolment, use of drugs known to increase the risk of seizures and presence of metallic fragments in the head. The study was approved by the ethics committee of the University of Trento (protocol number 2012-035). After being referred by their neurologist, patients and primary caretakers were invited for a briefing session. In this session the procedure was described, and informed written consensus was obtained. Table 5.1 provides a summary of participants' demographic and clinical characteristics. Detailed information about lesion sites is provided in Appendix B.

Table 5.1. Demographic and clinical characteristics of participants.

	Participant	Gender	Age	Han.	Education	Occupation	Lesion type	TPO
sham first	LF	M	45	Right	High school	Tinsmith	Ischemic	39
	GC	M	68	Right	Junior high school	Social worker	Ischemic	26
	GD	F	48	Right	University degree	Accountant	Hemorrhagic	17
	GP	M	52	Right	High school	Retired	Ischemic	80
	EC	M	54	Right	High school (incomplete)	Marble worker	Ischemic	92
tDCS first	SP	M	75	Right	University degree	Accountant	Ischemic	8
	RL	F	43	Right	High school	Accountant	Ischemic	88
	CK	F	76	Right	Junior high school	Secretary	Hemorrhagic	54
	PG	M	52	Right	University degree	Insurance actuary	Ischemic	36

Table 5.1. Han.: Handedness; TPO: Time Post-Onset (in months).

[10] Handedness was reported in the neurological assessment of each patient, and confirmed by patient and/or caregiver.

5.2.2 Procedure

Prior to the beginning of the experimental protocol, participants were engaged in a diagnostic assessment. A multiple-baseline, double-blind and sham-controlled, cross-over design was used to assess treatment effects. The entire experimental protocol lasted 10 weeks (Figure 5.1). There were three assessment phases (baseline, intermediate and final), and two treatment phases. In each assessment phase, three testing sessions were spread over a period of 2 weeks, to encompass an interval similar to that of treatment[11]. They served to establish pre-treatment stability in primary outcome and control measures. This allowed to control (unlikely) effects of spontaneous recovery on the changes observed after treatment. In addition, the data from the three sessions that preceded each treatment phase were used to construct two matched sets of verbs: one to be treated, one to measure generalization[12]. The scores obtained in the three pre-treatment assessment sessions were contrasted with those observed in the three post-treatment assessment sessions, to evaluate the effects of treatment on treated and untreated verbs, for each phase. Ten daily (five times per week) 1-h treatment sessions were provided in each treatment phase. Speech-Language Therapy was administered using the Italian version of the ACTION protocol (based on Links et al., 2010), described below. ACTION was administered in both phases, to each individual. Participants were randomly assigned to two possible treatment orders: 5 received Sham in the first, and tDCS in the second treatment phase; 4 received treatment in the reverse order.

[11] Patients PG and GD were tested in consecutive days because they had to travel to participate in the study.
[12] Please note that the baseline phase is the same as the item selection phase. Had patients been tested only on difficult items, data would have been susceptible to the problem of regression to the mean. In our case, 88 verbs were tested in all assessments, even though at each treatment stage only 40 (20 treated and 20 untreated) were selected for statistical analyses. This approach allows an economic use of time, as only one pre-treatment phase is needed, and circumvents the problem of regression to the mean, making it possible to reliably assess both item-specific improvement and generalization (Howard et al., 2015).

Figure 5.1. Treatment study design

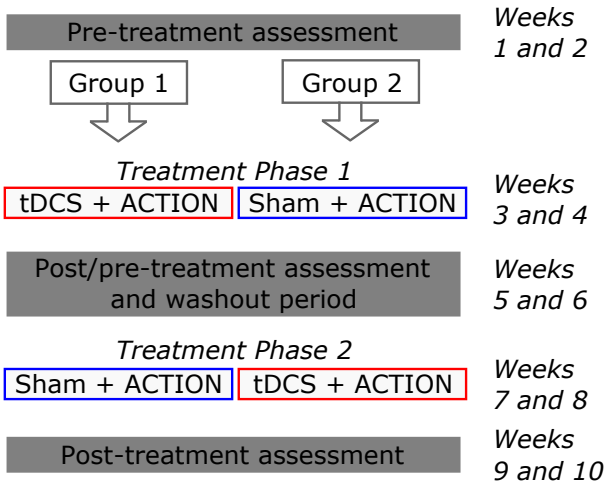

Figure 5.1. Each patient was involved in two treatment phases. Initially, participants were randomly assigned to one of two treatment orders. The entire protocol lasted 10 weeks.

5.2.2.1 Diagnostic assessment

A diagnostic language battery (Batteria per l'Analisi dei Deficit Afasici, BADA, Miceli et al., 2006) was administered to identify the functional locus of language impairment. Additional tests for cognitive screening were administered, including Digit Span (Orsini et al., 1987), Clock Drawing (Dal Pan et al., 1989), and Attentive Matrices (Spinnler & Tognoni, 1987).

5.2.2.2 Tests administered in each session of each assessment phase

Three verb production tests were developed to assess changes in verb retrieval accuracy. Black-and-white line drawings were used to elicit the verb, in all tests (for examples, see Figure 5.2). In the first task (henceforth, VTinfinitives), participants were asked to complete a sentence (e.g., "L'uomo vuole…," The man wants…) with the corresponding verb in the infinitive ("…mangiare," to eat). In the second (henceforth, VTfinite), the to-be-completed sentence included a temporal adverb (e.g., "Ieri/Oggi/Domani l'uomo…," Yesterday/Now/Tomorrow the man…) and the patient had to produce the finite verb in the correct tense ("…ha

mangiato/mangia/mangerà," ate, eats, will eat). In the third test (henceforth, VTsentence), the patient was prompted with the image, and asked to produce a Subject-Verb-Object (SVO, for transitive verbs, e.g., "L'uomo mangia la torta," The man eats the pie) or a Subject-Verb-Adjunct (SVA, for intransitive verbs, e.g., "L'uomo corre sulla spiaggia," The man runs at the beach). The adjunct was always a prepositional phrase expressing location. A complex scoring procedure was developed, but in this report only lexical accuracy is considered—a measure shared by the three verb tests. Responses were scored as correct if the patient produced the correct verb. Phonemic and morphosyntactic errors were disregarded.

Figure 5.2. Examples of stimuli used in the three verb production tests.

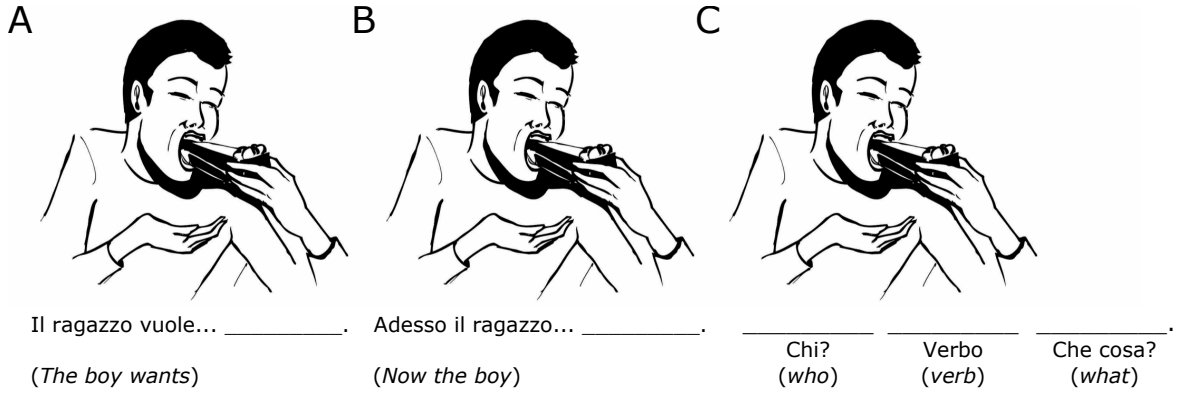

Figure 5.2. Panel A: VTinfinitive (sentence completion with a verb in the infinitive). Panel B: VTfinite (sentence completion with a verb in the correct tense). Panel C: VTsentence (sentence construction).

The same 88 verbs were used in the three verb production tests. They were divided in three sets (sets 1, 2, and 3). In session 1 of each phase, set 1 was used for VTinfinitive, set 2 for VTfinite and set 3 for VTsentence. In sessions 2 and 3, the three sets were assigned to the three tasks using a Latin Square design. The three sets were matched for relative frequency, length in phonemes, number of internal arguments, instrumentality, name relatedness, body part involved

(face, arm, leg), manipulation, inflectional paradigm and regularity. The comparison of lexical accuracy for 88 verbs across the three sessions that preceded each treatment phase allowed establishing pre-treatment stability.

Comprehension of these verbs was assessed using a picture verification test. The picture of a target verb was presented while the examiner pronounced a verb in the infinitive. The verb could be the target, a semantic distractor or an unrelated distractor (e.g., the picture corresponding to the verb "to eat" was paired, on different occasions, to the correct word "to eat," to the semantic foil "to drink" and to the unrelated foil "to mop"). On each day, 1/3 of the items was presented with the correct target, and the remaining 2/3 with distractors. Participants had to reply "yes" or "no" (verbally or by pressing a key) to indicate whether the verb presented auditorily corresponded to the picture. Targets, semantic and unrelated distractors were matched for frequency, length in phonemes, name relatedness, number of internal arguments, instrumentality and manipulation.

Performance on the nonword repetition test from the BADA (Miceli et al., 2006) was used as a control measure. This allowed assessing whether any observed improvement was treatment-related (i.e., restricted to verb tasks, which were the focus of treatment), or aspecific (nonword repetition measures phonological abilities, but is unrelated to verb retrieval). The test included 36 items, ranging in length between 1 and 3 syllables.

5.2.2.3 Behavioral treatment

In Italian, Subject-Verb-Object is the base word order in sentences. Inflected verbs occur in second position without overt movement. In this study, treatment was provided at the level of simple, declarative sentences, and a task specifically designed to address movement operations

was not included. Considering the rich morphology of Italian, steps three and four used in ACTION for Dutch were modified to include verb production in three different tenses. The Italian adaptation of ACTION (Bastiaanse et al., 1997), includes these four steps:

(1) Step 1, lexical level: Action naming

(2) Step 2, syntactic level: Sentence completion with infinitive

(3) Step 3, morphosyntactic level: Sentence completion with finite verb in three tenses

(4) Step 4, Sentence construction with finite verb in three tenses

Figure 5.3. Examples of stimuli used during treatment.

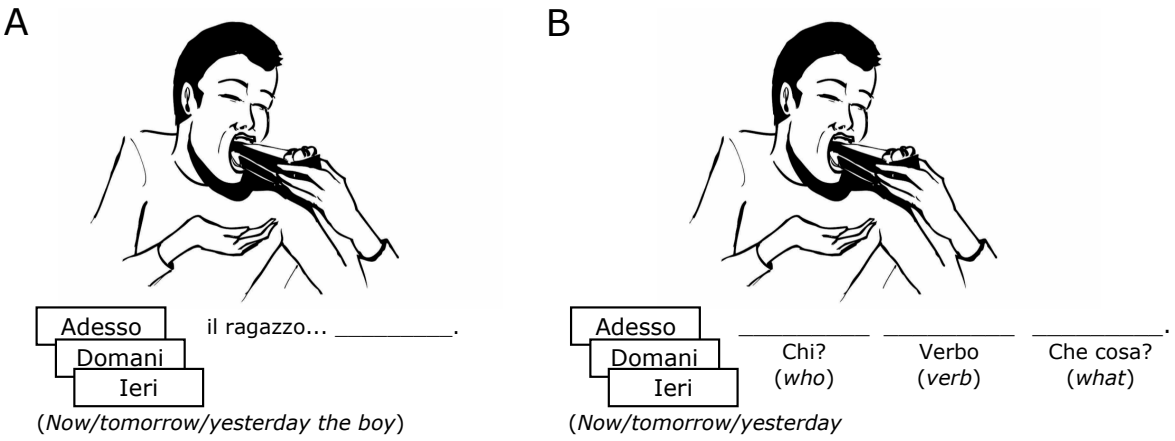

Figure 5.3. Panel A: Step 3 (sentence completion with a verb in three tenses). Panel B: Step 4 (sentence construction in three tenses). Detailed information about cueing procedures for each step is available in Appendix C.

Therapy was provided over ten 1-h sessions in each phase. Each phase lasted 2 weeks and entailed treatment with two different tasks. Participants completed Step 3 in the first week, and Step 4 in the second week. Examples of stimuli for each step are provided in Figure 5.3 (Figures 5.3A, and 3B for Steps 3 and 4, respectively). In Step 3, the patient saw an image with an adverb and a subject written below the picture (e.g., "Now the man…"), and was asked to complete the sentence with the verb inflected in the correct tense. In Step 4, the patient saw an image and a

written adverb (e.g., “now…”), and was requested to produce a full sentence that properly described the image (Subject-Verb-Object or Subject-Verb-Adjunct), with the verb inflected in the correct tense.

Structured increasing cues were provided. The cues provided to each subject depended on whether the participant produced retrieval errors or morphological errors, and on the constituent in which the error occurred. For a thorough description of the training procedure and of the cueing strategies provided during treatment steps three and four, the reader is referred to Appendix C. The 88 items included in ACTION were selected on the basis of a norming procedure. Ten healthy volunteers were asked to build sentences that described the picture stimuli. Items with less than 70% picture-sentence agreement across all constituents were excluded based on this data. The items surviving this procedure had a mean agreement of 90.11% (SD = 0.084%). In addition, these items were normed for a wide range of linguistic variables to create matched sets of verbs (with norms from Rofes, de Aguiar, & Miceli, 2015b).

For each participant, and prior to each treatment phase, two sets of 20 verbs were prepared: a to-be-treated set, to evaluate item-specific benefits of treatment, and a matched, not-to-be-treated set, to evaluate generalization to untreated items. Sets were matched for picture-sentence agreement, age of acquisition, imageability, relative frequency, length in phonemes, number of internal arguments, inflectional paradigm, instrumentality, name relatedness, manipulation, body part involved (face, arm, leg) using available norms (Rofes et al., 2015b). In addition, to ensure comparability of treated and untreated items, the two sets were individually tailored. They were matched for retrieval accuracy across the three verb tasks in the three assessments that preceded

each treatment phase, for error types produced by the patient, and for comprehension accuracy[13]. The details of set balancing for each patient are available in Appendix D.

5.2.2.4 tDCS

tDCS was administered using a battery-driven, programmable Eldith direct current stimulator (neuroConn, PLUS version), through two 35 cm2 electrodes. Current intensity was increased in a ramp-like fashion for 5 s until reaching 1 mA (current density = 0.2 mA/cm2). Each treatment session began with 20 min of real or sham bicephalic tDCS. Sham stimulation was administered with the same parameters used for real stimulation, but the stimulator was turned off after 30 s (Gandiga et al., 2006). The same procedure was repeated at the end of the 20-min period. To ensure blinding efficiency, participants were asked to fill a questionnaire at the end of each 2-week treatment phase (Fertonani et al., 2010), in which they indicated the nature and intensity of the sensations experienced during the treatment. Participants reported mild to moderate itchiness, pinching, burning, fatigue or heating under the electrode, mild pain. One patient reported mild headache and two others reported mild discomfort under the elastic strap.

Both the therapist who administered behavioral treatment and the experimenter who analyzed the data were blind to the stimulation condition, until individual outcomes for phase 1 and 2 were statistically analyzed. A third experimenter handled the tDCS device in each treatment session. The difference in number and intensity of symptoms observed across tDCS and Sham phases was not significant (Wilcoxon Signed-Rank test = 0.84, p = 0.200, one tailed).

Stimulation site was determined individually, after inspection of each patient's MRI scan (see Table 5.2). The anode was always centered over a left perilesional area. In three participants

[13] Whenever possible, only verbs that the patient failed to name but comprehended correctly were included in the treatment and control sets (see Appendix D for exact numbers). Exceptions were made only when fewer than 40 such verbs were available to prepare the two sets, due to poor comprehension.

(CK, PG and GD), this was Broca's area (BA 44–45), and in these cases the cathode was placed over the right hemisphere homolog of Broca's area. In two cases (LF and EC) the lesion partially encompassed Broca's area. In these subjects the anode was placed anterior and superior to Broca's area (BA45–46), and the cathode over the homologous area in the right hemisphere. In three other participants (GP, RL and SP) lesions were more anterior. Since they encompassed the entire IFG and caused considerable damage to the middle frontal gyrus, the anode was placed over the left superior and middle frontal gyri (BA9–10). In these cases, the cathode could not be positioned symmetrically, because shunting of current between electrodes (bypassing the brain) can occur with electrode distances under 8 cm (DaSilva et al., 2011). Therefore, the cathode was positioned over the right homolog of Broca's area. Finally, GC's lesion was parieto-occipital and parieto-temporal. In order to respect the rule of stimulating peri-lesional areas, the anode was positioned over the posterior middle and superior temporal gyri (encompassing Wernicke's area), and the cathode in a symmetrical position over the RH.

