TASK LOAD MODULATION OF tDCS EFFECTS ON BEHAVIOURAL AND NEURAL CORRELATES OF PHONOLOGICAL PROCESSING: A BRAIN-STATE-DEPENDENT STIMULATION APPROACH

by

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ABSTRACT

This thesis investigates the task load modulation of transcranial direct current stimulation (tDCS) effects on the behavioural and neural correlates of phonological processing in the healthy, dyslexic and aphasic brain. Tasks selected from a range of speech perception to speech production were assumed to engage the two main regions of the dorsal pathway of phonological processing, the targets left inferior frontal gyrus (LIFG) and left superior temporal gyrus (LSTG), differently: increasing engagement for the LIFG and decreasing engagement for the LSTG across the range. Anodal tDCS (facilitatory) and cathodal tDCS (inhibitory) were expected to have an effect as a direct function of target engagement with the task. Cathodal tDCS was also expected to induce indirect facilitation via network compensation negatively related to target engagement. These effects should be weaker in dyslexia and aphasia, and consistent with their altered pattern of brain activity. The findings suggest that task load modulation of tDCS effects occurred. Outcomes such as improved performance in a speech perception task caused by cathodal tDCS would suggest that cathodal tDCS induced network compensation. Results in dyslexia and aphasia were consistent with their altered pattern of brain activity, indicating that tDCS shows promise as both diagnosis and treatment tool.

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LIST OF ABBREVIATIONS

BA – Brodmann Area

BOLD – Blood-Oxygen-Level Dependent

CI – Confidence Interval

CP – Categorical Perception (of speech)

fMRI – Functional Magnetic Resonance Imaging

IFG – Inferior Frontal Gyrus

LD – Lexical Decision

LIFG – Left Inferior Frontal Gyrus

LSTG – Left Superior Temporal Gyrus

PWA – Person(s) with Aphasia

PWD – Person(s) with Dyslexia

RIFG – Right Inferior Frontal Gyrus

ROI(s) – Region(s) of Interest

RSTG – Right Superior Temporal Gyrus

SD – Standard Deviation

SMD – Standardised Mean Difference(s)

STG – Superior Temporal Gyrus

tDCS – Transcranial Direct Current Stimulation

TMS – Transcranial Magnetic Stimulation

WN – Word Naming

CHAPTER 1:

GENERAL INTRODUCTION

1.1 INTRODUCTION

Transcranial direct current stimulation (tDCS) is a brain stimulation technique widely used in research with humans. It is used to modulate neuronal activity inducing cortical excitation with anodal stimulation or cortical inhibition with cathodal stimulation in order to alter behaviour. Studies in a variety of domains such as language (Hussey et al., 2015; Monti et al., 2013), memory (Au et al., 2016; Hussey et al., 2015), visual processing (Heinen et al., 2016; Pirulli et al., 2014) and motor learning or motor processing (Rroji et al., 2015; Sasaki et al., 2016) have demonstrated that tDCS stimulation causes changes which improve or worsen behavioural performance. However, in the tDCS literature, it has been observed that predictions for behavioural outcomes based on the assumption that anodal tDCS always improves performance and cathodal tDCS always decreases performance often turns out to be incorrect, or results appear to be inconsistent across studies, especially in cognitive domains (see Jacobson et al., 2012 meta-analysis). This indicates that the conceptual models currently used to make such predictions are incomplete.

It has been suggested that the baseline level of brain activity plays an important role for the outcomes of brain stimulation, which is an important aspect that has been much overlooked in the literature (Bikson et al., 2013; Gharabaghi et al., 2014; Sergeeva et al., 2014; Silvanto et al., 2008; see Chapter 2 for a discussion on brain-state-dependent stimulation based on a meta-analysis in aphasia). Particularly in the cognitive domain, two factors have been considered to be important for informing predictions on tDCS effects: the relevance of the task for the area stimulated (Bikson et al., 2013) and the network structure that typically underlies cognitive functions (Jacobson et al., 2012). In this thesis, these factors were closely considered. I have first presented the two most commonly used conceptual frameworks to inform tDCS predictions, hereon defined as the dual polarity framework and the inhibitory framework. Then an extension of these frameworks into a

multi-node framework was devised in order to take into account the factors of task load and the typical network structure that underlies cognitive functions. Predictions based on the multi-node framework for the healthy brain were investigated throughout the experimental chapters of this thesis.

Last, it is important to take into account that populations who have a brain disorder will present with a pattern of baseline brain activity that likely differs from that observed in the healthy population. When planning tDCS interventions in such populations, this needs to be closely observed to allow appropriate predictions and interpretations for the effects of tDCS. In chapters 10 and 11, I investigated the additional brain state factor of disorders idiosyncratic pattern of brain activity. Specifically, I investigated (developmental) dyslexia in chapter 10 and (frontal) aphasia in chapter 11, which are language disorders where some disruption of phonological processing is observed. Developmental dyslexia is a difficulty of learning to read that is neither attributed to cognitive nor sensorial deficit nor to lack of educational opportunities (Ramus, 2004). The associated neural correlates are thought to involve altered patterns of brain activity and white matter integrity of the core areas for phonological processing (left inferior frontal gyrus – LIFG, and left superior temporal gyrus – LSTG) (Brunswick et al., 1999; Carter et al., 2009; Georgiewa et al., 1999; Klingberg et al., 2000; Rimrodt et al., 2010; Ruff et al., 2003). Typically, hypoactivation of the LSTG and hyperactivation of the LIFG are observed (Brunswick et al., 1999). Aphasia is a language disorder that affects speech production and speech comprehension to various degrees, and whose main cause is stroke (Koenig-Bruhin et al., 2013). Tissue loss commonly occurs in the left perisylvian region, involving the LIFG and the LSTG (Kiran, 2012). In frontal aphasia, the LIFG is the region expected to have the most damage. Typically, hypoactivity in the brain areas involved with language is found (Sandberg et al., 2017; Yang et al., 2016; Zhu et al., 2014). The

pattern of brain activity supporting language will depend on the pattern of brain recovery, and may include the activity of left perilesional area or the activity of right homologue areas (Torres et al., 2013).