Table 5.2. Stimulation sites and electrode positioning.

	Anode (LH)	EEG coordinates	Cathode (RH)
LF	Anterior and superior to Broca's area (BA45-46)	Centered between F7 and F3	Homologous
GC	Superior/middle temporal gyri (BA21-22)	Centered between T7 and TP7	Homologous
GD	Broca's area (BA 44-45)	Crossing point between T3-Fz and F7-Cz	Homologous
GP	Superior/middle frontal gyri	Centered above FP1	Right Broca
EC	Anterior and superior to Broca's area (BA45-46)	Centered between F7 and F3	Homologous
SP	Superior/middle frontal gyri (BA10)	Centered above FP1	Right Broca
RL	Superior/middle frontal gyri (BA10)	Centered above FP1	Right Broca
KC	Broca's area (BA 44-45)	Crossing point between T3-Fz and F7-Cz	Homologous
PG	Broca's area (BA 44-45)	Crossing point between T3-Fz and F7-Cz	Homologous

Table 5.2. EEG coordinates are expressed according to the international 10-20 system. LH: left hemisphere; RH: right hemisphere.

Broca's area was identified as the crossing point between T3-Fz and F7-Cz, following Friederici et al. (1998). All other coordinates were extracted from Okamoto et al. (2004), who studied the probabilistic mapping of 10-20 EEG coordinates and brain areas on the cortical surface.

5.3 Results

5.3.1 Diagnostic assessment and cognitive screening

Selected tests from the BADA (Miceli et al., 2006) were used to characterize the profile of language impairment in each subject. Results of this diagnostic assessment are presented in Table 5.3. Our sample included fluent (GC, GD, and PG) and nonfluent participants. In all cases, sentence production was characterized by omission of obligatory arguments, errors of thematic role assignment, morphological errors and difficulties in producing non-canonical sentences. Three participants had mild-to-moderate semantic impairment (GD, SP, and KC). All participants presented with damage to the phonological output lexicon. Different sublexical conversion mechanisms were impaired across subjects, but these always included phoneme-to-phoneme conversion. In addition, all participants presented with length-sensitive difficulties in tasks that required overt production, suggesting damage to phonological short-term memory. The diagnostic assessment of each patient is summarized in Appendix E.

LF, GP, SP, RL, CK, and PG performed below norm in the forward Digit Span, consistent with reduced phonological short-term memory. All participants except RL performed below norm in digit span backwards. SP, KC and PG did not complete this task. Visual attention, as assessed by Attentive Matrices, was impaired in LF, GC, EC, SP, and RL. Visuo-spatial cognition and two-dimensional construction, as assessed by the Clock-Drawing test, was below norm in LF, EC, SP, and RL. Subject GD did not complete these two tasks, due to difficulties following instructions. Scores for each participant are presented in Table 5.4.

Table 5.3. Scores (% error) in diagnostic assessment battery (BADA).

		Sham first					tDCS first			
		LF	GC	GD	GP	EC	SP	RL	CK	PG
Sublexical	Auditory discrimination	6.7	6.7	6.7	10.0	3.3	n.a.	10.0	10.0	3.3
	Visual-auditory discrimination	13.3	0.0	13.3	43.3	11.7	n.a.	20.0	n.a.	n.a.
	Nonword repetition	27.8	26.1	33.3	27.8	27.8	44.4	5.6	55.6	27.8
	Nonword reading	26.1	22.7	0.0	80.0	35.6	91.3	21.7	30.4	47.8
	Nonword writing	66.7	61.5	8.3	100.0	72.0	n.a.	41.7	75.0	41.7
	Nonword copy	50.0	n.a.	0.0	0.0	33.3	n.a.	0.0	16.7	16.7
Semantico-lexical	Auditory lexical decision	12.5	10.0	12.5	11.3	8.8	8.8	5.0	22.5	10.0
	Visual lexical decision	30.0	7.5	0.0	31.3	7.5	37.5	0.0	7.5	17.5
	Word repetition	27.3	0.0	4.5	2.2	2.2	55.6	9.1	4.5	27.3
	Word reading (aloud)	32.6	2.2	2.2	56.5	0.0	60.9	4.3	0.0	30.4
	Word writing to dictation	69.6	8.7	0.0	80.0	80.4	n.a.	8.7	17.4	17.4
	Word copy	40.0	20.0	0.0	20.0	40.0	100.0	0.0	0.0	40.0
	Auditory noun comprehension	10.0	2.5	20.0	2.5	0.0	30.0	0.0	5.0	0.0
	Visual noun comprehension	10.0	0.0	0.0	0.0	0.0	10.0	0.0	10.0	0.0
	Auditory verb comprehension	10.0	0.0	0.0	0.0	0.0	10.0	0.0	40.0	0.0
	Visual verb comprehension	10.0	5.0	0.0	30.0	0.0	40.0	0.0	30.0	0.0
	Oral object naming	66.7	20.0	60.0	16.7	43.3	60.0	0.0	13.3	33.3
	Written object naming	63.6	9.1	45.5	50.0	95.5	n.a.	27.3	18.2	36.4
	Oral action naming	71.4	28.6	57.1	78.6	57.1	64.3	0.0	14.3	42.9
	Written action naming	90.9	9.1	81.8	90.9	100.0	n.a.	27.3	36.4	54.5
Grammatical	Picture description - unconstrained	100.0	25.0	75.0	100.0	50.0	100.0	n.a.	100.0	100.0
	Picture description - constrained	100.0	70.0	80.0	100.0	80.0	100.0	n.a.	100.0	100.0
	Sentence repetition	40.0	30.0	10.0	60.0	5.0	n.a.	20.0	50.0	50.0
	Sentence reading	66.7	n.a.	0.0	100.0	0.0	n.a.	33.3	0.0	66.7
	Auditory comprehension	15.0	8.3	10.0	28.3	11.7	92.3	3.3	13.3	13.3
	Visual comprehension	26.1	3.3	13.0	26.7	4.4	n.a.	0.0	26.1	26.1

Table 5.3. Underlined scores fall below norm.

Table 5.4. Scores in cognitive screening tasks

			sham first					tDCS first			
		Cut-off	LF	GC	GD	GP	EC	SP	RL	CK	PG
STM and WM[1]	Forwards (0-8)	**3.75**	3.5	4.3	5.3	1.8	4.0	3.5	2.5	3.3	3.3
	Backwards (0-8)	**5±2**	2.0	2.0	2.0	1.8	2.0	n.a.	4.0	n.a.	n.a.
Visual attention		**31**	27.3	23.0	n.a.	46.0	16.0	12.3	15.8	45.5	28.3
Visual-spatial cognition and two-dimensional construction		**v.n. > 3**	3.0	4.0	n.a.	5.0	3.0	-1.0	3.0	10.5	12.0

Table 5.4. Digit Span (Orsini et al., 1987); Attentive matrices (Spinnler & Tognoni, 1987); Clock Drawing Test (Dal Pan et al., 1989). Underlined scores fall below norm.

5.3.2 Group Results

5.3.2.1 Treatment effects: lexical accuracy in verb production

Group data were analyzed by computing a generalized linear mixed model for logistic data, using model comparison to assess the need to include each factor (Jaeger, 2008). Models were computed using R package lme4 (Bates et al., 2014). The dependent variable was accuracy in verb production. Responses were scored as accurate if the target verb was produced, disregarding phonemic paraphasias and morphosyntactic errors. Pre-treatment stability was established by comparing accuracy between the three sessions that preceded each treatment phase, including all 88 verbs. For pre-treatment stability, the null model included random intercepts for Participants and Items. We tested this model against a model containing fixed effects for Session (assessment sessions 1, 2, and 3 prior to each treatment phase). The alternative model did not provide a better fit for the data in comparison to the null model in either phase 1 [$\chi2(1) = 0.3512$, $p= 0.5534$] or phase 2 [$\chi2(1) = 0.0708$, $p = 0.7902$], and the main effect of Session fell very far from significance (phase 1: $z = 0.593$, $p = 0.5530$; phase 2: $z = 0.266$, $p = 0.790$), showing stable behavior for this group of participants, before each treatment was administered (see Figure 5.4A).

Figure 5.4. Group results: pre-treatment stability and effects of treatment in verb retrieval.

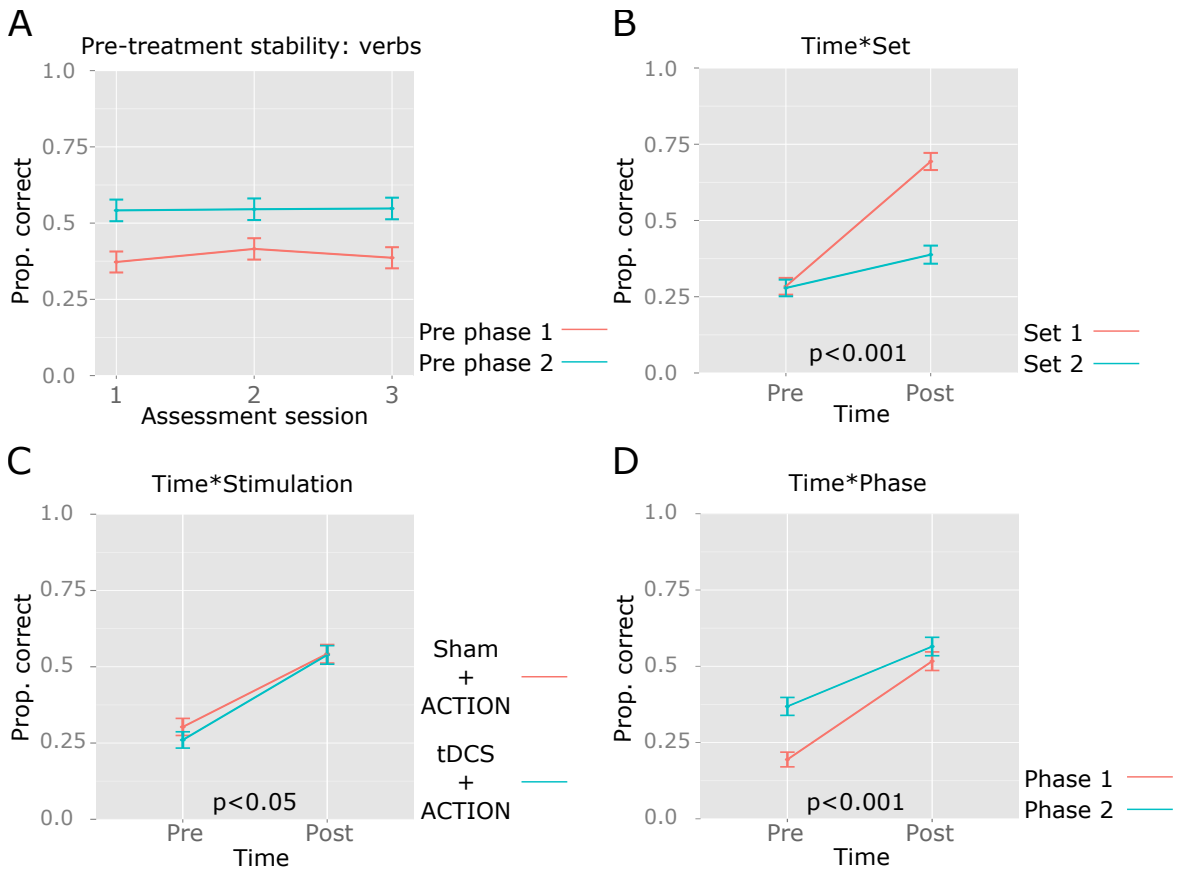

Figure 5.4. The mean proportion of correct responses is represented in the y axis. Panel A: Stability in performance in the three sessions that preceded each therapy phase (no significant differences observed for either phase). Panel B: Time*Set interaction. Panel C: Time*Stimulation interaction. Panel D: Time*Phase interaction. The p-value for each significant interaction is reported above the x axis. Set 1: treated verbs. Set 2: untreated verbs.

Treatment outcome was established by computing a second model. The model included random intercepts for participants, with random slopes for Set*Time (Set = treated, untreated; Time = pre, post-treatment), as patients may respond differently to treatment and show different degrees of generalization. Since differences are expected only in the post-treatment assessment, an interaction was relevant. We also included random intercepts for items, with random slopes for

Set, because differences between the treated and the untreated set may vary between items. The model improved significantly with the main effects of Time (pre-, post-treatment), Set (treated, untreated verbs), Phase (1 and 2), Stimulation (Sham, tDCS) and Verb Test (VTinfinitive, VTfinite, VTsentence), and the interactions Time*Set, Time*Phase, Time*Stimulation. Figures 5.4, 5.5 illustrate the relevant main effects and interactions, and corresponding statistics are reported in Table 5.5. Post-hoc pairwise comparisons were computed to characterize the main effect of VerbTest and significant interactions. For this purpose, we used the lsmeans package in R (Lenth & Hervé, 2015), and selected the Scheffe method for adjusting p-values for multiple comparisons.

Figure 5.5. Group results: differences in performance across the three verb tests.

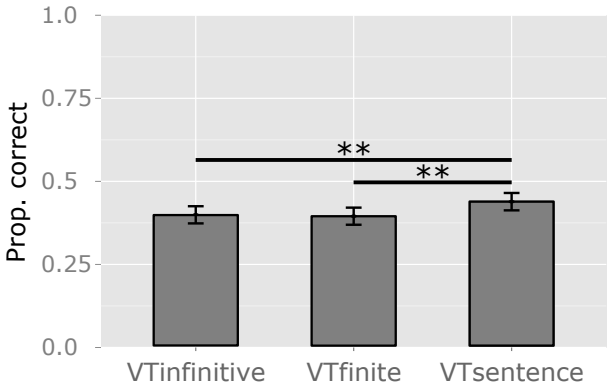

Figure 5.5. The y axis represents the mean proportion of correct responses (Prop. correct). VTinfinitive: sentence completion with a verb in the infinitive. VTfinite: sentence completion with a verb in the correct tense. VTsentence: sentence construction. Significant results are reported: **$p < 0.01$.

Table 5.5. Summary of fixed effects (verb accuracy)

	Estimate	Std. Error	z Value	Pr(>|z|)
(Intercept)	-1.5163	0.30917	-4.904	9.38E-07***
Time (pre vs. post)	2.58453	0.32153	8.038	9.11E-16***
Set (treated vs. untreated)	-0.0495	0.15385	-0.321	0.74787
Phase (1 vs 2)	0.97611	0.11365	8.589	<2E-16***
Stimulation (Sham vs. tDCS)	-0.3583	0.11301	-3.17	0.00152**
VerbTest				
(VTinfinitive vs. VTfinite)	-0.0252	0.091	-0.276	0.78223
(VTinfinitive vs. Vtsentence)	0.23501	0.09038	2.6	0.00932**
Time*Set	-1.6836	0.34451	-4.887	1.02E-06***
Time*Phase	-0.7923	0.152	-5.212	1.86E-07***
Time*Stimulation	0.33311	0.15142	2.2	0.02781*

Table 5.5. Formula: glmer(Accuracy ~ Time*Set + Time*Phase + Time*Stimulation + VerbTest +(1+Set*Time|Participant) + (1+Set|Item), data, family="binomial").

The significant main effect of Time reflected the efficacy of the treatment provided across two phases (ACTION + tDCS or ACTION + Sham), for both treated and untreated verbs. No main effect of Set was observed, as treated and untreated verbs were matched in baseline accuracy. However, the interaction Time*Set was significant (Figure 5.4B), showing greater improvement for treated verbs. Post-hoc tests confirm that the lack of differences between verb sets before treatment ($p > 0.9$), but after treatment patients responded more accurately to treated verbs ($z = 4.709$, $p = 0.0001$), and between the two assessments, accuracy improved significantly for both treated ($z= 7.713$, $p < 0.0001$) and untreated verbs ($z = 5.175$, $p < 0.0001$). A main effect of stimulation indicates that scores in the tDCS phase were lower than those collected in the Sham phase, and the interaction Time*Stimulation denotes greater improvement in the real tDCS condition. Post-hoc tests clarify that improvement was significant both in the Sham ($z = 7.686$, $p < 0.0001$) and tDCS phases ($z = 9.467$,$p < 0.0001$), and while pre-treatment accuracy was lower

in the tDCS condition ($z = -3.170$, $p = 0.018$), differences between tDCS and Sham are not significant after treatment ($p > 0.9$) (Figure 5.4C).

Scores observed in Phase 2 were higher than those observed in Phase 1, as shown by the main effect of Phase. The interaction Time*Phase indicates that the amount of improvement was smaller in Phase 2 (Figure 5.4D). In post-hoc tests, scores were higher in Phase 2 in comparison to Phase 1 before ($z = 8.589$, $p < 0.0001$) but not after treatment ($z = 1.708$, $p = 0.404$), and significant improvement was observed both in Phase 1 ($z = 10.631$, $p < 0.0001$) and in Phase 2 ($z = 6.448$, $p < 0.0001$). Patients fared better in VTsentence, than in VTinfinitive ($z = 2.600$, $p = 0.034$) and VTfinite ($z = 2.875$, $p = 0.016$), but differences in accuracy between VTinfinitive and VTfinite and the interaction with Time fell short of significance ($p > 0.9$ and $p > 0.4$, respectively) (Figure 5.5).

5.3.2.2 Control task: nonword repetition

Aspecific improvement was assessed with a nonword repetition task, administered in the three sessions of each assessment phase. Significant changes between assessments 1 and 2, and/or 2 and 3, would indicate aspecific improvement. The null model included random intercepts for Patient and Item. An alternative model introducing random slopes for Time, under the assumption that different patients may present different degrees of aspecific improvement, was the only model that significantly improved fit [$\chi2(5) = 23.673$, $p = 0.0003$]. This suggests that some participants may show improvement in nonword repetition. Main effects of Assessment phase (1, 2, and 3), Assessment Day (1, 2, 3, within each phase), and their interaction, did not improve model fit. At the group level, nonword repetition was stable within and between assessments (see Figure 5.6).

Figure 5.6. Group and individual results: performance in the control task nonword repetition.

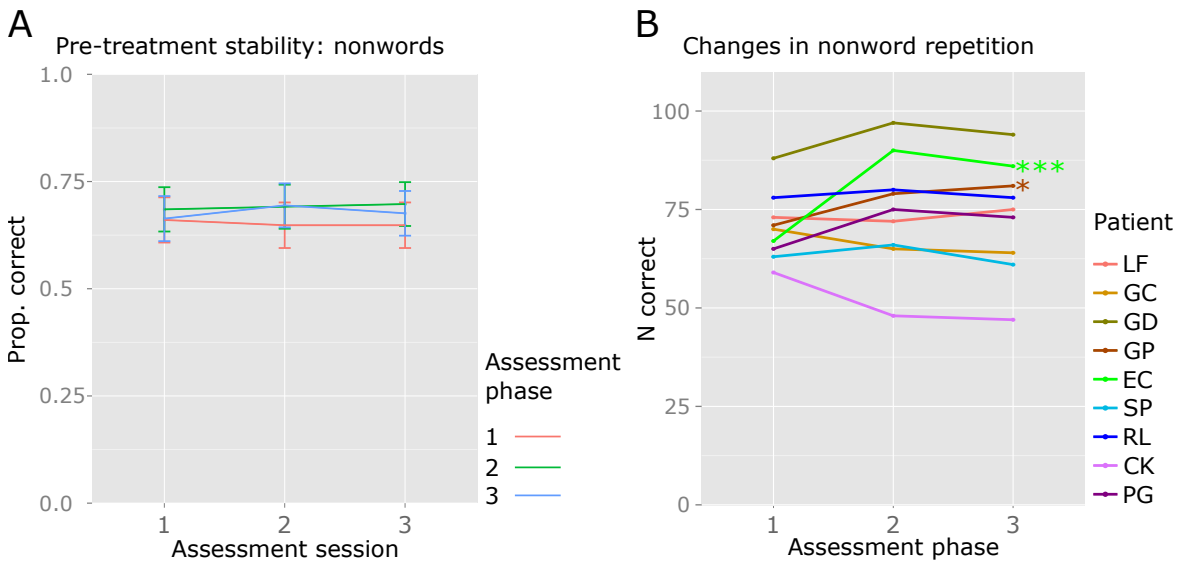

Figure 5.6. Panel A: Group data; the y axis represents the mean proportion of correct responses (Prop. correct), across the three sessions of each assessment phase, and the lines represent the different assessment phases (before treatment 1, after treatment 1, after treatment 2). Panel B: Individual data; the y axis represents the number of correct responses (N correct) across the three sessions of each assessment phase (max. 108). Significant results are reported: ***p < 0.001; *p < 0.05. For EC and GP, a significant increase in nonword repetition accuracy was observed between the first and the second assessment phases.

5.3.3 Individual Outcomes

5.3.3.1 Treatment effects: lexical accuracy in verb production

For each participant, baseline stability was checked before each treatment phase by comparing lexical accuracy in the three sessions preceding treatment, by means of Cochran's Q-test. All participants presented stable behavior prior to each phase (see Figure 5.7).

Figure 5.7. Individual results: behavioral stability prior to each treatment phase.

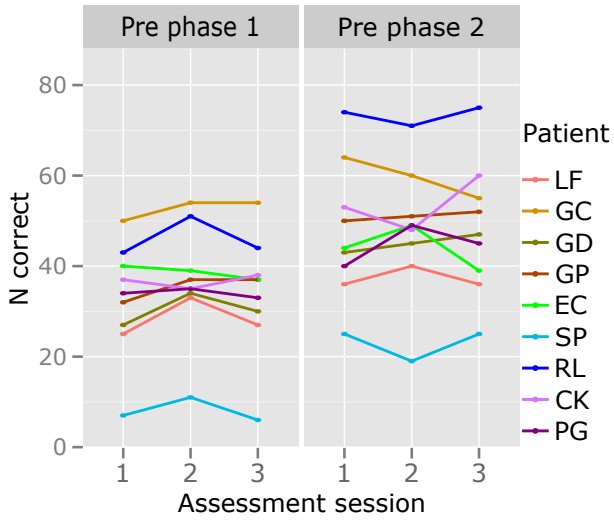

Figure 5.7. The y axis represents the number of correctly produced verbs (N correct; max. 88 in each of the three sessions that preceded treatment phases 1 and 2). No significant changes are observed.

Significant improvements between the pre- and post-assessments were computed for each treatment phase, for treated and untreated verbs. Given that each verb had been produced three times in the three sessions of pre- and post-therapy assessments, verb retrieval accuracy scores were calculated by collapsing across performance on the three administrations, thus reaching a final 3-point outcome measure of 3-day lexical accuracy. This procedure has been used to increase score sensitivity (Flöel et al., 2011). Differences between pre- and post-therapy assessments were tested using the Wilcoxon Signed-Rank Test.

Significant improvement of treated verbs was observed in all participants, in both stimulation conditions, except for EC in the real tDCS condition (coinciding with Phase 2) (see Table 5.6 and Figure 5.8). The extent of item-specific improvement in each phase was compared using Fisher exact tests. In EC, improvement was significantly greater in the Sham phase, as compared

to the tDCS phase (Fisher exact z= 3.5319, p = 0.0002). Item-specific improvement across phases did not differ significantly in the other participants.

Table 5.6. Individual treatment outcomes for treated and untreated verbs

			Treated verbs				Untreated Verbs			
Participant	ACTION+	Phase	Pre	Post	V	p	Pre	Post	V	p
LF	Sham	1	6	28	0.000	0.000	2	12	4.000	0.012
	tDCS	2	9	38	0.000	0.000	11	8	20.000	0.890
GC	Sham	1	13	34	0.000	0.000	15	23	19.500	0.025
	TDCS	2	23	56	0.000	0.000	24	27	27.000	0.307
GD	Sham	1	19	59	0.000	0.000	17	24	8.000	0.040
	TDCS	2	24	59	0.000	0.000	24	27	9.000	0.215
GP	Sham	1	14	46	0.000	0.000	14	21	15.000	0.049
	TDCS	2	23	45	10.000	0.001	21	21	33.000	0.519
EC	Sham	1	11	33	5.000	0.000	11	21	9.000	0.014
	TDCS	2	17	21	32.500	0.168	17	23	16.500	0.060
SP	Sham	2	5	18	0.000	0.006	5	9	4.000	0.205
	TDCS	1	0	25	0.000	0.000	0	6	0.000	0.047
RL	Sham	2	39	57	0.000	0.002	39	46	9.000	0.048
	TDCS	1	20	56	0.000	0.000	21	41	7.000	0.000
CK	Sham	2	25	43	0.000	0.002	23	34	18.000	0.012
	TDCS	1	16	42	0.000	0.000	13	29	9.000	0.005
PG	Sham	2	34	47	5.500	0.003	35	31	42.000	0.811
	TDCS	1	9	42	0.000	0.000	9	16	15.000	0.049

Table 5.6. Pre and Post scores are expressed by the total number of correct responses in each assessment phase (max=60). Pre- and post-treatment scores were compared by the Wilcoxon Signed-Rank Test.

The same procedure was used to assess generalization (improved production of untrained verbs). LF, GC, GD, GP, and EC improved significantly on untreated verbs in the Sham condition (coinciding with Phase 1), but not in the tDCS condition (Phase 2). SP and PG presented significant generalization in the tDCS phase (coinciding with Phase 1), but not in the Sham phase (Phase 2). RL and KC had significant generalization in both phases. The amount of generalization was significantly higher in the tDCS phase for PG (Fisher exact p< 0.001) and in

the Sham phase for LF (Fisher exact z = 4.4563, p = 0.0000) and GP (Fisher exact z = 2.1354, p = 0.0000).

Figure 5.8. Individual results: effects of treatment in verb retrieval

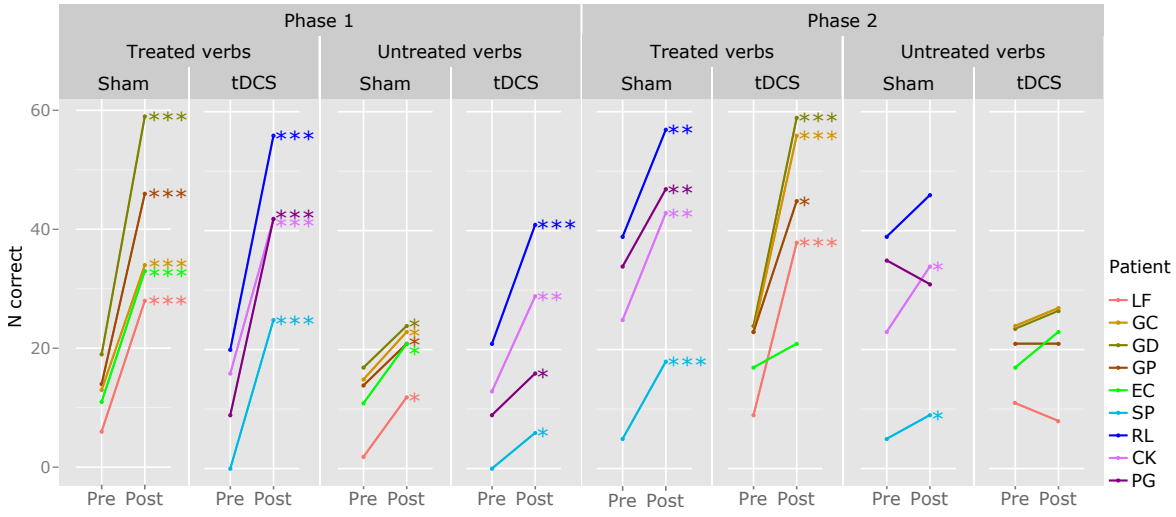

Figure 5.8. The y axis represents the number of correct responses (N correct; max. 60, corresponding to 20 verbs over 3 tests). This information is available for treated (left) and untreated verbs (right), for each treatment phase and stimulation condition. Significant results are reported: ***p < 0.001; **p < 0.01; *p < 0.05.

5.3.3.2 Control Task: Nonword Repetition

Nonword repetition scores during the three assessment phases were contrasted, to determine stability prior to each treatment phase. Performance was stable in all participants, except GC, before phase 2 [Cochran's Q-test (2) = 6.222, p = 0.0446]. In this subject, nonword accuracy increased significantly between sessions 1 and 2 of the assessment phase that preceded treatment phase 2 [McNemar's χ2test (2) = 4.1667, p = 0.0412], but did not increase further in the third session. We have no clear account for this observation, as session 3 was not significantly different from either session 1 (p > 0.2) or session 2 (p = 0.6).

Following the procedure used for verbs, the sum total of the correct responses produced during the three sessions of each assessment phase was calculated, to obtain a 3-point measurement of nonword repetition accuracy for each assessment in each participant. The comparison of this measure across assessments 1 (before phase 1), 2 (after phase 1 and before phase 2), and 3 (after phase 2), allowed to measure aspecific improvement in each participant. GP [Friedman's test $\chi2(2) = 6.889$, $p = 0.0319$] and EC [Friedman's test $\chi2(2) = 19.4783$, $p < 0.0001$] showed significantly increased accuracy in the second assessment compared to the first, that is, after Sham (treatment phase 1) (GP: Wilcoxon Signed-Rank test = 2.5, $p = 0.0282$; EC: Wilcoxon Signed-Rank test = 0, $p = 0.0007$). Neither patient's accuracy increased further in the third assessment (Figure 5.6).

5.4 Discussion

In this study, we found that patients had a stable performance accuracy across the three sessions that preceded each treatment phase. Analyses of pre- and post-treatment data revealed main effects of Time, Phase, Stimulation, and Verb Test. The interactions Time*Phase, Time*Set, and Time*Stimulation were significant. Performance in the control task (nonword repetition) was stable across assessments. Baseline stability and lack of significant changes in a control task allow to attribute the observed changes to therapy (Nickels et al., 2015). Overall, we observe better verb retrieval in sentence construction than in the other two verb tests. In addition, significant improvement is observed for both treated and untreated verbs. The amount of improvement is larger for treated verbs, in Phase 1, and in the real tDCS phase. Individually, all patients showed both item specific improvement and generalization, to different degrees across phases and stimulation conditions. In the following section we discuss the nature of treatment effects and the potential contribution of tDCS to these effects.

5.4.1 Item-specific effects and generalization with ACTION

Speech/Language Therapy (ACTION ± tDCS) effectively increased response accuracy, and this improvement was statistically significant for both treated and untreated verbs, at the group level. Albeit present for both sets, improvement was larger for treated verbs. This outcome was expected, as other studies have shown the efficacy of treating verb production in sentences (Edwards and Tucker, 2006), in particular when knowledge of predicate-argument structure is trained explicitly (Fink et al., 1992; Webster et al., 2005; Thompson et al., 2013). Semantic (Edwards and Tucker, 2006), phonemic (e.g., Fink et al., 1992), written word (Conroy et al., 2009a), and repetition cues (e.g., Weinrich et al., 1999) all improved retrieval of treated verbs. Indeed, the verbs included in ACTION-based treatment improved in every phase of therapy in all subjects, except for EC, who improved only in Phase 1.

Comparable pre-treatment accuracy across the two sets is essential to identify generalization. Post-treatment accuracy improved significantly for both sets at the group level. In addition, significant generalization occurred in individual cases. It was present in 9/9 participants, either in the first phase (9/9) or in both phases (2/9). ACTION treatment yielded generalization in Dutch and German individuals with aphasia (Bastiaanse et al., 2006; Links et al., 2010). Its Italian adaptation, that adds a specific focus on verb morphology, further encourages the adoption of a structured cueing hierarchy in order to provide patients with a strategy conducive to both item-specific and generalized improvement.

Stable nonword repetition performance at the group level suggests that improvement of verb retrieval was due to treatment, and not to task practice (Nickels et al., 2015). The same holds at the individual level, except in EC and GP, whose nonword repetition accuracy improved in the same phase in which generalization occurred. Prior to participating in this study, EC had not

received Speech-Language Therapy for 4 years, and GC had followed (not during his participation in this study) a treatment protocol that also included repetition tasks. For these two cases, improvement in an untreated task does not allow to establish the reasons for better performance on untrained verbs in experimental tasks—it could be attributed to treatment, but also to a charm effect or to the adoption of strategies external to ACTION. Nevertheless, since in both subjects performance in additional tasks (e.g., object naming) was stable throughout the protocol, and since in the other participants nonword repetition did not improve, it is reasonable to attribute generalization to ACTION, at least in part, also in the case of EC and GP.

Which mechanisms may have resulted on generalization? The representation of a verb specifies, in addition to supra-segmental and syllabic/segmental features (represented also for nouns), lexical-grammatical properties that are exclusive to verbs, such as conjugation, inflectional paradigm, transitivity, predicate-argument structure, etc.). Such properties are verb-specific, but are similar for large sets of items. In fact, there is evidence that different verbs share information about the syntactic structures in which they occur (Pickering and Branigan, 1998), and that this can result in structural priming between sentences that include different verbs (Bock, 1986). Consequently, training predicate-argument structure production in the context of a specific verb can facilitate retrieval of the same predicate-argument structure for another verb. And in turn, it can facilitate activation of lexical items that are semantically appropriate to the active predicate-argument structure (Bock, 1986). This lexical selection bias can enhance access to the representations of untreated verbs. In short, participants might have benefited from improved retrieval of treated verbs, and from recovered knowledge of typical argument structure to cue the retrieval of untreated verbs. At the end of the treatment protocol, this might have yielded both item-specific recovery and generalization.

Interestingly, generalization was observed in protocols that require production of verbs in sentence context (Bastiaanse et al., 2006; Links et al., 2010; Thompson et al., 2013), but not in protocols focusing on verb production at the single-word level, even when action naming was preceded by explicit discussion of that verb's argument structure (e.g., with modified semantic feature analysis for verbs; Wambaugh & Ferguson, 2007). This suggests that generalization depends not only on training lexical verb retrieval or on recovering abstract knowledge of argument structure, but also on actually producing predicate argument structures.