1.2 OUTLINE OF THE THESIS AND OBJECTIVES

Concretely, in this thesis I conducted experiments in language, as a representative function of the cognitive domain, to investigate whether the relevance of the task for the target area (task load) and the presence of a typical network structure that underlies cognitive functions were relevant factors to understand the effects of tDCS on behaviour and its corresponding neuronal activity. To accomplish this aim, a language network involved with phonological processing, the dorsal pathway (Liebenthal et al., 2013; Saur, 2008), was chosen. Phonological processing involves the analysis of auditory and motor properties of speech sounds and their categorisation according to a system of contrastive sound units that can change the meaning of words in a given language (Liebenthal et al., 2013). This language function is present in various degrees from speech perception to speech production, and is assumed to rely to different extents on the endpoints of the dorsal pathway, the LIFG and the LSTG (Burton et al., 2001; Okada & Hickok, 2006a, 2006b). That is, whilst both the LIFG and LSTG are always involved in phonological processing, this language function relies more on the LSTG than on the LIFG in tasks of speech perception (Chang et al., 2010; Leonard & Chang, 2014), whereas it relies more on the LIFG than on the LSTG in tasks of speech production (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011). The non-uniform distribution of phonological processing between the LIFG and the LSTG across the range from speech perception to speech production motivated the choice of tasks to match this range and of LIFG and LSTG as targets of tDCS in order to investigate the task load

modulation of tDCS effects in this thesis. Predictions based on the multi-node framework for the healthy brain were investigated with samples of healthy young adults. Such predictions were also investigated with samples of populations presenting with some disruption of phonological processing, namely persons with dyslexia (PWD) and persons with aphasia (PWA). For these groups, adjustments to predictions for the healthy brain according to the corresponding pattern of underlying brain malfunction were discussed. The objectives of this thesis were:

A) General objective: to use a brain-state-dependent stimulation approach to investigate the role of task load on the effects of tDCS in phonological processing in healthy young adults, PWD and PWA.

B) Specific objectives:

1. to investigate the behavioural and neural correlates of task load modulation of the effects of anodal and cathodal tDCS on the LIFG and on the LSTG in healthy young adults;
2. to investigate the neural correlates of task load modulation of the effects of anodal and cathodal tDCS on the LIFG in PWD;
3. to investigate the neural correlates of task load modulation of the effects of anodal and cathodal tDCS on the LIFG in PWA.

The thesis is structured as follows. Chapter 2 is a meta-analysis of studies that used tDCS for the treatment of aphasic anomia and discussed the brain-state-dependent stimulation framework, which was used as a framework for theoretical motivation for this thesis. In chapter 3, I provided a background on the conventional, and on the most recent conceptual frameworks used to inform tDCS predictions. I also presented the specific cognitive function (phonological

processing) that the experiments on this thesis were based on and showed the corresponding brain regions that were the target of stimulation in these experiments (the LIFG and the LSTG). In chapter 4, I presented a detailed overview of the methods used in these experiments. In chapters 5 and 6, I reported behavioural tDCS experiments with healthy young adults, the first one with the LIFG as target of stimulation, and the second one with the LSTG as target of stimulation. Baseline task load modulation of brain activation for healthy young adults, PWD and PWA were outlined in chapter 7. In chapters 8 and 9, I reported fMRI experiments with similar design as those in chapters 5 and 6, but whose aim was to investigate the neural correlates of tDCS stimulation. In chapters 10 and 11, I reported experiments where a similar version of the study reported in chapter 8 was performed respectively with PWD and PWA. In chapter 12, the general discussion of the thesis was presented.

CHAPTER 2:

A PANORAMA OF THE EFFECTIVENESS OF tDCS IN APHASIC ANOMIA UNDER A BRAIN-STATE-DEPENDENT STIMULATION PERSPECTIVE

2.1 INTRODUCTION

Transcranial direct current stimulation (tDCS) is a brain stimulation technique that modulates behavioural performance and that has been used extensively in research with humans (Jacobson et al., 2012; Nitsche et al., 2008). However, stimulation outcomes have been questioned due to inconsistent results, especially in cognition (Elsner et al., 2015; Horvath et al., 2015; Jacobson et al., 2012). This suggests that further research is required to understand the key principles in which tDCS has an effect. Protocols for tDCS only consider and control for tDCS polarity, stimulation and duration, but do not consider other sources of modulation for baseline brain activity in participants receiving tDCS stimulation. However, they may be too simplistic. Instead, the brain-state-dependent stimulation framework seeks to include all factors leading to relevant differences in baseline brain activity together with their interactions with brain stimulation (Crinion, 2016; de Aguiar et al., 2015; Hartwigsen, 2015; Miniussi et al., 2013; Nozari, Woodard, & Thompson-Schill, 2014; Sandars et al., 2016; Sergeeva et al., 2014; Silvanto et al., 2008). It could therefore be suggested that there is a wider appreciation of the factors that contribute to the modulation of baseline brain activity, which would likely increase the efficacy of tDCS for the treatment of aphasia. In this chapter I have provided a novel meta-analysis of studies that used tDCS for the treatment of aphasic anomia. I have assessed the effects of brain stimulation on behaviour attributed to the choice of the typical parameters of tDCS. In particular, I discussed the underlying interactions between brain-state factors and typical tDCS parameters that are likely to have occurred.

Aphasia is a neurological language disorder that impairs speech production and comprehension to various degrees. The main causes of aphasia are stroke, head injury, tumours and degenerative dementias (Damasio, 1992). Naming impairments are one of the most common

symptoms of aphasia (Budd et al., 2010) and have been explored at length in the literature. The present meta-analysis focused on noun naming impairments, the most frequently reported type of aphasic anomia, as a measurement of language performance over which transcranial direct current stimulation (tDCS) could have an effect. Research in aphasia has shown tDCS to be a catalyst for conventional speech and language therapy (Monti et al., 2013), assisting PWA to improve their impaired language abilities faster or more effectively (Sandars et al., 2016). However, since understanding of the effects of tDCS and reproducibility of the results are not yet satisfactory, further investigation is needed.

Two recent reviews of tDCS studies for the treatment of aphasic language disorders (de Aguiar et al., 2015 and Crinion, 2016) highlighted a number of factors that can modulate the baseline brain activity, or brain state, that should be observed for rehabilitation with tDCS on PWA to be successful. These include the behavioural profile of the disorder together with the profile of brain (mal)functioning that subserves performance. The current study discussed some of these aspects as potential underlying reasons for successes and failures of different typical tDCS protocols for the treatment of anomia. The discussion focused primarily on factors such as the type of naming impairment and expected atypical neural profile that underlies performance, the profile of post-stroke neuronal reorganisation, the population the participants receiving tDCS treatment belonged to, the relevance of the task for the area target of tDCS, the time of stimulation and the interaction of those with the typical tDCS parameters of polarity, brain hemisphere and site of stimulation. Following this discussion, the issue of tDCS for cognition will be approached within the brain-state-dependent stimulation framework. The most relevant findings in the literature on factors that modulate the baseline brain activity will be presented. These findings support my interpretation of the outcomes of the current meta-analysis and, ultimately, the claim that brain

state factors are worth considering when tDCS protocols for the treatment of aphasic anomia are designed.