The role of structural complexity should also be considered here. In the second week of each therapy phase, the treatment task reached a higher level of complexity than that used in any of the tasks used during assessment. At this stage, participants were prompted with an image and an adverb and were asked to produce full sentences with verbs inflected in the correct tense. Even the most demanding task used to measure improvement (sentence construction) was simpler than this treatment task in some respects, as participants need not inflect the verb in one of three tenses. Importantly, all tasks tackled related linguistic operations. The Complexity Account for Treatment Efficacy predicts improvement in linguistically related, less complex tasks (Thompson et al., 2003). Improved verb retrieval for untreated verbs in less complex, related structures, was also reported (Thompson et al., 2013), with 3-argument verb treatment resulting in improved production of 1- and 2-argument verbs in sentences. In addition, morphosyntactic complexity was shown to have an impact in verb retrieval, with aphasic patients displaying poorer retrieval of finite than non-finite verbs (Bastiaanse, 2011). By treating the production of tense morphology (a knowledge that can be generalized), we may have decreased task complexity for both treated and untreated verbs, thereby allowing resource allocation for lexical selection processes.

In most participants, difficulties in sentence construction were associated with damage to multiple levels of language processing, including semantics, lexical retrieval, sublexical conversion procedures, working memory and grammar (thematic role assignment, realization of predicate-argument structure, and morphosyntactic processes). Focusing treatment on verb retrieval, verbal morphology and predicate-argument structure in sentence-level tasks may have indirectly yielded additional benefits (generalization) by alleviating associated impairments and/or implicitly teaching participants how to circumvent them. For example, training may have increased working memory capacity, and the improvement of grammatical processing may have decreased the cognitive load associated with sentence construction, resulting in more efficient allocation of resources to lexical retrieval.

Given that verb accuracy was calculated by collapsing accuracy across three different tasks, we also considered whether this scoring procedure influenced the evaluation of performance and the resulting patterns of improvement. There was a main effect of Verb Test, indicating that participants retrieved verbs more accurately in the VTsentence (sentence construction) than in the other two tasks, possibly because in this task patients read cues about the nature of the constituents to produce (see Figure 5.2), and this may have facilitated access to predicate-argument structure. Patient also had more time to respond in this task (30 s, in comparison to 20 s in the other tasks), to account for the higher number of words that needed to be produced. Importantly, after therapy, lexical verb retrieval improved in all tests (VTinfinitive, VTfinite, VTsentence), without significant across-task differences.

Since participants were treated in two phases, and were randomly assigned to the two stimulation sequences (tDCS, then sham vs. sham, then tDCS), the effect of timing on treatment is worth considering. Participants improved more in Phase 1 than in Phase 2. This may have occurred

because there was more room for improvement in Phase 1 (subjects had not received any treatment for several months), and recovery plateaued by the end of Phase 2. Following TUF-based treatment (Thompson and Shapiro, 2005), Dickey and Yoo (2013) showed that improvement of treated and untreated verbs depends on different dose-response relations. Treated verbs were acquired faster and linearly, whereas generalization emerged more slowly, its learning curve accelerating over time. In the present study, both item-specific improvement and generalization were larger in Phase 1, and the pattern for untreated verbs was opposite to that reported by Dickey and Yoo (2013).

5.4.2 tDCS

Scores before and after the tDCS treatment phase were lower than those before and after the Sham phase, as shown by the main effect of Stimulation. In fact, we successfully controlled pre-treatment accuracy across treated and untreated verbs in each phase, but accuracy across phases was more difficult to balance, as it depended on the extent to which each participant improved in Phase 1. The Time*Stimulation interaction suggests that, in spite of lower initial scores, improvement was greater in the tDCS phase. However, this result must be taken cautiously, as the steeper slope for real tDCS may reflect a true enhancement due to successful neuromodulation, but also a ceiling effect for the Sham condition. In other words, if participants could not improve further than observed, the slope may be steeper in the tDCS condition just because participants started off with lower accuracy. We discuss these possibilities (a true stimulation effect and a ceiling effect) in the next paragraphs.

To our knowledge, this is the first time that tDCS is applied together with a treatment program that targets verb production in sentence context and includes explicit morphosyntactic training. Neuroimaging studies suggest that sentence production and verb inflection require computations

that are widely distributed in the brain (e.g., Perani et al., 1999; Thompson et al., 2007). Given that tDCS is more effective when the electrodes are placed directly above areas involved in the cognitive processes associated with stimulation (Marangolo et al., 2013a), it is possible that tDCS is more effective when associated with cognitive functions that have a more circumscribed representation. Thus, ACTION could be considered a less optimal protocol to pair with tDCS. Nevertheless, previous research contradicts the idea that widespread representation of the cognitive processes engaged by a task may decrease efficacy of neuromodulation. For example, benefits from tDCS were reported in association with conversational therapy (Marangolo et al., 2013b).

Stimulation was delivered to different sites in different participants. We did this to ensure that tDCS was applied over healthy tissue in each case. In previous research (Baker et al., 2010), stimulation sites were identified based on each individual's fMRI activation during correct naming. This procedure was selected to ensure that the stimulated area was involved in the to-be-treated task, and to putatively allow tDCS to enhance patterns of activation known to correlate with good performance. While this approach has pragmatic limitations (discussed in de Aguiar et al., 2015b), it is indeed relevant to target areas for stimulation that have at least the potential to be involved in the task. Our decision in terms of stimulation site may have resulted in a more efficient pairing of functional role of the area and treatment task in some cases than in others (see Marangolo et al., 2013a), but this approach was preferred to stimulation of lesioned tissue. First, because lesioned tissue can disturb current flow (Datta et al., 2011) and, most importantly, because recovery is typically associated with activation of peri-lesional or contra-lesional areas (Schlaug et al., 2008) and tDCS directly over lesioned areas was reported to be ineffective (Hesse et al., 2007).

Individual data analyses highlight another important issue. For treated verbs, EC had larger improvement in the Sham condition. For untreated verbs, improvement was greater after tDCS for PG, and after Sham for LF and PG. Crucially, these participants showed greater improvement in Phase 1 than in Phase 2, regardless of stimulation condition. The same was true at the group level. Therefore, it is not clear whether across-phase differences are due to type of stimulation (tDCS vs. Sham) or to treatment phase (1 vs. 2). In cross-over designs, in which typically two treatments are administered over two phases, treatment order can massively influence outcome. In our sample, five participants received Sham first and four received tDCS first. With an uneven number of subjects, and a significantly larger improvement in Phase 1, the design is somewhat biased toward larger improvements in the Sham condition. Nonetheless, group analyses show greater improvement in the tDCS phase, for both treated and untreated verbs.

All things considered, in the same way that we cannot rule out a ceiling effect for Sham, we can also not exclude the possibility that data reflect a true, tDCS-related enhancement. Assuming a real effect of tDCS, our data is in line with previous research. Performance in tasks using verbs, such as action naming (Marangolo et al., 2013a) and spontaneous speech (Marangolo et al., 2013b, 2014), showed significant therapy enhancement after stimulation of Broca's area. In our study, the anode was placed over Broca's area in three participants and over the neighboring left hemisphere cortex in five. Considering that we focused on verb retrieval accuracy, our data are consistent with those of Marangolo et al. (2013a), showing that stimulation of Broca's area (and of the surrounding cortex)[14] can enhance verb production. Since a bi-cephalic montage was used in all participants, the observed effects could be due to a combination of the excitation induced by the anode placed over LH perilesional areas, and of the active role of the cathode over

[14] Note that the anode was positioned over this area for 8/9 patients.

contralesional areas (Nitsche et al., 2008), which may have contributed to balancing interhemispheric competition (Murase et al., 2004).

In addition, lack of a three-way interaction involving Set (Time*Stimulation*Set) suggests that greater improvement in the tDCS phase involves both treated and untreated verbs. Moreover, control for aspecific improvement in verb production was achieved (pre-treatment performance was stable, and no group-level effects were observed for nonwords), and therefore data indicate that improvement of untreated items reflects generalization. Of the five participants who received Sham first, all showed generalization in Phase 1 and none in Phase 2. Of the four participants who received tDCS first, all generalized in Phase 1, but two also generalized in Phase 2 (when they received Sham). This could either mean that Sham increased generalization in both phases, or that administering tDCS in the first phase extended the generalization potential to the subsequent Sham phase. This latter possibility receives some support from group data, through the observation of larger item-specific improvement and generalization in the tDCS phase. Nevertheless, we reiterate that the results regarding tDCS are not conclusive, as it is not possible to distinguish between a real tDCS-induced modulation and a ceiling effect in the Sham condition. Furthermore, it should be highlighted that we report data from a relatively small sample. Considering the fact that response to tDCS is characterized by a large inter-subject variability (Horvath et al., 2014), replication with a larger sample is essential to support the findings reported in the current study.

5.5 Conclusion

The ACTION protocol improved lexical retrieval for both treated and untreated verbs. With generalization considered as the ultimate goal of aphasia therapy (Dickey and Yoo, 2013), results highlight the importance of engaging explicit morphosyntactic knowledge during rehabilitation

of verb retrieval. Item-specific improvement was considerably larger than improvement of untreated items, but all participants improved significantly on both sets of verbs. Improvement was more marked in the first phase of treatment. Even though this study was not designed to assess the timing constraints of therapy, results stress the need to investigate the time-course of both item-specific and generalized improvement. The effects of bi-cephalic tDCS administered concurrently with ACTION are to be interpreted carefully, but while a ceiling effect cannot be excluded, larger therapy effects were observed during tDCS than Sham, for treated and untreated verbs.

CHAPTER 6

General Discussion

The aims of this dissertation were to provide a better understanding of the mechanisms of change that support experience-related language facilitation in healthy individuals, and of the mechanisms that underlie item-specific improvement and generalization in aphasia recovery. Furthermore, I aimed to increase the understanding of how tDCS may be used to enhance the effects of aphasia therapy, and to test the extent to which it enhances the effects of behavioral techniques for language facilitation in healthy individuals and the effects of aphasia therapy. In addition, in order to provide a direct clinical application for this knowledge, I planned to develop a theory-driven treatment program and test its efficacy.

6.1. Mechanisms of language facilitation and recovery induced by behavioral techniques

The meta-analysis of single-case studies reported in Chapter 4 highlighted different mechanisms that may underlie item-specific improvement and generalization. Improved production of treated verbs was predicted by an interaction of pre-treatment scores in verb comprehension, word repetition ability, and frequency of treatment. Considering the role of pre-treatment verb comprehension, the data included in the meta-analysis allowed us to go beyond interpretations based on severity alone. We identified two possible accounts. The predictive role of verb comprehension may reflect a generic effect (poor comprehension may disrupt the therapeutic process). Alternatively, it may reflect the role played by preservation of conceptual and grammatical information (at the lemma level). In this latter interpretation, better pre-treatment preservation of semantics/lemmas will in turn enable better access to lexemes during verb production (Baum, 1997). Consequently, a minimally preserved access may increase significantly the chances of improvement in the production of treated verbs.

Patients with milder semantic impairment had greater chances of improvement for treated verbs when they achieved higher scores in word repetition. In Chapter 4 we discussed how this may reflect the contribution of phonological short-term memory (Baldo et al., 2008), which is instrumental for long-term learning (Atkinson & Shiffrin, 1968). We proposed that short-term memory skills can support the restoration or re-activation of output lexical representations, in particular when access to lexemes through semantics or the lemma level is viable (that is, in patients with higher comprehension scores). Furthermore, good word repetition skills suggest relative preservation of post-lexical segmental processing (ability to retrieve target phonemes or produce them in the correct order), and motor programming (conversion of an abstract

phonological representation into a correct speech plan). In patients with verb retrieval deficits, post-lexical processing damage could interfere with the success of therapy. Even in the face of improved lexical retrieval, post-lexical impairments would generate errors resulting in uninterpretable responses. In these cases, a combination of poor verb production and poor word repetition would be expected.

We hypothesized that the predictors of item-specific improvement would be different from those of generalization, reflecting the different cognitive mechanisms of change at work in these types of outcome. As expected, the predictors of generalization in lexical retrieval of verbs were distinct from those predicting item-specific improvement. Generalization to lexical retrieval of untreated verbs was predicted by the interaction of morphological cueing during treatment, presence of grammatical impairment, pre-treatment noun comprehension scores, and frequency of treatment. Our analysis suggests that there are two pathways for generalization: one depends on the nature of the underlying language disorder, and the other on the type of treatment. Patients with impairments at the level of generalizable features (both grammatical and conceptual features, with the latter indexed by noun comprehension scores) were more likely to improve, as proposed by Miceli et al. (1996). In addition, treatment entailing morphological cueing (in particular for the production of verb tense) increased the chances of improvement, as suggested by Links, Hurkmans, and Bastiaanse (2010), and Thompson and Shapiro (2005).

With these mechanisms of improvement in mind, we developed the Italian adaptation of ACTION (Bastiaanse, Jokers, Quak, & Varela Put, 1997; Links et al., 2010). In order to take into consideration the predictive role of morphological cueing (Chapter 4) in generalization, this treatment protocol was adapted to Italian with a specific focus on the usage of verb morphology to refer to different time frames. The efficacy data reported in Chapter 5 are based on two tasks:

sentence completion with finite verbs, and sentence construction with finite verbs. The cueing strategy engaged explicit access to knowledge of verb's argument structure and of the relation between tense and time reference, hence tackling access to knowledge that is generalizable across many verbs (see Supplementary materials for a detailed description of cueing). As predicted by the results of the meta-analysis, all patients showed both item-specific improvement and generalization. All patients showed stable performance in verb retrieval over the three sessions that preceded each therapy phase and, with few exceptions, their non-word repetition scores remained unchanged after each treatment. This licenses the conclusion that improved retrieval of treated and untreated verbs was related to therapy, and not to a "charm" effect.

The treatment study was not designed to examine whether patients with different types of underlying language disorders presented with different patterns of generalization (e.g., Miceli et al., 1996). In fact, participants presented with damage to various aspects of language processing, including the lemma level, lexical retrieval, sublexical conversion procedures, working memory and grammatical processing (involving, to various extents in different participants, thematic role assignment, realization of predicate-argument structure, and morphosyntactic processes). In our experimental sample, noun comprehension was above 84% (the level of comprehension that changed the probability of generalization, Chapter 4) in 7 out of 9 cases. This might have made these subjects less likely to show generalization. However, all treated patients presented with grammatical impairment and were treated with morphological cueing – both of which predict generalization, according to the meta-analysis in Chapter 4.

Individual data analysis and comparison of treatment outcome across phases were crucial in order to identify patterns of generalization: all patients generalized after the first 10 treatment sessions (phase 1), but only two generalized after phase 2. It is possible that there was a larger

potential for improvement in phase 1 (for both item-specific improvement and generalization) as performance before this phase was lower. Nonetheless, 8 of the 9 patients still presented with item-specific improvement in phase 2, suggesting that a general ceiling-effect cannot account for the lack of generalization in this phase. It is possible that patients learned abstract properties of language rapidly, and that further improvement was contingent almost exclusively on their ability to learn verbs to which they were exposed during treatment. Hence, the potential for generalization from a specific treatment may saturate once related abstract properties are learned.

While generalization was mostly restricted to phase 1, improved production of treated verbs occurred in both phases. Absence of item-specific improvement was observed only for one patient in phase 2; all other patients showed improved production of treated verbs in both phases. High scores on verb comprehension (above 67% accuracy in all patients except CK), and word repetition (above 49% in all patients except SP) may have increased the likelihood of treatment success. The two subjects whose pre-treatment scores in verb comprehension (CK) and word repetition (SP) fell below the values that predict recovery in the meta-analysis scored below norm also in a short-term memory test. Yet, both patients showed treated-item improvement. This may be explained by had high scores in repetition (for CK), and high scores in comprehension (SP), which are associated with high chances of improvement (also based on the meta-analysis in Chapter 4).

Chapter 3 provides additional insight into the mechanisms that may support item-specific improvement. This ERP experiment assessed the neurophysiological correlates of repetition priming in verb production. We observed an attenuation of the N400 effect. As indicated in the literature, repetition-related changes in the N400 amplitude may index implicit processes necessary to perform the task at hand (Olichney et al., 2013). In this context, facilitation of

naming as a consequence of repeated exposure to the to-be-named stimuli is thought to reflect easier retrieval of lexical-phonological representations (Barry et al., 2001). In addition, we observed modulations of the Late Positive Component, with different polarity across scalp sites. This component is typically thought to reflect episodic retrieval of the prior occurrence of the stimulus (Olichney et al., 2000, 2002). We found that the amplitude of the ERP effects correlated with action naming times, in time windows that corresponded to both the N400 and the Late Positive Component. This correlation indicates that the observed ERP modulations are relevant to the behavioral facilitation effect that occurs with repetition.