2.1.1 tDCS in cognition and perspectives of a brain-state-dependent stimulation approach

The tDCS is regarded as a safe technique that changes the cortical excitability of the brain through a low current administered to the scalp (Poreisz et al., 2007). Changes are assumed to be polarity dependent, cortical excitability increases with anodal stimulation, while it decreases with cathodal stimulation (Nitsche & Paulus, 2000). On the behavioural side, anodal stimulation is expected to induce improvement in performance, whereas cathodal stimulation is expected to decrease performance. This outcome is usually observed for stimulation of the motor cortex, although this is not always the case in the cognitive domain, especially for language (Jacobson et al., 2012). Null or contradictory findings, such as improved performance induced by cathodal stimulation, are occasionally reported (see Monti et al., 2008 and Flöel et al., 2011 for examples in aphasia). Two recent meta-analyses, one whose samples of studies comprised healthy adults (Horvath et al., 2015), and another one whose samples comprised PWA (Elsner et al., 2015), suggest that tDCS has no effect on cognition at all. However, it is too hasty to conclude that tDCS has no effect when brain-state factors are disregarded. In Horvath et al. (2015), most of the studies were offline (i.e., brain stimulation precedes task administration), which may justify their null results. This is because the task-induced engagement of the target during stimulation is an important factor for tDCS to have an effect on behaviour (Miniussi et al., 2013; Nozari, Woodard, & Thompson-Schill, 2014). In Elsner et al. (2015), the criterion for target of stimulation used to group the studies was brain hemisphere. This criterion was probably too broad and therefore weakened effects that otherwise could have appeared with a more specific target (Sandars et al.,

2016), along with the consideration of the task administered and the particular deficit presented by the participants. Our understanding of the basic requirements for tDCS to have consistent (and successful) effects is still limited and should be further explored before definitive conclusions like Elsner et al. (2015)'s and Horvath et al. (2015)'s could be drawn.

The brain-state-dependent stimulation framework shows promise as a direction further research should be conducted to. Currently, the tDCS literature shows mixed (or inconsistent) findings that are a result of different exploratory protocols and methodological factors (see Nitsche et al., 2015; Price & Hamilton, 2015). Critically, the baseline brain activity (or brain state) undergoing stimulation has been shown to influence brain stimulation outcomes, but it is still widely overlooked in many brain stimulation studies (as remarked by Nitsche et al., 2015; Sergeeva et al., 2014; Silvanto et al., 2008). The brain-state-dependent stimulation framework suggests that the functional state of the target area before and during stimulation is sufficiently relevant to determine how performance will be modulated by brain stimulation (Sergeeva et al., 2014; Silvanto et al., 2008), which has already been observed for both healthy adults (e.g., Nozari, Woodard, & Thompson-Schill, 2014) and stroke survivors (e.g., Gharabaghi et al., 2014). For example, Nozari, Woodard and Thompson-Schill (2014) conducted a study with such approach using tDCS. They manipulated the relevance of the tasks used for the target and the timing of stimulation with regard to the presentation of the tasks to evaluate behavioural responses to cathodal tDCS. They found that behavioural responses to the stimulation was modulated by the interaction of task relevance to the target and timing of stimulation (see next section).

In the next section I present the main brain state factors explored to date that are relevant for my discussion on the effects of tDCS on the treatment of aphasic anomia.

2.1.1.1 Task load and time of stimulation

Task load for the target area and time of tDCS stimulation are factors that have been shown to have an effect on the baseline brain activity in cognitive tasks such as WN and working memory tasks (e.g., Crinion, 2016; de Aguiar et al., 2015; Fertonani et al., 2014; Friederici et al., 2013; Nozari, Woodard, & Thompson-Schill, 2014; Pope et al., 2015). It appears that for tDCS to have a demonstrable effect in the brain area being stimulated, the task administered must be relevant for that brain area and sufficiently demanding to induce full neuronal engagement (Crinion, 2016; Metuki et al., 2012; Miniussi et al., 2013; Pope et al., 2015). Additionally, more interpretable results arise when the target brain area is engaged in the task at the same time as tDCS stimulation is applied (Nozari, Woodard, & Thompson-Schill, 2014). Both these factors (i.e., relevance of the task for the target and timing of tDCS stimulation) were included in a study by Nozari, Woodard, and Thompson-Schill (2014), who conducted three experiments to test the effects of cathodal stimulation of the prefrontal cortex in the context of working memory tasks. The experimental conditions were stimulation during a relevant task for the target (Flanker task), stimulation during an irrelevant task (simple categorisation task) followed by a relevant task (Flanker task, the only task assessed in this condition) and stimulation during a relevant task (swapping names of familiar objects task) followed by an equally relevant task (Flanker task, the only task assessed in this condition). Crucially, the authors found that the inhibitory effect usually assumed for cathodal stimulation only arose when the target area was engaged in a relevant task during stimulation.

Results from studies that do consider the state of the brain during stimulation, such as the Nozari, Woodard and Thompson-Schill's (2014) study, may change how we interpret findings that have previously been considered paradoxical or null. For example, the period in time when tDCS stimulation is applied is a factor that could easily have influenced the meta-analysis of tDCS studies

in cognition conducted by Horvath et al. (2015). Most of the studies included are offline, that is to say, the time period for brain stimulation and the time period for task administration do not overlap. When focusing on the language section of their meta-analysis, all but three studies used (anodal) offline stimulation. However, there is evidence (such as Nozari, Woodard, & Thompson-Schill, 2014) to suggest that brain engagement during stimulation needs to be ensured in order for tDCS to have an interpretable result. This means that online stimulation (when the time periods for brain stimulation and task administration do overlap) is more likely to have an effect on behaviour. Therefore, the null results reported by Horvath et al. (2015) for language, which mostly comprised offline studies, may well be consistent with the brain-state-dependent stimulation concept. The only language sample of online studies also showed non-significant results, but this may have been due to the reduced statistical power of a sample that contained only three studies (Price & Hamilton, 2015). All the three studies of that particular sample demonstrated positive results of anodal stimulation in the expected direction, as checked by accessing the studies individually. In addition, one of them also showed a significant and considerable effect size of 0.73 in Horvath et al.'s (2015) meta-analysis. Although Horvath et al. (2015) did not fully account for possible brain-state-dependent factors, such as time of stimulation, they acknowledged in their conclusions that this might be an explanation for the non-significant results of tDCS stimulation that they found. In general, it would seem that to properly assess the strength of evidence, which has been uncertain, state-dependent factors need to be taken into account more systematically.

Pharmacological studies of tDCS also support the concept that engagement of the target area during brain stimulation is necessary for significant performance changes to be detectable (Fritsch et al., 2010; Nitsche et al., 2007). Fritsch et al. (2010), for example, applied direct current stimulation in mouse brain slices of motor cortex and demonstrated that long-term synaptic

potentiation (LTP) only occurred when current was coupled with ongoing low-frequency synaptic activation. This was detected by increased brain-derived neurotrophic factor (BDNF) secretion. This may be particularly important for ongoing research with ageing populations, for whom online stimulation may be the only viable intervention able to effectively induce cognitive changes (Fertonani et al., 2014). Given the fact that PWA are usually older adults, these findings may become especially relevant in the planning of rehabilitation studies with tDCS (de Aguiar et al., 2015).