As discussed above, in the meta-analysis (Chapter 4) pre-treatment word repetition scores predicted improvement in verb therapies, with greater chances of improvement observed in patients with more than 49% accuracy in repetition. Repetition scores were higher than this threshold in all the patients in the treatment study (Chapter 5) except for SP, as already discussed. Importantly, all patients presented item-specific improvement. As discussed above, the effect of repetition may reflect the contribution of phonological short-term memory to recovery (Baldo et al., 2008). In addition, in healthy individuals, word repetition effects reflect the episodic retrieval of the prior occurrence of the word (see Chapter 3 and above). In the context of a therapy session, a patient who is able to repeat words correctly may produce the target more often, as correct production can be cued via repetition. In subsequent sessions, the same patient may benefit from the episodic retrieval of prior occurrences of that word and the facilitation in implicit processing (easier retrieval of lexical-phonological representations), similar to what occurs in healthy individuals in repetition priming. While the parallel between the mechanisms of facilitation in healthy individuals and patients with aphasia is, at the moment, highly speculative, cognitive architecture and mechanisms of change in healthy individuals

should be used to derive hypotheses about impaired language processing and mechanisms of change during recovery (Baddeley, 1993; Caramazza & Hillis, 1993).

In Chapter 4, we observed an inverse relationship between frequency of treatment and the likelihood of improvement. Patients with more than three (for treated-item improvement) and 2-3 therapy sessions per week (for generalization) were less likely to improve. These results are obviously at odds with the observation of positive treatment outcomes mentioned in Chapter 5, in which five 1-hour therapy sessions per week were provided. As we discussed, the factors influencing improvement are multidimensional, and certainly neither study could account for all the variables that may determine treatment outcome. It is possible that the inverse frequency effect also reflects aspects related to the overall duration of treatment (see Dickey & Yoo, 2010), as in our meta-analysis patients who did not show generalization also received treatment for a longer period. An alternative explanation is that patients are less motivated or less able to cope with the demands of very intensive therapy, as suggested by the higher dropout rate from intensive than non-intensive therapy protocols (Brady et al., 2012). At the moment, these explanations are speculative. Further research should examine systematically the relation between dose-related parameters and treatment outcome, also taking into account the linguistic/cognitive content of treatment.

6.2. tDCS in language facilitation and rehabilitation

Previous research showed that tDCS can enhance the effects of behavioral training and rehabilitation (e.g., Baker et al., 2010). In healthy individuals, anodal stimulation increased the success of artificial grammar learning *(*de Vries et al., 2010) and novel word learning paradigms (Fiori et al., 2011; Flöel et al., 2008). Nonetheless, while our repetition priming paradigm yielded large facilitation effects, tDCS did not contribute to the decrease in vocal reaction times

associated with repetition. We consider several accounts for this outcome in Chapter 3. Given that the repetition priming effect may be the composite product of facilitation in implicit stimulus processing and explicit retrieval of the prior occurrence of the stimuli, we raise the possibility that stimulation would have been more effective if the anode had been placed over areas involved in episodic memory (e.g., temporoparietal cortex). Nonetheless, tDCS-related enhancement via anodal stimulation to Broca's area should be expected, considering the role of this area in verb processing (e.g., Marangolo et al 2013a, b, 2014; Rofes & Miceli, 2014). We note that in another study based on repeated naming (Sparing et al. 2008), tDCS stimulation resulted in a short-lived (5 min.) performance enhancement after the 11th naming trial. It is then possible that tDCS may have a substantial effect in enhancing performance only when the potential of behavioral facilitation is exhausted.

Our review of the literature indicated that tDCS is typically effective in enhancing treatment effects in aphasia (Chapter 2). In our treatment study, patients showed a larger treatment effect (for treated and untreated verbs altogether) in the tDCS than in the Sham condition. Nonetheless, this effect could not be unambiguously interpreted. On the one hand, the amount of change in pre- vs post-treatment test was larger in the real tDCS than in the Sham condition. On the other hand, differences between tDCS and Sham were substantial only before treatment (higher scores in the Sham condition), whereas verb retrieval was comparable after treatment with tDCS and with Sham. There are two alternative explanations for these data. They may reflect a ceiling effect: patients improved less in the Sham phase because, having started at a higher level of accuracy, they had less potential to improve. Alternatively, results may reflect a true tDCS-related enhancement of treatment effects. This latter account finds support in prior studies

showing enhanced treatment effects when tDCS to similar sites is associated with verb therapies (Marangolo et al., 2013a, b, 2014).

Neither interpretation of the stimulation-related results can be proven based on our data. Nonetheless, the aphasia rehabilitation literature supports the efficacy of tDCS in enhancing treatment effects: significant increases in the effects of treatment have been reported in many studies, notwithstanding considerable differences in treatment approaches, stimulation parameters and patient characteristics (e.g., Baker et al., 2010; Flöel et al., 2011; Monti et al., 2008; Vines et al., 2011). In addition, we note that in our treatment study four patients were treated with tDCS in the first treatment phase, and five in the second treatment phase. As a group, patients showed larger improvement in Phase 1. Therefore, the design was somewhat biased to finding better treatment outcomes after Sham than tDCS. Even so, we still find that improvement was larger after real tDCS, which indicates that, while a ceiling effect cannot be excluded, a real tDCS-related increase of treatment effects should still be considered seriously. Moreover, this may indicate that tDCS enhances not only treated-item improvement, but also generalization in lexical retrieval.

In summary, considering the review of the literature and experimental chapters together, in what concerns aphasia recovery, we may conclude that verb retrieval can improve after treatment with behavioral and neuromodulation techniques. A critical review of the literature (Chapter 2) highlighted the potential of tDCS to enhance item-specific improvement, and experimental data indicate that tDCS may also enhance generalization (Chapter 5).

Our data indicate that item-specific improvement and generalization are supported by different cognitive mechanisms (Chapter 4). Item-specific improvement after Speech-Language Therapy

is more likely when activation of lexemes by semantics and lemma-level information is substantially preserved, and is supported by short term-memory skills (indexed by word repetition). Generalization of treatment effects to untreated items, in turn, occurs more often when knowledge of abstract features (conceptual and/or grammatical) shared by many verbs is difficult to access, or is engaged by treatment (for example, by training tense production). When recovered, this knowledge is made available for verbs sharing the same features, resulting in generalization.

The results of the efficacy study (Chapter 5) are well in line with the mechanisms outlined above. Item-specific improvement was reported for all patients. With few exceptions, participants had high comprehension scores, and good phonological short-term memory. In addition, all showed generalization. This is predicted (based on Chapter 4), given that the patients presented with damage to abstract grammatical features, and were treated with ACTION (a linguistically motivated aphasia treatment program, in Chapter 5) which engaged processing of these features.

In healthy individuals, verb retrieval is enhanced by repeated exposure to the same stimuli and the same task. Reduction of the N400 effect reflects facilitation in implicit, task-related processes, potentially occurring at the level of lexical retrieval and phonological encoding for production. Episodic retrieval of prior occurrence of the same stimuli may also contribute to experience-related facilitation. This was reflected by a modulation of the Late Positive Component (Chapter 3).

Some observations should be examined in further research. In the meta-analysis (Chapter 4), we have no specific account for why individuals with aphasia show an inverse effect of treatment

frequency (Chapter 4). Additional research is needed to examine the relation between treatment dosage and frequency, in relation to other treatment-related and patient-related characteristics. Furthermore, the mechanisms of change suggested for aphasia recovery (both for item-specific improvement and for generalization) should be confirmed by independent research. Further studies will have to establish whether a ceiling effect or a real tDCS-related modulation is responsible for the improvement observed when tDCS is paired with linguistically motivated aphasia therapy, and to independently replicate the finding that tDCS may enhance both item-specific effects and generalization.

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APPENDIX

Appendix A: Example R code

In Chapter 4 we ran all statistical analyses using R (R Development Core Team, 2009). The procedures are largely based on Tagliamonte and Baayen (2012). We used functions from the R packages randomForest, party, and lattice. These packages can be loaded with:

```
> library(randomForest)

> library(party)

> library(lattice)
```

Missing data was estimated using random imputation with:

```
> dat = rfImpute(database ~ .,data=metaAnalysis,iter=100,ntree=2000)
```

A random forest with unbiased conditional inference trees is obtained using:

```
> fit<-cforest(OutcomeVar ~ . , data = dat, control=cforest_unbiased(mtry=5,ntree=5000))
```

We assessed the relative importance of predictors using conditional permutation variable importance:

```
> imp<-varimp(fit, conditional=TRUE)
```

Plots with variables orders by variable importance can be obtained with:

```
> dotplot(sort(imp))
```

For assessment of classification accuracy, the index of concordance C can be calculated using:

```
> fit.trp = treeresponse(fit)

> dat$PredFit = sapply(fit.trp, FUN=function(v)return(v[1]))

> dat$datFit = (dat$ImprUntreated=="0")+0

> Concordance<-somers2(dat$PredFit, dat$datFit)
```

Conditional inference trees were produced with:

```
> MyTree = ctree(Outcome ~ ., data=dat);plot(MyTree)
```

Appendix B: Lesion description of patients included in treatment study (Chapter 5)

LF

Partial involvement of the inferior frontal gyrus, extending to deep structures, including the head of the caudate; extensive temporal damage, involving the pole, the superior, middle and (partly) inferior temporal gyrus and the temporo-occipital junction, and extending to the insula, claustrum, external capsule; massive involvement of angular and supramarginal gyrus, superior and inferior parietal lobule. The left lateral ventricle is markedly dilated.

GC

Angular and supramarginal gyrus; planum polare and planum temporale extending into the insula; middle temporal gyrus extending to the temporo-occipital junction; postcentral gyrus. Damage involves cortical structures and, extensively, the underlying white matter, with the exception of the insula, where damage is more superficial. The anterior portions of the superior and middle temporal gyrus are partially spared; damage to the superior aspect of the superior temporal gyrus and to the angular and supramarginal gyri spares cortical tissue and mostly affects subcortical structures.

GD

Sequelae of a vast intraparenchimal, left temporal hemorrage (anteroposterior diameter: approximately 8 cm). Damage involves the temporal lobe and the temporoparietal junction

(temporal pole, superior and middle temporal gyrus, extending to the angular and supramarginal gyrus), and is associated with marked dilation of the temporal horn of the lateral ventricle). Additional (probably post-traumatic), mild right-hemisphere damage to basal and medial frontal areas, to mesial parietal areas and to the anterolateral portions of the temporal lobe. DTI shows damage to the white matter of the left hemisphere, interrupting the arcuate fasciculus almost entirely and damaging the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus and the uncinate (only a minimal number of streamlines of the latter can be recovered). All these fiber bundles are fully reconstructed in the right hemisphere.

GP

Extensive damage to the anterior branches of the left middle cerebral artery. The lesion massively affects frontal and temporal regions. In the temporal lobe, the pole is entirely disrupted, and damage affects the superior, middle and inferior temporal gyri, to a decreasing extent (the lesion destroys the entire superior temporal gyrus, but only the anterior half of the inferior temporal gyrus). In the frontal lobe, damage disrupts entirely the inferior and middle gyri, but affects the superior gyrus only marginally. Frontal and temporal damage affects all the white and grey matter structures underlying the affected cortex, all the way to the ventricular ependyma. Damage partially extends to the angular and supramargimal gyri.

EC

Sequelae of a hemorrhage seated deeply in the left hemisphere, centered around the lenticular nucleus (head of the caudate, putamen, pallidus, anterior portion of the thalamus), and extending superiorly to the level of the roof of the lateral ventricle. The post-hemorrhage cavity is surrounded by white matter damage. Damage affects most of the insula, a sizeable portion of the

inferior frontal gyrus (especially subcortically) and part of the planum temporale. Subcortically, the lesion extensively disrupts critical fiber tracts (direct and indirect segments of the arcuate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, corona radiata). Very marked *ex-vacuo* dilation of the lateral ventricle is present.

SP

Massive damage to the entire middle cerebral artery territory. The lesion involves the inferior and middle frontal gyrus, the insula, the inferior and superior parietal lobule, the superior and middle temporal gyrus (sparing the temporal pole), the angular and supramarginal gyrus, remarkably sparing the motor cortex and the anterior aspect of the post-central gyrus, and the corona radiata. Damage involves both the cortex and the subcortical white matter.

RL

Extensive lesion in the territory of the anterior branches of the left middle cerebral artery. Damage involves the inferior frontal gyrus (pars opercularis and pars triangularis), the middle frontal gyrus, precentral and postcentral cortices, the superior temporal gyrus and the head of the hippocampus. It extends to the insula and to deep grey matter nuclei (caudate, globus pallidus, thalamus), also involving white matter tracts. Mild dilation of the left lateral ventricle is present.

CK

Damage followed a basal ganglia hemorrhage and is almost entirely subcortical. The post-hemorrhage cavity centers around the basal ganglia (head of the caudate, putamen, pallidus, internal capsule). It extends superiorly to the level of the roof of the lateral ventricle, and is surrounded by a large gliotic area. The site of the hemorrhage is such that in all likelihood it

undercuts most critical white matter bundles (arcuate fasciculus, inferior longitudinal fasciculus, corona radiata/internal capsule, possibly the uncinate and part of the inferior fronto-occipital fasciculus). Cortical damage is limited to the insula.

PG

Massive lesion in the territory of the parietotemporal branches of the middle cerebral artery. Damage spares almost entirely the pre-rolandic regions above the sylvian fissure, but extensively affects the temporal lobe (pole, superior temporal gyrus, middle temporal gyrus and the anterior half of the inferior temporal gyrus), the temporoparietal junction (angular and supramarginal gyrus), the parietal lobe (postcentral gyrus, superior and inferior parietal lobule) and the temporo-occipital junction. Temporal damage spares the middle portion of the pole, the hippocampus, the lingual and fusiform gyrus. The temporal isthmus and the insula are marginally involved; the temporal and occipital horn of the lateral ventricle are moderately dilated.

Appendix C. Cueing procedure use in ACTION steps 3 and 4

In Step 3, the participant saw an image with an adverb and a subject written below the picture (e.g., "Now the man…"), and was asked to complete the sentence with the verb inflected in the correct tense. If the subject failed to retrieve the correct verb, increasing cues were provided depending on error type, following a structured schema (Figure C.1).

Figure C.1. Cueing hierarchy for Step 3.

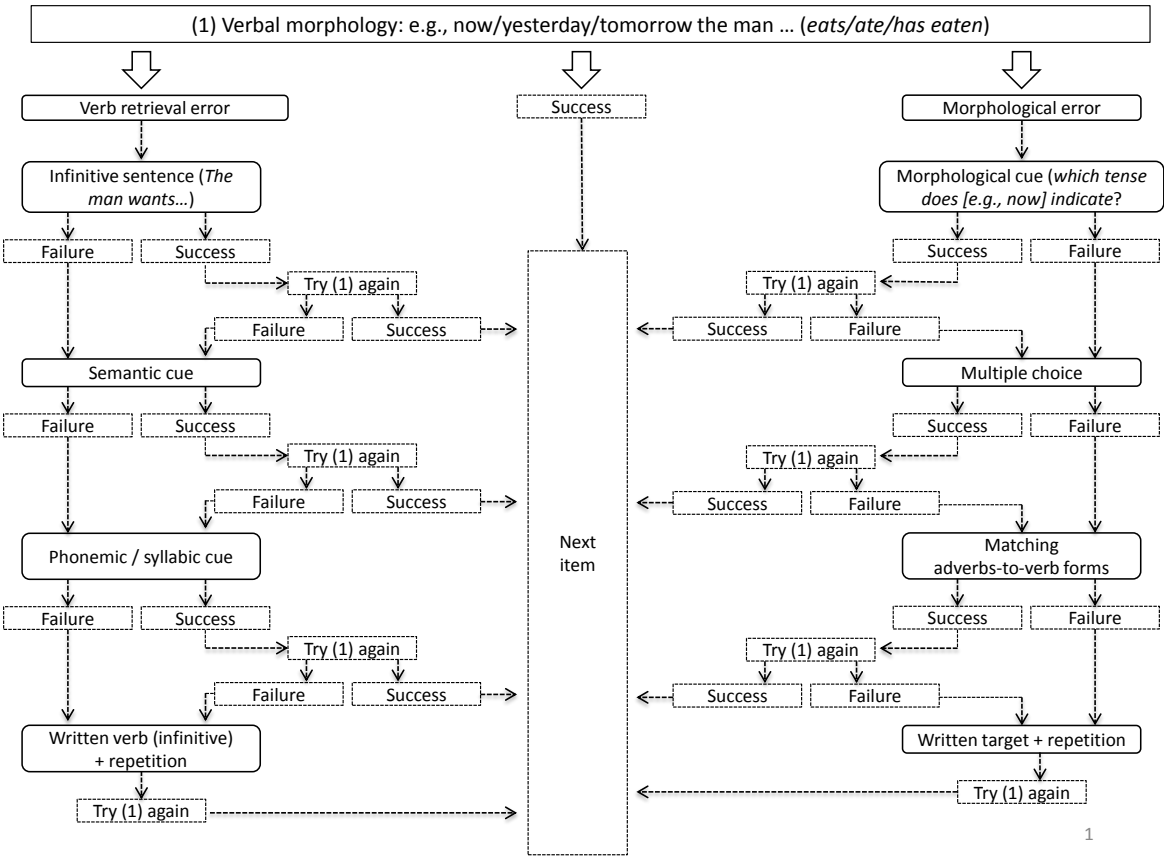

Figure C.1. Cues for verb retrieval and for the production of verb morphology were provided depending on error type.

a) The participant was presented with a sentence to be completed with an infinitive verb ("The man wants…"). If the correct verb was retrieved, Step 3 was tried again. In the event of a successful attempt, to the next item was presented. If case of failure, the therapist proceeded to (b).

b) The participant was presented with a semantic cue, related to the function or characteristics of the action. The semantic cue was a semantically loaded sentence that led to produce the infinitive. If retrieval was successful, the participant tried Step 3 again and, in case of correct response, the therapist went on to the next item. In the case of failure, the therapist proceeded to (c).

c) A phonemic cue (initial sound) was added to the semantic cue. If it did not precipitate the correct response, the whole first syllable was produced by the therapist (syllabic cue). If the correct verb was retrieved, the participant tried Step 3 again. If the attempt was successful, the therapist went on to the next item. If the participant failed the therapist proceeded to (d).

d) A card with the written verb in the infinitive was provided and at the same time the therapist said the word aloud. The participant was asked to repeat/read the target verb in the infinitive. The cue was presented until the participant succeeded to read/repeat (in case of excessive frustration, the therapist moved on to the following verb). After producing the verb the participant tried Step 3 again. In case of success the therapist

moved to the next item; in case of failure (d) was provided again. Then the therapist administered the following item, even if the response was not correct.