2.1.1.2 Profile of post-stroke neuronal reorganisation in aphasia

The post-stroke profile of neuronal reorganisation is far from unique across individuals in aphasia (Dominguez et al., 2014; Saur et al., 2006; Torres et al., 2013). There are three basic models of aphasia recovery (Torres et al., 2013), and these ought to be considered when seeking a more effective use of brain stimulation tools. In the first model, perilesional areas can assume, to some degree, the role of the brain area damaged by the stroke. In the second model, the homologous language area in the (contralateral) right hemisphere satisfactorily assumes the language function impaired by the stroke in the left hemisphere. In the third model, the right homologous language area is maladaptive, working inefficiently per se or inhibiting the left perilesional area that would be able to assume the language function that has been impaired. Effective choices of, for example, polarity of tDCS stimulation, therefore, may depend on the model of recovery that fits a particular PWA. Anodal tDCS is expected to benefit the left perilesional area that is able to assume the language function (Dominguez et al., 2014), as well as the right homologous area with potential to perform satisfactorily (Flöel et al., 2011). Cathodal stimulation is expected to be beneficial to contain the maladaptive performance of the right homologous area (Dominguez et al., 2014).

2.1.1.3 Noun naming mapping in the brain and perspectives for tDCS rehabilitation of noun naming impairments

Noun naming is usually considered to involve two key language regions of the brain (Geschwind, 1965; Lichtheim, 1885): temporo-parietal regions associated with the phonological lexicon and semantic representations of the words and frontal areas, associated with the motor programming for speech. More recently, Ullman (2004) fitted this naming scheme in the memory system. In this approach, lexical storage corresponds to declarative memory, relying mostly on the temporal lobe, whereas lexical retrieval is a procedural memory process, and would rely on regions of the frontal and parietal lobes, basal-ganglia and cerebellum. Further, the dual-stream model for language processing (Hickok & Poeppel, 2004) posits that different language abilities are processed via two different white matter pathways, either a dorsal stream or a ventral stream (Hickok & Poeppel, 2004; Rauschecker, 2012; Saur et al., 2008). Findings from functional magnetic resonance imaging and diffusion tensor imaging suggest that the dorsal stream consists of a connection between the superior temporal lobe and premotor regions of the frontal lobe via the arcuate and the superior longitudinal fascicles (Kümmerer et al., 2013; Saur et al., 2008). This stream is thought to be responsible for sublexical processing, mapping phonological code into articulatory code (Hickok & Poeppel, 2004; Saur et al., 2008). The ventral stream, on the other hand, connects the middle temporal lobe to the ventrolateral prefrontal cortex (including BA areas 45 and 47) via the extreme capsule (Kümmerer et al., 2013; Saur et al., 2008). This pathway is considered to map sound into meaning, the highest level of language comprehension (Hickok & Poeppel, 2004; Saur et al., 2008). It should also be noted that word naming paradigms which invoke reading-related processes for orthographic decomposition will in addition involve the recruitment of a large subset of visual processing areas in the occipital, fusiform and parietal areas of the brain.

These areas are, themselves, considered to be organized into at least two visual processing streams (Goodale & Milner, 1992; Ungerleider & Mishkin, 1982), with the more inferior stream connecting to the dual language streams described above.

Noun naming impairments in aphasia are usually attributed to disorders of semantic representations or disorders of phonological processing and lexical access (van Hees et al., 2013). However, there is usually no unique lesion site ascribed to noun naming impairments, since this impairment is often a secondary effect of different aphasic syndromes (Alexander & Hillis, 2008). Some lesion studies, nonetheless, have localised regions associated with specific categories, such as people, animals and tools (Damasio et al., 2004), living and non-living objects and single and compound nouns (Henseler et al., 2014). Such results suggest that noun naming impairments may need to be evaluated; treatments predicated on simple categorisations may have the potential for more precise refinement.

According to Bikson et al. (2013), behavioural and neuronal modulation induced by direct current stimulation relies on the engagement of relevant neuronal populations for a given function (e.g. speech production) which in turn needs to be elicited by appropriate tasks (e.g. a naming task). Accurate functional targeting can only occur if tDCS is applied to a brain region that is being actively engaged in the function represented by the task. In the case of aphasia, the aim is to target a region that can potentially assume the damaged function, according to the profile of post-stroke neuronal reorganisation (Torres et al., 2013). It should be noted, however, that since cognitive functions are usually distributed across different regions of a neural network (Jacobson et al., 2012), accurate functional targeting might need to be guided by the neuronal engagement of different regions in sub-functions rather than in functions. This is the case for naming. The ability to name is a complex cognitive linguistic task and requires processing distributed over multiple

brain regions (Baldo et al., 2013; Henseler et al., 2014). Therefore, it is crucial to consider more detailed aspects of naming ability when assessing naming impairments to achieve a high level of accuracy in functional targeting when applying tDCS for rehabilitation. However, the rough assignment of lexico-semantic impairments to temporal regions, and phonological-to-articulatory impairments to frontal regions provides an approximate targeting template for consideration. Future improvements in tDCS focality can be expected to render the functional targeting required for effective stimulation more precise (Datta et al., 2009; Gulers et al., 2016).

2.1.2 The current study

To the best of my knowledge, there are no meta-analyses of tDCS studies in aphasia that discuss the results from a brain-state-dependent stimulation perspective. The two most recently published meta-analyses of tDCS studies in aphasia have analysed their data with a different focus from the present meta-analysis (Elsner et al., 2015; Shah-Basak et al., 2016). Elsner et al. (2015) prioritised a detailed statistical report of findings, but only superficially explained the potential reasons for tDCS (in)effectiveness. Shah-Basak et al. (2016) investigated the role of statistical design and stroke chronicity for TMS (transcranial magnetic stimulation) and tDCS outcomes, showing that overall brain stimulation had an effect across different statistical designs and for chronic and subacute aphasia. Their account is also rather statistical, but they acknowledge that a number of other factors beyond statistical design and chronicity may have had an effect and should be considered in further research.

I conducted this meta-analysis to assess the effectiveness of tDCS in the treatment of aphasic anomia under a brain-state-dependent stimulation perspective. I analysed studies according to the most typical tDCS parameters (and combinations) that the studies adopted in their protocols

(namely polarity, brain hemisphere and site of stimulation) and interpreted the outcomes by discussing the potential role that the main brain state factors explored in the literature to date had for the results. Whilst interpreting the results, I especially discussed the role that factors of task load, time of stimulation, the population participants receiving tDCS belonged to (as per age and aphasia), profile of post-stroke neuronal reorganisation and profile of the language deficit were expected to have on the baseline brain activity, or brain state, of the target of tDCS, as well as the expected outcomes of their interaction with typical tDCS parameters.

Studies that applied tDCS for the treatment of aphasic anomia were selected and grouped according to different protocols and ultimately analyses. The different combinations of the most typical tDCS parameters considered in this meta-analysis were called protocols, as well as so was the combination consisting of the parameter time of stimulation and time of task administration. Each protocol gave rise to a number of analyses depending on data available for different levels of each parameter involved. I predicted that the most significant results, if any, would arise rather from analyses that controlled for a larger number of parameters than from those that controlled for a smaller number. This was likely to be the case because when more parameters are controlled for, the likelihood that a particular selection of studies would meet the ideal setting for tDCS to have an effect was higher than when less parameters were controlled for. For example, if relaxed inclusion criteria were used such that studies that applied anodal tDCS to the left hemisphere were grouped together, studies that targeted a frontal area or that targeted a temporal area would be equally eligible and included. Consider, however, that this hypothetical pool of studies had only PWA whose brain injury was frontal, but with a functional perilesional area, and the profile of their naming deficit was frontal, i.e., with sound-to-articulation phonological deficits. Given this clinical picture, anodal tDCS on the frontal area would probably succeed in improving PWA's naming

performance, whilst anodal tDCS on the temporal area would not. With the relaxed inclusion criteria, both types of studies, i.e., with a frontal or a temporal target, would be included, but the studies with a temporal target would act as noise and weaken the effect of tDCS coming from the studies with a frontal target, for which tDCS was successful. The overall effect for the group would be smaller than for the "frontal" group alone, and might not be detected. On the other hand, with a more stringent inclusion criteria where site of stimulation was also controlled, it might be expected that the effect of tDCS would be detected in the "frontal" group, with a significant effect, whilst the "temporal" group would be expected to show a non-significant effect. In Elsner et al.'s (2015) meta-analysis of tDCS studies on the treatment of aphasia, for example, no significant effect sizes were observed for the sample of studies broadly classified according to the brain hemisphere of stimulation only, described as lesioned or non-lesioned. Sandars et al. (2016), similarly, found a non-significant trend suggesting that anodal stimulation is more effective on the left hemisphere of the brain, whereas cathodal stimulation is more effective on the right hemisphere. However, as Sandars et al. (2016) highlighted, such a broad approach for the target area is probably not good enough to detect consistent changes in behaviour.

Regarding underlying factors that modulate the baseline brain activity of the target area and were likely to have interacted with the typical parameters of tDCS, I found particularly relevant to discuss the effects of task load, time of stimulation and time of task administration, profile of post-stroke neuronal reorganisation and profile of the language deficit. In most cases, the discussion predominantly relied on inferences based on premises the brain-state-dependent stimulation framework set for each of those factors. The role of time of stimulation and time of task administration relied additionally on hard evidence drawn from the data, since studies included in the sample overtly reported this information in their papers.

I stressed that the specificity of the target area for the cognitive function of interest should be always carefully considered. The noun naming ability relies on both the anterior and posterior regions of language networks (Henseler et al., 2014; Ullman, 2004). Matching the commonly agreed function of such regions for noun naming, damage to the left frontal lobe would be expected to lead to naming difficulties with a phonological-to-articulation profile, or a deficit in word retrieval (Saur et al., 2008; Ullman, 2004), whereas brain damage in the left temporal lobe would more likely lead to semantic processing difficulties. Furthermore, the literature suggests that the mapping of object representations in the brain can be even more fine-grained to the level of subcategories of objects (Chan et al., 2011; Henseler et al., 2014; Hillis & Caramazza, 1991; Warrington & Shallice, 1984). Brain damage, hence, may lead to highly selective naming deficits (Damasio et al., 2004; Henseler et al., 2014; Jodzio et al., 2008). Therefore, investigation of naming deficits need to be more detailed in order to increase the potential of tDCS to be more successful for rehabilitation. However, description of the language deficit profiles in tDCS studies of aphasia is usually rather broad (de Aguiar et al., 2015), and this was the case in the sample of the current study. As I was limited by the information made available, I could only infer based on brain-state-dependent stimulation premises that protocols of anodal stimulation of the left frontal lobe and protocols of anodal stimulation of the left temporal lobe had the highest chance of inducing improvement in performance since these two brain areas are the main ones involved with the naming ability. Satisfactory outcomes for each protocol would depend, in addition, on a successful match between the language deficit (frontal versus temporal) and the brain area chosen for stimulation.

Having the target of tDCS engaged during the stimulation was also stressed as crucial, as research on the parameter of time of stimulation and time of task administration suggests (Fertonani

et al., 2014; Nozari, Woodard, & Thompson-Schill, 2014). Furthermore, stimulation that overlaps with task administration, as opposed to that that precedes it, could be the only type effective for older populations (Fertonani et al., 2014). Therefore, I hypothesised that a significant effect of stimulation on performance would only be observed within the group of studies where tDCS and a language task were simultaneously administered.

Specifically, in this meta-analysis I used a brain-state-dependent stimulation interpretation to try to find potential explanations for successful and unsuccessful outcomes of tDCS stimulation applied for the rehabilitation of aphasic anomia. This approach takes into consideration the interaction of tDCS parameters in the stimulation protocols and the state of the brain receiving stimulation. Under this perspective, it is assumed that tDCS can only have an effect on performance if appropriate parameters are controlled for. This should be reflected in meta-analyses that are performed to assess the efficacy of tDCS. That is, the grouping of studies for each category of analysis within a meta-analysis must have inclusion criteria sufficiently stringent to avoid the weakening of effects, as discussed above. When inclusion criteria are too relaxed, non-significant results should come as no surprise, such as in Elsner et al.'s (2015) meta-analysis. Therefore, my first step was to analyse the studies of my pool in subgroups corresponding to increasingly more stringent inclusion criteria with regard to the number and type of tDCS parameters included in the studies protocols. This was done to highlight the relevance of this methodological aspect of the inclusion criteria for meta-analyses. Subgroups with more stringent inclusion criteria were expected to have more significant results. However, although stringency of inclusion criteria is relevant, it is not sufficient by itself, since two subgroups with equally stringent inclusion criteria may well present differences in terms of significant results, as discussed above. This is because the tDCS parameters interact with aspects of the state of the brain receiving stimulation. My second

step, therefore, was to discuss and speculate on the aspects of the state of the brain that interacted with the tDCS parameters of the protocols analysed to justify successful and unsuccessful interventions with tDCS. Brain state factors such as task load, pattern of post-stroke neuronal recovery, profile of language deficit and time of stimulation (supported by the extra statistical analyses of subgroups which received online and offline stimulation) were considered.

2.2 METHODS

2.2.1 Search criteria

The Web of Science and Pubmed databases were searched on February 2016 for journal articles using the keywords "tDCS OR 'transcranial direct current stimulation' AND apha* AND naming". The search was constrained to studies published in English.

2.2.2 Inclusion criteria

To be selected for inclusion in the meta-analysis the following criteria were applied: participants manifested aphasia after a left hemisphere stroke, conventional (not high definition - HD) tDCS was used, stimulation was only applied to one hemisphere, real (anodal or cathodal) and sham stimulation conditions were administered, and mean, standard deviation and number of participants were provided or could be derived (from plots or tables) as a measurement of performance in noun naming (even if as a secondary measurement).

The latter criteria meant that single case studies were excluded because they did not provide the standard deviation measure necessary to calculate the standardised mean difference (SMD) for the within-study step of the meta-analysis. A standard deviation measure is also needed to calculate the random-effects weight by study based on the inverse of the study's variance (Borenstein et al.,

2009). Treating individual participant data equally, as if they originated from the same sample, is generally considered inadequate (Riley et al., 2010). Single case designs require special statistics to summarise within-study information (Manolov et al., 2014), and therefore would need to be separately considered. In addition to the statistical constraint, inclusion of single case studies in meta-analyses is not advisable due to their high potential for bias (Fitzpatrick-Lewis et al., 2009).