In Step 4, the participant saw an image and a written adverb (e.g., "now…"), and was requested to produce a full sentence that properly described the image (SVO or SOA), with the verb in the correct tense. If no response was provided, the following cues were used (Supplementary Figure 2):

a) The participant was asked to name each constituent, prompted by a question: for the subject "Who does this action?"; for the verb "What is the action/the verb?"; for the object "What is the object/the thing?" or adjunct "Where does this happen?". The therapist started by asking the participant to name the constituents that had been retrieved successfully. Those to which the subject had failed to produce any response were the last to be prompted. If no constituent was named correctly, subject, object/adjunct and then verb were presented, in this order. If the participant succeeded in naming each word, Step 4 was tried again. If retrieval errors prevailed, verb retrieval cueing proceeded with (b) and cueing of the subject or object/theme with (c).

b) The participant was presented with a sentence to be completed with an infinitive verb ("The man wants…"). If the participant failed to retrieve the verb, the therapist proceeded to (c). In case of success, the remaining constituents were named and then Step 4 was repeated. If retrieval errors persisted, cue (c) was provided. In case of success, the therapist proceeded to the following item.

c) The participant was presented with a semantic cue, that is, a semantically-loaded sentence (with information about the function or other features of the target word) that

led to producing the target word (for the verb, in the infinitive). If the participant still failed to retrieve the word, the therapist proceeded to (d). Upon success, the participant named the other constituents and tried Step 4 again. If no errors occurred, the therapist proceeded to the next item. If the participant still failed, the therapist proceeded to (d).

d) A phonemic cue was added to the semantic cue. If this did not help, the whole first syllable was produced by the therapist (syllabic cue). If the participant failed, (e) was provided. If the correct word was retrieved, the participant named the other constituents and then tried Step 4 again. If no errors occurred the therapist went on to the next item. If the participant failed, the therapist proceeded to (e).

e) A card with the written word (for the verb, the infinitive form) was provided and at the same time the therapist said the word aloud. The participant repeated/read the target word. The cue was presented until the participant succeeded to read/repeat (but if the participant was too frustrated, the therapist moved on to the next item). After producing the word the participant named the remaining constituents, and then tried Step 4 again. If no errors occurred the therapist went on to the next item. In case of failure, the therapist proceeded to (f).

f) Sentence anagrams: the participant saw 3 cards with the 3 sentence constituents, in random order. The participant arranged the constituents to form the correct sentence, and then read it aloud. If the participant failed, the therapist ordered the constituents correctly and asked the participant to read the sentence aloud. Subsequently, the three cards were removed and the participant tried Step 4 again. After this attempt, the therapist moved on to the next item, even if the response was not correct.

Figure C.2. Cueing hierarchy for Step 4.

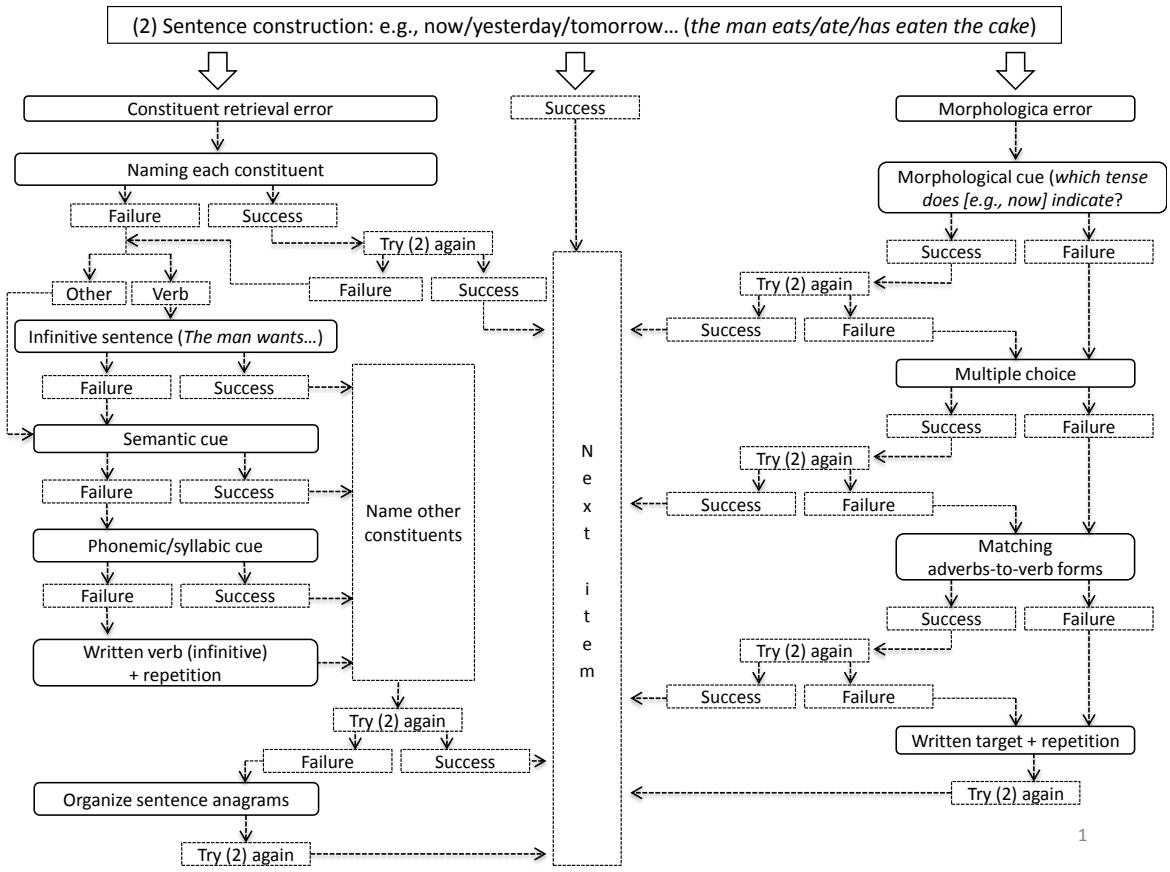

Figure C.2. Cues for verb retrieval and for the production of verb morphology were provided depending on error type.

When participants produced morphological errors, the following cues were given in both Steps 3 and 4:

a) The participant was asked the following question "which tense does X indicate?", where X is the adverb that was provided. The participant could reply verbally, or indicate the correct option on a sheet of paper, as long as knowledge of the correct time reference could be verified. If the correct tense was indicated, the participant tried again. If the

participant succeeded, the therapist moved on to the next item; if the morphological error persisted, the therapist proceeded to (b). If the wrong tense was indicated, the therapist provided the correct information (e.g. “Now indicates the present tense”) and moved on to (b).

b) Multiple-choice: the therapist provided three cards with three verb forms. The participant was asked to choose the card was correct for the presented adverb. After selecting the correct option the participant read it aloud. The card was then hidden and the participant tried step 3 or 4 again. If the response was correct, the therapist moved on to the next item; if the morphological error still occurred, the therapist moved on to (c). When the participant chose the wrong tense card the therapist moved on to (c).

c) Adverb/verb-form matching: the therapist placed the card for each adverb on the table while saying the time-frame indicated by the adverb (e.g., “Now indicates the present”) and placed the cards for each verb form while also saying the time-frame that form indicated (e.g., “eats indicates the present”). Adverbs were placed in a column and verbs in another column, in mismatching positions, and the participant was asked to place each verb-form next to the corresponding adverb. If matching was correct, the participant tried Step 3 or 4 again and upon success the therapist moved on to the next item; if the morphological error still occurred, the therapist moved on to (d). If the participant failed to provide the correct matching, the therapist performed it and then moved on to (d).

d) The therapist provided cards with the adverb and the inflected verb and completed the sentence with the correctly inflected verb (“Now the man eats” or “Now the man eats the pie.”, for Steps 3 and 4, respectively). The participant repeated/read the correctly

inflected verb. Then the participant was asked to try again. If the participant was successful, the therapist moved on to the next item; otherwise (d) was provided again.

Appendix D: Item matching for verb sets used in treatment study (Chapter 5)

Table D.1. Matching of treated and untreated verbs for psycholinguistic variables: LF

	Phase 1					Phase 2				
	Untreated		Treated		T-test	Untreated		Treated		T-test
	Mean	*std*	*Mean*	*std*	*P-value*	*Mean*	*std*	*Mean*	*std*	*P-value*
Sentence agreement	88.00%	0.077	88.50%	0.081	0.843	89.50%	0.083	90.50%	0.076	0.692
Age of Acquisition	2.184	0.604	2.079	0.473	0.546	2.100	0.475	1.977	0.730	0.533
Imageability	1.401	0.314	1.419	0.421	0.878	1.366	0.315	1.300	0.178	0.419
Relative frequency	30.809	47.520	27.395	33.734	0.795	53.186	85.751	59.012	80.649	0.826
Length in phonemes	7.900	1.252	8.250	1.372	0.405	8.100	1.252	8.150	1.268	0.901
	Count		*Count*			*Count*		*Count*		
Transitivity	14		14			13		13		
Internal arguments	14		14			13		13		
Instrumental	12		10			8		9		
Name related	4		3			3		2		
Manipulable	14		12			11		11		
Face/arm/leg										
*face actions	2		1			1		3		
*arm actions	14		16			14		13		
*leg actions	0		1			2		3		
*face & arm actions	1		0			0		0		
*arm & leg actions	0		0			1		0		
*"NA" actions	3		2			2		1		
Conjugation										
*first	16		16			15		14		
*second	2		1			3		4		
*third	2		3			2		2		

Table D.2. Matching of treated and untreated verbs for psycholinguistic variables: GC

	Phase 1					Phase 2				
	Untreated		Treated		T-test	Untreated		Treated		T-test
	Mean	*std*	*Mean*	*std*	*P-value*	*Mean*	*std*	*Mean*	*std*	*P-value*
Sentence agreement	92.00%	0.083	88.50%	0.081	0.187	90.00%	0.086	89.00%	0.079	0.703
Age of Acquisition	2.052	0.588	2.232	0.541	0.320	2.098	0.688	2.034	0.496	0.739
Imageability	1.425	0.323	1.352	0.327	0.483	1.379	0.351	1.331	0.127	0.567
Relative frequency	25.391	31.264	24.940	36.034	0.966	23.406	24.878	21.564	32.208	0.841
Length in phonemes	8.200	1.056	8.050	1.432	0.708	8.550	1.356	7.850	1.137	0.085
	Count		*Count*			*Count*		*Count*		
Transitivity	15		14			14		14		
Internal arguments	15		14			14		14		
Instrumental	10		11			11		10		
Name related	3		2			4		4		
Manipulable	12		13			13		13		
Face/arm/leg										
*face actions	1		1			2		1		
*arm actions	15		15			14		14		
*leg actions	0		1			1		0		
*face & arm actions	0		0			1		1		
*arm & leg actions	1		0			0		1		
*"NA" actions	2		2			2		3		
Conjugation										
*first	16		16			16		16		
*second	1		2			2		2		
*third	3		2			2		2		

Table D.3. Matching of treated and untreated verbs for psycholinguistic variables: GD

	Phase 1					Phase 2				
	Untreated		Treated		T-test	Untreated		Treated		T-test
	Mean	*std*	*Mean*	*std*	*P-value*	*Mean*	*std*	*Mean*	*std*	*P-value*
Sentence agreement	91.50%	0.075	89.00%	0.085	0.330	92.00%	0.077	91.50%	0.093	0.854
Age of Acquisition	1.958	0.547	1.885	0.575	0.683	1.849	0.391	1.961	0.600	0.489
Imageability	1.292	0.159	1.344	0.433	0.613	1.354	0.333	1.387	0.324	0.758
Relative frequency	37.343	49.045	42.514	75.243	0.798	42.173	45.499	37.188	44.657	0.729
Length in phonemes	8.000	1.414	7.750	1.517	0.593	7.900	1.294	7.750	1.118	0.697
	Count		*Count*			*Count*		*Count*		
Transitivity	13		13			12		12		
Internal arguments	13		13			12		12		
Instrumental	9		8			9		9		
Name related	1		3			3		3		
Manipulable	12		11			11		11		
Face/arm/leg										
*face actions	1		1			2		3		
*arm actions	13		11			11		14		
*leg actions	2		2			3		2		
*face & arm actions	1		1			1		0		
*arm & leg actions	1		0			1		0		
*"NA" actions	2		5			2		1		
Conjugation										
*first	16		15			15		16		
*second	3		3			3		3		
*third	1		2			2		1		

Table D.4. Matching of treated and untreated verbs for psycholinguistic variables: GP

	Phase 1					Phase 2				
	Untreated		Treated		T-test	Untreated		Treated		T-test
	Mean	*std*	*Mean*	*std*	*P-value*	*Mean*	*std*	*Mean*	*std*	*P-value*
Sentence agreement	91.50%	0.081	91.50%	0.081	1.000	91.00%	0.091	91.50%	0.075	0.850
Age of Acquisition	2.067	0.598	2.036	0.594	0.868	1.953	0.605	1.910	0.493	0.807
Imageability	1.384	0.308	1.345	0.204	0.639	1.357	0.339	1.303	0.188	0.536
Relative frequency	28.643	36.505	28.880	36.208	0.984	40.351	47.126	46.047	54.615	0.726
Length in phonemes	7.550	1.432	7.550	1.050	1.000	7.750	1.517	7.600	1.095	0.722
	Count		*Count*			*Count*		*Count*		
Transitivity	15		15			14		14		
Internal arguments	15		15			14		14		
Instrumental	8		9			9		11		
Name related	3		3			2		3		
Manipulable	13		12			12		12		
Face/arm/leg										
*face actions	1		2			0		3		
*arm actions	12		14			14		13		
*leg actions	2		1			1		3		
*face & arm actions	2		1			2		0		
*arm & leg actions	0		0			0		0		
*"NA" actions	3		2			2		1		
Conjugation										
*first	16		15			15		15		
*second	2		2			3		4		
*third	2		3			2		1		

Table D.5. Matching of treated and untreated verbs for psycholinguistic variables: EC

	Phase 1					Phase 2				
	Untreated		Treated		T-test	Untreated		Treated		T-test
	Mean	*std*	*Mean*	*std*	*P-value*	*Mean*	*std*	*Mean*	*std*	*P-value*
Sentence agreement	88.50%	0.075	88.00%	0.070	0.828	89.50%	0.089	90.50%	0.083	0.714
Age of Acquisition	2.124	0.449	2.087	0.513	0.812	2.005	0.518	2.002	0.626	0.987
Imageability	1.302	0.159	1.312	0.198	0.859	1.428	0.405	1.297	0.331	0.269
Relative frequency	23.741	35.207	21.366	24.570	0.806	41.679	72.521	46.439	87.876	0.853
Length in phonemes	7.850	1.040	7.750	1.209	0.781	8.050	1.356	7.600	1.353	0.300
	Count		*Count*			*Count*		*Count*		
Transitivity	15		15			14		14		
Internal arguments	15		15			14		14		
Instrumental	11		10			9		11		
Name related	4		3			2		3		
Manipulable	14		14			14		13		
Face/arm/leg										
*face actions	1		0			3		3		
*arm actions	18		16			13		14		
*leg actions	1		2			0		0		
*face & arm actions	0		0			1		1		
*arm & leg actions	0		1			0		0		
*"NA" actions	2		1			4		1		
Conjugation										
*first	16		16			14		14		
*second	2		2			4		3		
*third	2		2			2		3		

Table D.6. Matching of treated and untreated verbs for psycholinguistic variables: SP

	Phase 1					Phase 2				
	Untreated		Treated		T-test	Untreated		Treated		T-test
	Mean	*std*	*Mean*	*std*	*P-value*	*Mean*	*std*	*Mean*	*std*	*P-value*
Sentence agreement	89.50%	0.089	92.50%	0.079	0.265	90.00%	0.086	92.00%	0.077	0.442
Age of Acquisition	1.930	0.608	2.009	0.462	0.648	1.916	0.519	2.071	0.568	0.375
Imageability	1.333	0.196	1.271	0.143	0.257	1.381	0.414	1.359	0.188	0.825
Relative frequency	33.599	44.969	34.283	48.647	0.963	30.458	34.667	35.385	47.477	0.710
Length in phonemes	8.200	1.399	8.050	1.432	0.739	7.850	1.268	7.900	1.334	0.904
	Count		*Count*			*Count*		*Count*		
Transitivity	13		13			14		15		
Internal arguments	13		13			14		15		
Instrumental	9		7			10		9		
Name related	3		2			2		3		
Manipulable	13		8			13		11		
Face/arm/leg										
*face actions	1		3			1		1		
*arm actions	12		10			13		13		
*leg actions	1		3			2		1		
*face & arm actions	1		1			0		1		
*arm & leg actions	1		0			0		1		
*"NA" actions	3		3			2		3		
Conjugation										
*first	15		16			15		15		
*second	3		2			3		3		
*third	2		2			2		2		

Table D.7. Matching of treated and untreated verbs for psycholinguistic variables: RL

	Phase 1					Phase 2				
	Untreated		Treated		T-test	Untreated		Treated		T-test
	Mean	*std*	*Mean*	*std*	*P-value*	*Mean*	*std*	*Mean*	*std*	*P-value*
Sentence agreement	89.50%	0.083	91.00%	0.085	0.575	90.50%	0.076	90.50%	0.083	1.000
Age of Acquisition	2.006	0.568	1.968	0.623	0.843	2.080	0.526	2.071	0.440	0.956
Imageability	1.399	0.212	1.357	0.316	0.632	1.351	0.187	1.333	0.190	0.761
Relative frequency	44.113	75.507	38.218	43.068	0.763	38.108	75.190	26.581	39.205	0.547
Length in phonemes	7.800	1.196	7.650	1.182	0.692	7.800	1.576	8.000	1.076	0.642
	Count		*Count*			*Count*		*Count*		
Transitivity	14		14			14		14		
Internal arguments	14		14			14		14		
Instrumental	9		8			10		12		
Name related	2		2			4		4		
Manipulable	10		10			12		12		
Face/arm/leg										
*face actions	3		3			2		3		
*arm actions	13		13			13		13		
*leg actions	0		0			2		2		
*face & arm actions	0		0			0		0		
*arm & leg actions	1		0			0		0		
*"NA" actions	3		4			2		2		
Conjugation										
*first	15		16			15		14		
*second	2		2			2		3		
*third	3		2			3		3		

Table D.8. Matching of treated and untreated verbs for psycholinguistic variables: KC

	Phase 1					Phase 2				
	Untreated		Treated		T-test	Untreated		Treated		T-test
	Mean	*std*	*Mean*	*std*	*P-value*	*Mean*	*std*	*Mean*	*std*	*P-value*
Sentence agreement	88.00%	0.077	89.50%	0.083	0.555	90.50%	0.083	91.00%	0.085	0.852
Age of Acquisition	1.962	0.516	1.925	0.504	0.818	1.906	0.614	1.897	0.404	0.957
Imageability	1.386	0.423	1.362	0.342	0.846	1.401	0.484	1.349	0.221	0.664
Relative frequency	33.098	32.132	39.749	47.896	0.609	43.678	68.340	49.073	56.607	0.787
Length in phonemes	7.900	1.165	8.150	1.461	0.553	7.800	1.473	7.750	1.070	0.903
	Count		*Count*			*Count*		*Count*		
Transitivity	12		13			15		15		
Internal arguments	12		13			15		15		
Instrumental	8		11			11		10		
Name related	3		2			3		4		
Manipulable	11		11			14		12		
Face/arm/leg										
*face actions	2		2			1		3		
*arm actions	13		12			14		15		
*leg actions	3		0			2		1		
*face & arm actions	0		1			1		0		
*arm & leg actions	0		1			0		0		
*"NA" actions	2		3			2		1		
Conjugation										
*first	15		15			13		15		
*second	3		2			4		3		
*third	2		3			3		2		

Table D.9. Matching of treated and untreated verbs for psycholinguistic variables: PG

	Phase 1					Phase 2				
	Untreated		Treated		T-test	Untreated		Treated		T-test
	Mean	*std*	*Mean*	*std*	*P-value*	*Mean*	*std*	*Mean*	*std*	*P-value*
Sentence agreement	91.00%	0.091	90.50%	0.076	0.852	88.50%	0.081	91.00%	0.072	0.309
Age of Acquisition	2.135	0.470	2.036	0.473	0.511	1.942	0.429	2.002	0.633	0.729
Imageability	1.392	0.327	1.322	0.326	0.503	1.378	0.341	1.373	0.304	0.962
Relative frequency	27.897	42.606	27.432	53.424	0.976	45.614	45.994	38.532	73.549	0.717
Length in phonemes	8.100	1.373	8.200	1.240	0.810	7.800	1.281	8.050	1.468	0.570
	Count		*Count*			*Count*		*Count*		
Transitivity	14		14			15		15		
Internal arguments	14		14			15		15		
Instrumental	10		10			9		6		
Name related	5		4			2		1		
Manipulable	13		13			13		11		
Face/arm/leg										
*face actions	2		2			3		1		
*arm actions	14		14			15		12		
*leg actions	1		1			1		0		
*face & arm actions	0		1			1		2		
*arm & leg actions	1		0			0		0		
*"NA" actions	2		1			0		4		
Conjugation										
*first	17		16			20		18		
*second	1		2			0		2		
*third	2		2			0		0		

Table D.10. Matching of treated and untreated verbs for baseline accuracy and error types: LF

	Phase 1 (sum)		Phase 2 (sum)	
	Sum		Sum	
	Untreated	Treated	Untreated	Treated
Semantic paraphasia	8	3	6	8
Anomia (no response)	31	36	32	29
Phonemic paraphasia	2	6	4	3
Unrelated word	1	3	1	4
Word fragment	0	0	1	2
Neologism	3	6	0	0
Other	5	3	3	4
Baseline accuracy (max=60)	2	6	11	9
Comprehension errors (max=60)	0	4	2	4

Table D.11. Matching of treated and untreated verbs for baseline accuracy and error types: GC

	Phase 1 (sum)		Phase 2 (sum)	
	Sum		Sum	
	Untreated	Treated	Untreated	Treated
Semantic paraphasia	24	26	15	12
Anomia (no response)	10	11	13	12
Phonemic paraphasia	1	2	1	0
Unrelated word	5	7	2	1
Word fragment	1	0	1	1
Neologism	0	2	0	0
Other	3	2	3	5
Baseline accuracy (max=60)	15	13	24	23
Comprehension errors (max=60)	5	5	1	1

Table D.12. Matching of treated and untreated verbs for baseline accuracy and error types: GD

	Phase 1 (sum)		Phase 2 (sum)	
	Sum		Sum	
	Untreated	Treated	Untreated	Treated
Semantic paraphasia	12	10	3	5
Anomia (no response)	19	17	16	19
Phonemic paraphasia	1	1	1	0
Unrelated word	1	2	0	0
Word fragment	1	0	2	1
Neologism	0	0	0	0
Other	1	1	2	4
Baseline accuracy (max=60)	17	19	23	24
Comprehension errors (max=60)	0	0	0	0

Table D.13. Matching of treated and untreated verbs for baseline accuracy and error types: GP

	Phase 1 (sum)		Phase 2 (sum)	
	Sum		Sum	
	Untreated	Treated	Untreated	Treated
Semantic paraphasia	9	18	22	23
Anomia (no response)	2	2	5	3
Phonemic paraphasia	2	1	4	3
Unrelated word	7	10	3	2
Word fragment	0	0	0	0
Neologism	1	0	0	0
Other	1	1	1	0
Baseline accuracy (max=60)	14	14	21	22
Comprehension errors (max=60)	0	0	0	0

Table D.14. Matching of treated and untreated verbs for baseline accuracy and error types: EC

	Phase 1 (sum)		Phase 2 (sum)	
	Sum		Sum	
	Untreated	Treated	Untreated	Treated
Semantic paraphasia	6	7	11	9
Anomia (no response)	20	17	17	18
Phonemic paraphasia	0	0	0	0
Unrelated word	3	3	3	4
Word fragment	2	1	1	0
Neologism	0	0	0	0
Other	8	9	11	7
Baseline accuracy (max=60)	11	11	17	17
Comprehension errors (max=60)	0	0	0	0

Table D.15. Matching of treated and untreated verbs for baseline accuracy and error types: SP

	Phase 1 (sum)		Phase 2 (sum)	
	Sum		Sum	
	Untreated	Treated	Untreated	Treated
Semantic paraphasia	7	4	9	9
Anomia (no response)	28	27	29	29
Phonemic paraphasia	1	3	1	1
Unrelated word	11	12	11	8
Word fragment	0	0	0	0
Neologism	5	6	2	4
Other	2	0	0	2
Baseline accuracy (max=60)	0	0	5	5
Comprehension errors (max=60)	6	7	8	7

Table D.16. Matching of treated and untreated verbs for baseline accuracy and error types: RL

	Phase 1 (sum)		Phase 2 (sum)	
	Sum		Sum	
	Untreated	Treated	Untreated	Treated
Semantic paraphasia	6	7	9	6
Anomia (no response)	2	2	1	0
Phonemic paraphasia	5	1	5	2
Unrelated word	0	3	0	1
Word fragment	5	3	4	9
Neologism	0	1	0	0
Other	11	15	0	0
Baseline accuracy (max=60)	1	0	39	39
Comprehension errors (max=60)	0	0	0	1

Table D.17. Matching of treated and untreated verbs for baseline accuracy and error types: KC

	Phase 1 (sum)		Phase 2 (sum)	
	Sum		Sum	
	Untreated	Treated	Untreated	Treated
Semantic paraphasia	8	9	6	9
Anomia (no response)	17	21	5	8
Phonemic paraphasia	2	3	1	3
Unrelated word	2	3	2	2
Word fragment	3	2	6	4
Neologism	0	0	0	1
Other	12	6	15	10
Baseline accuracy (max=60)	13	15	23	24
Comprehension errors (max=60)	2	0	3	3

Table D.18. Matching of treated and untreated verbs for baseline accuracy and error types: PG

	Phase 1 (sum)		Phase 2 (sum)	
	Sum		Sum	
	Untreated	Treated	Untreated	Treated
Semantic paraphasia	16	14	7	8
Anomia (no response)	2	1	0	1
Phonemic paraphasia	5	6	10	12
Unrelated word	3	4	2	2
Word fragment	4	9	3	6
Neologism	5	6	0	1
Other	15	16	13	7
Baseline accuracy (max=60)	9	9	35	34
Comprehension errors (max=60)	0	3	1	2

Appendix E. Diagnostic assessments of patients included in treatment study (Chapter 5)

LF

LF presents non-fluent speech characterized by slow, laborious and often imprecise articulation. His output consists mostly of isolated noun phrases, with frequent pauses, word fragments, phonemic and semantic paraphasias. The informative value of his production is overall low, even though he uses nonverbal strategies to increase communicative efficacy. He performs below norm in all diagnostic tasks. Auditory discrimination is mildly impaired. Mild-to-moderate difficulty in all sublexical tasks and a mild length effect suggest damage to all sublexical conversion mechanisms. Mild impairment is observed for auditory and visual lexical decision, as well as for verb and noun comprehension. Oral and written naming of both nouns and verbs is more severely impaired than input tasks. Naming errors result mostly in anomias, as well as in phonemic and semantic paraphasias. Given the substantially greater impairment in naming (66.7% errors for nouns and 71.4% for verbs) than in comprehension tasks (10% errors for nouns and verbs), at least some naming errors are more likely to arise at a post-semantic stage (either at the level of access to the lexicons from semantic, or at the output lexicon stage). Segmental errors in all spoken output tasks suggest that the phonological working memory may also be compromised. Oral naming of nouns and verbs is impaired to a similar degree (Fisher exact p=1.000). At the sentence level, morphological errors and errors of thematic role assignment are observed in comprehension (7/9 errors) and production. Sentence construction may be disrupted due to a complex deficit - reduced working memory, sublexical processing deficits (phonemic

paraphasias), difficulties of lexical retrieval, and of grammatical encoding (thematic role reversals, argument omissions, morphosyntactic errors (e.g., determiner-noun agreement).

GC

GC presents fluent, effortless, well-articulated speech with appropriate speed and prosodic contour. Length of utterances is normal and informative content is adequate, but occasional phonemic and semantic paraphasias as well as word fragments and circumlocutions are observed. Auditory discrimination is mildly impaired. Though no length effect is observed, non-word repetition, reading and writing are below norm, consistent with damage to sublexical conversion mechanisms. Auditory and visual lexical decision are mildly impaired, but auditory and visual word comprehension are within norm, suggesting substantially unimpaired semantic processing. Pathological performance in writing to dictation, written object naming and word copying is consistent with an impairment of post-lexical and more peripheral processes (orthographic working memory, or later, writing-specific processes). Naming is impaired for verbs and nouns to a similar extent (20% errors for objects and 28.6% errors for actions; Fisher exact p=0.682). Errors consist of anomias, semantic paraphasias, visual and unrelated-word errors. Considering normal performance in word comprehension tasks (verbs: 0.0% errors; nouns: 2.5% errors), naming difficulties for nouns and verbs are very likely to arise at lexical, post-semantic levels. Auditory sentence comprehension is mildly impaired, with one error of thematic role assignment, one error on morphological foils and two errors on semantic foils. In sentence construction, difficulty with passives is observed, resulting in omissions of the auxiliary and thematic role reversals. There are also conduites d'approche, morphologically related words, circumlocutions, semantic and phonemic paraphasias. In the light of associated deficits in

sentence repetition, results suggest that sentence production difficulties result from a complex impairment affecting sublexical, lexical and grammatical encoding, as well as working memory.

GD

GD presents fluent, effortless speech with appropriate articulation, prosody and speed. Sentences are of adequate length, but frequent semantic paraphasias and circumlocutions reduce their informative value. Auditory discrimination is below norm. Nonword repetition is relatively more impaired, consistent with damage to phoneme/phoneme conversion mechanisms. Auditory lexical decision and auditory noun comprehension (20% errors) are both mildly impaired. Auditory comprehension of verbs and visual comprehension of nouns and verbs are normal. In a picture verification task (described in the Methods section), GD makes errors on semantic foils, suggesting mild semantic impairment. Comparably severe naming difficulty for nouns and verbs (60% errors for nouns and 57.1% for verbs; Fisher exact p=1.000) may then arise from a semantic, or post-semantic deficit involving the phonemic output lexicon. Impairment in all spoken output tasks (naming, reading aloud, word and non-word repetition) and a length effect in non-word repetition, are consistent with an impairment of phonological working memory. Accordingly, errors in sentence repetition occur mostly at the end of the sentence. Sentence comprehension is mildly impaired, with three errors of thematic role inversion. Thematic role reversals are also observed in sentence production, together with omission of the auxiliary and by-phrase in passive constructions. Both the lexical verb and its argument are frequently omitted, and semantic paraphasias occur.

GP

GP presents non-fluent, slow, effortful speech, with appropriate prosody and precise articulation. He produces very short sentences, mostly consisting of isolated noun phrases. He produces very few verbs, in non-finite forms. Nevertheless, he is able to convey complex messages (e.g., plans for the coming holidays) using telegraphic sentences. He performs below norm in all sublexical processing tasks (except non-word copying), suggesting impairment to phoneme/phoneme, phoneme/grapheme, and grapheme/phoneme conversion mechanisms. Performance is below norm in auditory and visual lexical decision, but comprehension is only impaired in the visual modality, for verbs. This suggests normal or mildly impaired semantic processing. Spoken and written naming are impaired for nouns and verbs. Oral naming impairment is significantly more severe for verbs (16.7% errors for nouns and 78.6% for verbs; Fisher exact $p<0.001$). Paired with intact comprehension, poor naming suggest that naming difficulties arise at a post-semantic locus (lexical access and/or storage). In addition, GP performs below norm in all oral output tasks, shows a length effect in naming and produces occasional phonemic paraphasias, consistent with additional damage to the phonemic output buffer. In sentence comprehension GP makes errors with thematic role assignment, and with morphological and semantic distractors. In sentence production he tends to reverse thematic roles. Most errors occur on the verb, and involve both verb retrieval (nominalizations, perseverations and, less often, omissions) and inflectional processes (subject-verb agreement errors, mostly resulting in the production of a non-finite verb form).