Those articles that survived these criteria underwent backward snowballing (i.e., search for additional articles from the reference list of the first sample of articles). As this meta-analysis was intended to be comprehensive, all available data that met the inclusion criteria were therefore included, thus avoiding "unnecessary and biased data reduction" (Nitsche et al., 2015, p. 667).

2.2.3. Analysis

I performed a two-stage individual participant data (IPD) meta-analysis with a random-effects model to estimate standardised mean differences (SMD) with 95% confidence intervals (CI). It should be noted that although the meta-analysis technique is labelled "individual participant data" it does not require that *all* individual participants' data be accessible, only that sufficient individual data can be accessed or calculated in order to create summary statistics (group mean and standard deviation) per experiment. As aforementioned, the requirement for a within-group measure of standard deviation therefore precludes the inclusion of single case studies in IPD analyses. IPD is regarded as being the gold standard of meta-analyses in comparison to older meta-analysis methodologies which sought to use only aggregated data (Thomas et al., 2014).

SMDs are a method to render the different measurements provided by the studies uniform and comparable and are therefore ideal for my somewhat variable sample. In the first stage, SMDs were generated from summary individual participant data by experiment. In the second stage these

SMDs were then aggregated into group analyses by experimental condition (tDCS stimulation type, site of stimulation, hemisphere of stimulation and online/offline stimulation). Some articles included more than one separate experiment (for example by tDCS condition or by site of stimulation). In these cases, experiment was used as the basic group unit from where the individual participant data originated. Statistical heterogeneity was evaluated through the Q statistic and I^2 index.

The group effect sizes were first calculated for the largest possible group of experiments, which included all the data points, aiming to compare real tDCS stimulation of any type to sham stimulation. I then performed analyses for subsamples of studies increasingly including or controlling for different types of tDCS parameters for real stimulation compared to sham: polarity of stimulation (cathodal or anodal), hemisphere of the brain stimulated (left or right) and site of stimulation (frontal or temporal lobe). Finally, effect sizes were calculated for experiments that used "online stimulation" (i.e., task and stimulation were simultaneously administered), or "offline stimulation" (i.e., stimulation was applied alone preceding the task). A possible parameter combination was only considered quorate for analysis if it included at least two data points.

Experiments included in the analysis compared one type of real stimulation (cathodal or anodal) to a sham control. Sham stimulation was never considered an experiment on its own. In studies which more than one real stimulation was administered for a given task, but sham stimulation was administered only once, the sham condition was repeatedly used as a control for all of the real stimulation conditions.

Some articles provided more than one measurement to test naming ability, including accuracy and reaction times, or even presented more than one naming test. In such cases, only the first measurement that matched the inclusion criteria was selected from the article. That is, the first

measurement of naming ability from which mean, standard deviation and number of participants for both real and respective sham stimulation could be calculated, in order to enable the calculation of the effect sizes. When deriving these measures from plots, I used a graph digitizer (Web Plot Digitizer, Rohatgi, 2016) to extract the values. Table 1 displays means, standard deviations and sample sizes by experiment, and indicates the tasks from which measurements were extracted.

Table 1. Measurements of performance in naming induced by tDCS and sham by experiment (mean raw score and standard deviation)

Experiment	Real stimulation		Sham		Task which provided the measurements
	Mean (SD)	N	Mean (SD)	N	
Baker 2010	17.80 (9.44)	10	15.60 (9.81)	10	noun PN
Campana 2015	55.55 (25.50)	20	43.60 (21.45)	20	noun PN
Fiori 2011	70.82 (9.92)	3	49.32 (12.46)	3	noun PN
Fiori 2013(1)	18.43 (6.13)	7	10.57 (5.44)	7	BADA - oral noun PN
Fiori 2013(2)	13.14 (5.98)	7	10.57 (5.44)	7	BADA - oral noun PN
Flöel 2011(1)	89.25 (15.32)	12	81.50 (26.96)	12	noun PN
Flöel 2011(2)	84.17 (27.93)	12	81.50 (26.96)	12	noun PN
Kang 2011	31.90 (21.86)	10	29.90 (19.76)	10	noun PN
Marangolo 2013(1)	20.29 (5.88)	7	16.29 (5.68)	7	BADA - oral noun PN
Marangolo 2013(2)	15.43 (5.71)	7	16.29 (5.68)	7	BADA - oral noun PN
Monti 2008(1)	11.83 (5.6)	6	12.88 (5.00)	6	noun PN
Monti 2008(2)	14.50 (4.14)	6	12.88 (5.00)	6	noun PN
Rosso 2014(1)	30 (12)	14	31 (13)	14	noun PN
Rosso 2014(2)	26 (12)	11	24 (13)	11	noun PN
Vestito 2014(1)	26.71 (8.44)	3	17.99 (6.94)	3	noun PN
Vestito 2014(2)	30.64 (5.02)	3	16.89 (9.57)	3	noun PN
Volpato 2013	85.63 (16.35)	8	86.88 (17.72)	8	noun PN
Wu 2015	30.8 (12.2)	12	19.50 (9.50)	12	PACA - reduced noun PN
You 2011(1)	9.57 (9.62)	7	6.43 (10.01)	7	K-WAB
You 2011(2)	13.57 (17.51)	7	6.43 (10.01)	7	K-WAB

PACA = Psycholinguistic Assessment in Chinese Aphasia. BADA = Battery for the analysis of aphasic disorders. K-WAB = Korean version of the Western Aphasia Battery. PN = picture naming.

Table 2 summarises the characteristics of the studies by design (within-subjects or between-subjects), age of participants, duration and intensity of stimulation per session, number of days of stimulation, time interval between real and sham conditions in within-subject studies and timing between tDCS stimulation and task (online or offline). Polarity of tDCS and site of stimulation were also reported. The correlation between the length of tDCS stimulation in days and the effect sizes of the experiments was also calculated.

Table 2. Studies characterisation

Study	N of PWA	Age mean (SD)	Design	Polarity	Location of stimulation	Online / offline	Task for online stimulation	Intensity / duration	Time interval (days)	Days of stimulation
Baker (2010)	10	65.50 (11.44)	WS	A	left middle, inferior and superior frontal gyri, precentral gyrus	online	noun PN	1mA/ 20min	7	5
Campana (2015)	20	57.10 (10.26)	WS	A	left inferior frontal gyrus (IFG)	online	ST	2mA/ 20min	14	10
Fiori (2011)	3	61.33 (14.84)	WS	A	Wernicke's area	online	noun PN	1mA/ 20min	6	5
Fiori (2013)	7	58.43 (9.50)	WS	A	Broca's and Wernicke's area	online	verb and noun PN	1mA/ 20min	6	5
Flöel (2011)	12	52.25 (8.75)	WS	A/C	right temporo-parietal	online	noun PN	1mA/ 20min	21	3