EC

EC presents non-fluent, slow, effortful speech, with reduced prosodic contour and accurate articulation. He produces short sentences, filled with pauses, repairs and omissions, with low informative value. He performs below norm in all sublexical processing tasks, except auditory discrimination. These scores reflect widespread impairment of sublexical conversion mechanisms. Auditory and visual lexical decision is impaired, but auditory and visual comprehension of nouns and verbs is intact, suggesting spared semantic processing. Below norm performance in word writing (both to dictation and in written naming) and word copy suggests damage to peripheral processes (graphemic output buffer, allographic or graphomotor realization). Oral object and action naming are similarly impaired (43.3% errors for nouns and 57.1% for verbs; Fisher exact p=0.431), resulting in anomias, and (less frequently) in semantic and phonemic paraphasias. The naming difficulty seems to arise from damage to lexical mechanisms. In sentence comprehension, EC makes two errors of thematic role reversal, and incorrectly selects two morphological and two semantic foils. In sentence production, EC omits arguments, and in passive sentences replaces the past participle construction with a reflexive construction. He also produces occasional semantic paraphasias.

SP

SP presents non fluent speech, characterized by slow and imprecise articulation, and short sentences with preserved prosodic contour. Paraphasias occur frequently and consist most often of words unrelated to the target, semantic paraphasias or, less often, neologistic and phonemic paraphasias. Stereotypical phrases are present and so is palilalia. His output conveys very little information, and he is often unaware of his errors. Due to difficulty in task comprehension,

several diagnostic tasks were not administered. Phoneme/phoneme and grapheme/phoneme conversion are impaired, as shown by poor scores in sublexical processing tasks. Auditory and visual lexical decision are below norm, denoting input lexicon damage. Modality-independent difficulties in input and output word processing tasks suggest semantic damage. Action and object naming are impaired to a similar extent (60% errors for nouns and 64.3% for verbs; Fisher exact p=1.000), and word frequency affects performance. Naming difficulties in this subject may arise at semantic and/or post-semantic levels (access to or processing within the phonological output lexicon). Scores are below norm in all output tasks and there is a mild length effect, suggesting additional post-lexical impairment. Sentence comprehension is severely impaired, with errors occurring in stimuli presented with semantic (n=3), morphological (n=5) and role reversal foils (n=4). In sentence production, SP produces mostly nouns, both related and unrelated to targets. When verbs are produced, they are often unrelated to the target and inappropriate to its predicate argument structure, consistent with a semantic deficit. Function words and verbs are frequently omitted.

RL

RL's speech is non-fluent, slow and effortful, with a mild articulation deficit, and normal prosody. She produces short sentences with frequent pauses, semantic paraphasias and word fragments. Nevertheless, she makes good use of verbal and non-verbal strategies and communication is usually sufficiently informative. All sublexical processing tasks except for nonword copying are mildly-to-moderately impaired, as a consequence of damage to phoneme/phoneme, phoneme/grapheme and grapheme/phoneme conversion. Auditory lexical decision is only mildly impaired, and auditory and visual word comprehension is within norm, suggesting spared semantic processes. Written naming is particularly impaired, but even though

spoken naming is within norm, correct performance is achieved after multiple naming attempts and only if time-to-respond is not taken into account. We considered first-response accuracy in assessing verb production performance, and RL produced 37.5% errors when retrieving verbs in the infinitive in sentence context. Most errors on first attempt are word fragments, semantic and phonemic paraphasias and occasionally, nominalizations or substitutions of a non-related verb for the target. A post-semantic, lexical deficit is likely in this subject. In addition, mild impairment in word and sentence repetition, and the length effect in non-word repetition are consistent with a mild disorder of phonological working memory. Sentence comprehension (auditory and visual) is normal. Sentence production was assessed with VTsentence. Responses were scored for first-response accuracy, with a time limit of 30 seconds per sentence. The most frequent errors were of the semantic and anomic types, followed by word fragments and phonemic paraphasias. Attempts were generally made to produce each constituent (11.6% of omissions), revealing good knowledge of verb argument structure. Sentence production seems to be impaired mostly due to lexical retrieval and post-lexical impairments.

KC

KC presents non-fluent, slow, effortful, dysarthric speech with very low informative value. Prosody is adequate. Communicative initiative is also low. Auditory discrimination is mildly impaired. Nonword repetition, reading and writing are below norm, suggesting damage to phoneme/phoneme, grapheme/phoneme and phoneme/grapheme conversion. Scores below norm in auditory lexical decision, associated with a frequency effect, indicate that poor auditory comprehension can partially be accounted for by deficits in the phonological input lexicon. In addition, poor performance in all (input and output) tasks that require access to word meanings is consistent with damage to the semantic system. Oral naming is comparably impaired for nouns

and verbs (13.3% errors for nouns and 14.3% for verbs; Fisher exact p=1.000). In sentence comprehension, KC makes errors with semantic and thematic role distractors. In sentence production, she tends to use light verbs or to omit the lexical verb and one or more of its arguments. Her speech contains word fragments, semantic, phonemic and neologistic paraphasias, and occasionally, unrelated words. In addition, if forced to use passives, she produces thematic role assignment errors. Sentence repetition is also impaired, and errors in repetition tasks are influenced by word length, suggesting reduced phonological working memory.

PG

PG's speech is fluent, effortless, with adequate articulation, prosody, speed, and sentence length. He conveys information appropriately, although he resorts to repeated attempts at production, including circumlocutions and reformulations. Sublexical phoneme/phoneme, grapheme/phoneme, and phoneme/grapheme conversion are impaired. While scores in auditory and visual lexical decision are slightly below norm, phoneme discrimination is within norm. This suggests mild damage to the phonological and orthographic input lexicons. Auditory and visual comprehension of nouns and verbs are within norm, consistent with spared semantic processing. Oral and written naming is impaired for nouns and verbs (to a similar extent, 33.3% errors for nouns and 42.9% for verbs; Fisher exact p=0.710), suggesting post-semantic damage. Pathological word reading is consistent with damage to the phonological output lexicon. The high proportion of segmental errors in delayed word copy is consistent with post-lexical damage. Impaired sentence repetition and effects of length in sublexical conversion tasks suggest reduced working memory. In sentence comprehension, most errors result from thematic role reversals, but also occur when target sentences are presented with morphological foils. In sentence

production, fragments, and circumlocutions are frequent. In addition, PG produces frequent phonemic paraphasias, followed by conduites d'approche.

Epilogue

About the author

I am a PhD candidate in the IDEALAB program (International Doctorate in Experimental Approaches to Language and the Brain), at Universities of Trento, Groningen and Macquarie University. I work under the supervision of Prof. Dr. Gabriele Miceli, Prof. Dr. Roelien Bastiaanse and Prof. Dr. Lyndsey Nickels.

I studied Speech and Language Therapy and specialized in Cognitive Neuroscience and Neuropsychology at the University of Algarve (Portugal). From 2007 to 2010, I worked as a Speech and Language Therapist at a neurorehabilitation center (*Centro de Medicina Física e de Reabilitação do Sul*, Portugal). There, I asssessed and treated patients with speech, language and swallowing deficits following brain damage. I graduated from the Joint European Masters in Clinical Linguistics (MSc), held at the Universities of Potsdam and Groningen. My master's thesis was a psycholinguistic study using event related potentials (ERPs) to investigate the neurophysiological correlates underlying the processing of personal and reflexive pronouns.

Currently, I am an assistant professor in Speech and Language Pathology at the Department of Clinical Speech and Language Studies of Trinity College Dublin, in Ireland. I am also an active member of the Collaboration of Aphasia trialists. My research interests embrace clinical and neurolinguistics (morphosyntactic deficits in aphasia; aphasia assessment and rehabilitation with a cognitive neuropsychological and linguistic approach; coadjuvant rehabilitation techniques; neural substrates and cognitive mechanisms of language recovery after stroke), and psycholonguistics (discourse processing, in particular, anaphoric dependencies). In the future, I would like to continue in the academic path, do more research, and contribute to the advance of theoretical and practical approaches to the study of language disorders.

Publications, published abstracts, and awards

Published articles:

de Aguiar, V., Bastiaanse, R., Capasso, R., Gandolfi, M., Smania, N., Rossi, G., & Miceli, G. (2015). Can tDCS enhance item-specific effects and generalization after linguistically motivated aphasia therapy for verbs? *Frontiers in Behavioral Neuroscience, 9*, 190. doi: 10.3389/fnbeh.2015.00190

Rofes, A., de Aguiar, V., & Miceli, G. (2015). A minimal standardization setting for language mapping tests: an Italian example. *Neurological Sciences, 36*, 1113-1119. doi:10.1007/s10072-015-2192-3

de Aguiar, V., Paolazzi, C., Miceli, G. (2015). tDCS in post-stroke aphasia: The role of stimulation parameters, behavioral treatment and patient characteristics, *Cortex,* 63, 296-316, doi: 10.1016/j.cortex.2014.08.015.

Martínez-Ferreiro, S., de Aguiar, V., Rofes, A. (2015). Non-fluent aphasia in Ibero-Romance: Morphosyntactic deficits. *Aphasiology, 29*(1), 101-126, doi: 10.1080/02687038.2014.958915

Submitted articles (under review):

de Aguiar, V., Nickels, L., Miceli, G., & Sowman, P. ERP signatures of repetition priming in spoken word production and the absence of tDCS-related enhancement. Manuscript submitted for publication. [Neuropsychologia]

de Aguiar, V., Bastiaanse, R., Reis, A. & Dragoy, O. Event related potentials of the processing of reflexives, pronouns and referential violations. Manuscript submitted for publication. [Language, Cognition, and Neuroscience]

Proceedings:

de Aguiar, V., Bastiaanse, R., Capasso, R., Gandolfi, M., Iellici, E., Smania, N., & Miceli, G. (2014). Effects of tDCS and morpho-syntactic therapy in lexical retrieval of treated and untreated verbs. *Stem-, spraak- en taalpathologie. 20*(2015), 4-7. doi: 32.8310/supplement/1914

de Aguiar, V., & Miceli, G. (2014). Can pre-treatment scores predict treatment success and failure? The case of verb therapies. *Stem-, spraak- en taalpathologie. 20*(2015), 122-125. doi: 32.8310/supplement/1914

de Aguiar, V., Bastiaanse, R., Odorizzi, F., & Miceli, G. (2014). Aphasia rehabilitation from a linguistic perspective and the role of tDCS. *Society for the neurobiology of language, conference proceedings.* http://www.neurolang.org/programs/SNL2014_Program_with_Abstracts.pdf

de Aguiar, V., Bastiaanse, R., Miceli, G. (2014). Aphasia rehabilitation from a linguistic perspective and the role of tDCS. *Stem-, spraak- en taalpathologie. 19*(2014), 131-134. doi: 32.8310/supplement/1914

de Aguiar, V., Bastiaanse, R., Reis, A. & Dragoy, O. (2013). Event related potentials of the processing of reflexives, pronouns and referential violations. *Stem-, spraak- en taalpathologie. 18*(S01), 8-12. doi: 32.8310/S01/1813-8

Conference presentations/posters:

de Aguiar, V., Bastiaanse, R., Capasso, R., Gandolfi, M., Iellici, E., Smania, N., & Miceli, G. (2014). Effects of tDCS and morpho-syntactic therapy in lexical retrieval of treated and untreated verbs. Aveiro, Portugal. September 18th, 2015 [talk]

de Aguiar, V., & Miceli, G. (2014). Can pre-treatment scores predict treatment success and failure? The case of verb therapies. Aveiro, Portugal. September 19th, 2015 [talk]

de Aguiar, V., Miceli, G. (2015). Predictors of verb treatment success. Collaboration of Aphasia Trialists Conference: Future directions for aphasia research. London, UK. March 6th, 2015 [talk]

de Aguiar, V., Bastiaanse, R., Capasso, R., Odorizzi, F., & Miceli, G. (2014). Item specific and generalization effects of linguistically motivated therapy and tDCS. CIMeC Doctoral School Day, Rovereto, Italy, September 26th, 2014. [talk]

de Aguiar, V., Bastiaanse, R., Miceli, G. (2014). Aphasia rehabilitation from a linguistic perspective and the role of tDCS. Science of Aphasia Conference, Venice, Italy, September 19-24th, 2014. [talk]

de Aguiar, V., Bastiaanse, R., Odorizzi, F., & Miceli, G. (2014). Aphasia rehabilitation from a linguistic perspective and the role of tDCS. Society for the neurobiology of language, August 27-29th, 2014. [poster]

de Aguiar, V. on behalf of the Collaboration of Aphasia Trialists (2014). Fostering a collaborative international aphasia research network. I Jornadas em Comunicação Linguagem e fala, June 20-21st, 2014. Faro, Portugal [talk]

de Aguiar, V., Bastiaanse, R., Odorizzi, F., Capasso, R., & Miceli, G. (2014). Reabilitação afasia com uma perspectiva linguística e o papel da tDCS. I Jornadas em Comunicação Linguagem e fala, June 20-21st, 2014. Faro, Portugal [talk]

de Aguiar, V., Nickels, L., Miceli, G., Sowman, P. (2014) Language facilitation via repetition priming and neurostimulation. Rovereto Workshop on Concepts, Actions, and Objects: Functional and neural perspectives. May 8-11th, 2014, Rovereto, Italy [poster]

de Aguiar, V., Bastiaanse, R., Miceli, G. (2014) Aphasia rehabilitation from a linguistic perspective and the role of tDCS. ARC Centre of excellence in Cognition and its Disorders (CCD) – Annual workshop. Sydney. November 27th-28th, 2013. [poster]

de Aguiar, V., Bastiaanse, R., Reis, A. & Dragoy, O. Event related potentials of the processing of reflexives, pronouns and referential violations. Science of Aphasia (SOA). Brussels. September 20-25, 2013. [talk]

Invited talks:

de Aguiar, V. (2015). Neuromodulation and rehabilitation of verb production. Neurolinguistics research group, University of Groningen, The Netherlands, April 23rd, 2015.

de Aguiar, V. (2015). The ACTION protocol: morphosyntactic therapy for aphasia. Meeting of the Dutch association of clinical linguistc (Vereniging voor Klinische Linguïstiek), Amersfoort, The Netherlands, April 10th, 2015.

de Aguiar, V. (2015) Research in speech and language pathology [Portuguese: Investigação em Terapia da Fala]. University of Algarve, ESSUAlg, Faro, Portugal, March 26th, 2015

de Aguiar, A. & Miceli, G. (2014). La neuromodulazione (tDCS) nella riabilitazione dei disturbi del linguaggio [Italian: Neuromodulation (tDCS) in the rehabilitation of language deficits] Habilita: La rieducazione neurocognitiva nelle malattie degenerative del sistema nervoso centrale. November 22nd, Bergamo, Italy

de Aguiar, V., Bastiaanse, R., Capasso, R., Odorizzi, F., & Miceli, G. (2014). Aphasia rehabilitation from a linguistic perspective and the role of tDCS. Neurolinguistics research group, University of Groningen, The Netherlands, July 2nd, 2014.

de Aguiar, V., Nickels, L., Miceli, G., Sowman, P. (2014) Training di denominazione via repetition priming e tDCS [Italian: Language facilitation via repetition priming and neurostimulation]. Centro di Riabilitazione Neurocognitiva, at University of Trento. March 13th, 2014, Rovereto, Italy

Miceli, G., & de Aguiar, V. (2014). La tDCS nella rieducazione dei disturbi del linguaggio. [Italian: tDCS in the treatment of language deficits] Workshop: Stimolazione e Training Cognitivo nelle Malattie Neurologiche. May 15th, 2014. Brescia, Italy.

de Aguiar, V., Nickels, L., Miceli, G., Sowman, P. (2014) Training di denominazione via repetition priming e tDCS [Italian: Language facilitation via repetition priming and neurostimulation]. Centro di Riabilitazione Neurocognitiva, at University of Trento. March 13th, 2014, Rovereto, Italy

de Aguiar, V., Bastiaanse, R., Miceli, G. Aphasia rehabilitation from a linguistic perspective and the role of tDCS. Aphasia research group, ARC Centre of excellence in Cognition and its Disorders (CCD) at Macquarie University. Sydney. November 13th, 2013.

de Aguiar, V., Bastiaanse, R., Miceli, G. Aphasia rehabilitation from a linguistic perspective and the role of tDCS. University of Verona Neurorehabilitation Unit, University Hospital. Verona. August 9th 2013.

de Aguiar, V. Speech therapy in stroke patients. 1st Health Meeting at ESSAF, University of Algarve, Portugal. 2009.

Awards, Scholarships, Grants, and Honors:

2013 MACCS POSTGRADUATE GRANT "Training verb production with tDCS: neurophysiological effects of naming facilitation via repetition priming"

2012-2015 Erasmus Mundus Joint Doctorates (EMJDs) grant, in the IDEALAB PhD program (International Doctorate in Experimental Approaches to Language And the Brain) - em-idealab.com

2010-2012 Erasmus Mundus Master Course (EMMCs) grant, in the EMCL program (European Master in Clinical Linguistics) - emcl-mundus.com