Kang (2011)	10	61.90 (8.65)	WS	C	right Broca's homologue area	online	K-BNT	2mA/ 20min	7	5
Marangolo (2013)	7	62.43 (9.59)	WS	A	Broca's and Wernicke's area	online	verb naming	1mA/ 20min	6	5
Monti (2008)	8	60.38 (11.99)	WS	A/C	Broca's area	offline	na	2mA/ 10min	7	1
Rosso (2014)	25	57 (18)	WS	C	right inferior frontal gyrus	offline	na	1mA/ 15min	0.083	1
Vestito (2014)	3	64.67 (2.52)	WS	A	Broca's area	online	noun PN	1.5mA/ 20min	0.0416	5
Volpato (2013)	8	58.63 (10.18)	WS	A	Broca's area	offline	na	2mA/ 20min	ni	10
Wu (2015)	12	43.2 (5.6)	WS	A	left posterior perisylvian region (PPR)	online	ST	1.2mA/ 20min	ni	5
You (2011)	21	66.57 (10.76)	BS	A/C	left superior temporal gyrus (A) and right superior temporal gyrus (C)	online	ST	2mA/ 30min	na	10

2.3 RESULTS

2.3.1 Characterisation of the studies included in the meta-analysis

The search in the databases returned 49 unique records, from which 13 articles matched the inclusion criteria (Figure 1). A backward snowballing procedure was utilised to search for further data. This provided no additional articles for the sample. The 13 selected publications (see Table 2) included 20 experiments that were meta-analysed.

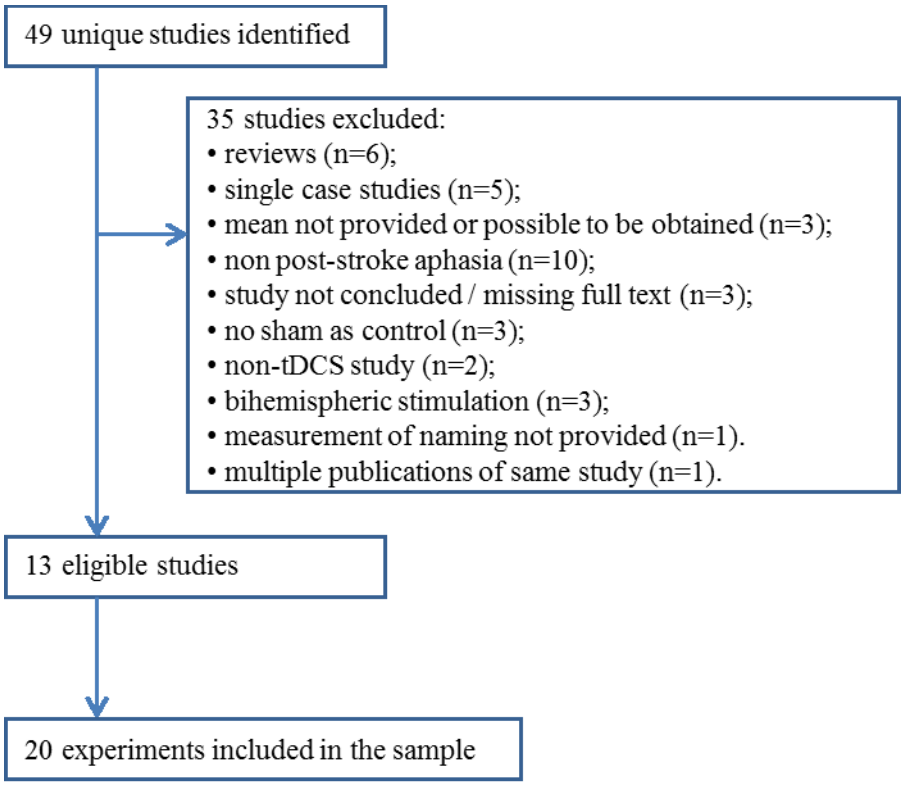

Figure 1. Selection of tDCS stimulation studies in aphasia. Unique studies identified by the literature search and selection process of studies included in the final sample.

Most of the publications (12) used a within-subjects design. The studies involved 146 participants in total, with a weighted mean age of 58.63 years (SD = 6.22). One hundred and thirteen participants had chronic aphasia, i.e., the time since onset of stroke was longer than 6

months (Elsner et al., 2015). Only those in You et al.'s (2011) and Wu et al.'s (2015) studies included participants with a time after stroke smaller than or equal to 6 months. There is insufficient evidence to expect results of brain stimulation in non-chronic aphasia to differ significantly from those in chronic aphasia (Elsner et al., 2015; Shah-Basak et al., 2016). The literature rather suggests that the prognosis of responsiveness to language therapy and brain stimulation is better predicted by factors beyond chronicity, such as level of education and aphasia severity (Laska et al., 2011; Seniow et al., 2013 with TMS). However, the number of tDCS studies in non-chronic aphasia is very limited and more data is needed before strong conclusions can be drawn. Therefore, data from participants with chronic aphasia and from participants with non-chronic aphasia were considered equally suitable to be part of the sample without a separate treatment in the analyses.

Ten studies applied tDCS during a language task (online stimulation). The tasks used during stimulation consisted of noun or verb naming exercises or conventional speech therapy. However, no specific information was provided concerning the relevance or difficulty of the tasks for the target areas. The number of sessions in which the stimulation or sham was applied ranged from one to ten consecutive days (mean = 5.38, SD = 3.01) among the studies. Nonetheless, no correlation between the duration in days and the effect size by experiment was found ($r = 0.14$, $p = 0.55$). Most of the studies with multiple sessions only provided a final measure of language performance and not session by session performance.

The interval between real stimulation and sham was also quite variable, ranging from one hour to 21 days (mean = 7.41 days, SD = 6.17). The mean duration of stimulation per session was 19.62 minutes (range = 10-30, SD = 4.31), and the mean intensity was 1.44 mA (range = 1-2, SD = 0.48). Table 2 summarises study characteristics, including information on the tDCS polarity used and the site of the brain targeted for stimulation.

2.3.2 Meta-analysis of experiments

The data arising from the 20 experiments in the sample allowed 15 analyses to be performed. I labelled "protocols" the different combinations of the typical tDCS parameters considered in the current study (namely tDCS polarity, brain hemisphere and site of stimulation). For example, tDCS polarity alone is a protocol and brain hemisphere with tDCS polarity regardless of site of stimulation is another protocol. I also called a "protocol" the combination comprising the parameter of time of stimulation and time of task administration. Each protocol gave rise to as many analyses as data available for the levels of each parameter involved allowed. For example, the protocol "tDCS polarity alone" gave rise to two analyses: anodal tDCS and cathodal tDCS. The protocol "time of stimulation and time of task administration" gave rise to two analyses: online stimulation and offline stimulation. The 15 different analyses I was able to perform are: real tDCS irrespective of polarity, anodal tDCS, cathodal tDCS, left hemisphere stimulation, right hemisphere stimulation, frontal lobe stimulation, temporal lobe stimulation, anodal tDCS on the left hemisphere, cathodal tDCS on the right hemisphere, anodal tDCS on the left frontal lobe, anodal tDCS on the left temporal lobe, cathodal tDCS on the right frontal lobe, cathodal tDCS on the right temporal lobe, online stimulation and offline stimulation. The experiments were grouped within each of these analyses as appropriate. Each type of protocol is reported in a separate subsection below together with the effect sizes, significances and confidence intervals of each analysis they gave rise to. No significant value of heterogeneity was observed for the Q statistic. The I^2 index amounted to 0% in all conditions.

2.3.2.1 Effect of real tDCS irrespective of polarity

All 20 experiments were included in an initial general analysis to contrast real stimulation of any polarity compared to sham stimulation. The outcome was significant but with a small effect size (SMD = 0.35, $p = 0.0015$), as depicted in Figure 2.

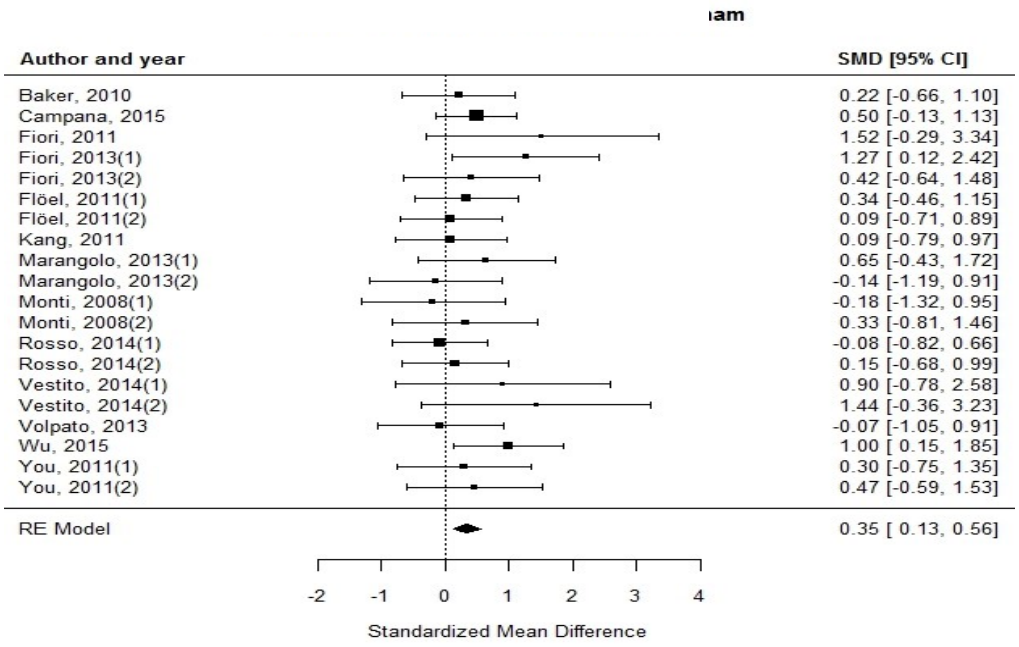

Figure. 2. Effect size of any tDCS stimulation condition vs sham stimulation. Forest plot of SMD and 95% CI for any real tDCS stimulation compared to sham stimulation.

2.3.2.2 Effect of tDCS polarity alone (anodal, cathodal)

Figure 3 (A and B) shows the impact of the parameter of tDCS polarity alone, summarising the effect sizes of studies applying anodal tDCS stimulation and studies applying cathodal tDCS stimulation compared to sham stimulation as a control condition. Only change in performance induced by anodal stimulation showed a significant result with a medium effect size (SMD = 0.47, $p < 0.001$).

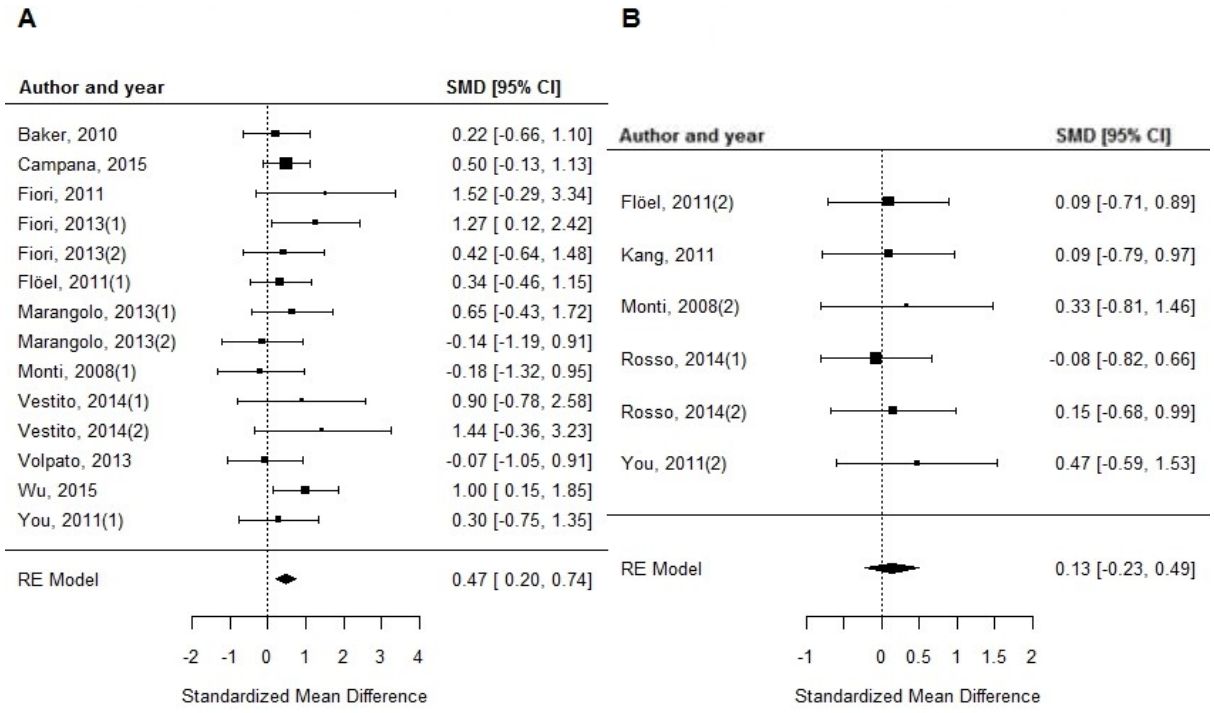

Figure 3. A. Effect size of anodal tDCS stimulation vs sham stimulation. B. Effect size of cathodal tDCS stimulation vs sham stimulation. Forest plot of SMD and 95% CI for anodal (A) and cathodal (B) tDCS stimulation compared to sham stimulation.

2.3.2.3 Effect of brain hemisphere alone (left, right)

I conducted the two possible analyses for this protocol. Real stimulation on the left hemisphere compared to sham stimulation yielded a significant result with a medium effect size (SMD = 0.48, $p < 0.001$), whereas real stimulation on the right hemisphere compared to sham stimulation showed non-significant results. Figure 4 gives an overview of both conditions of this protocol.

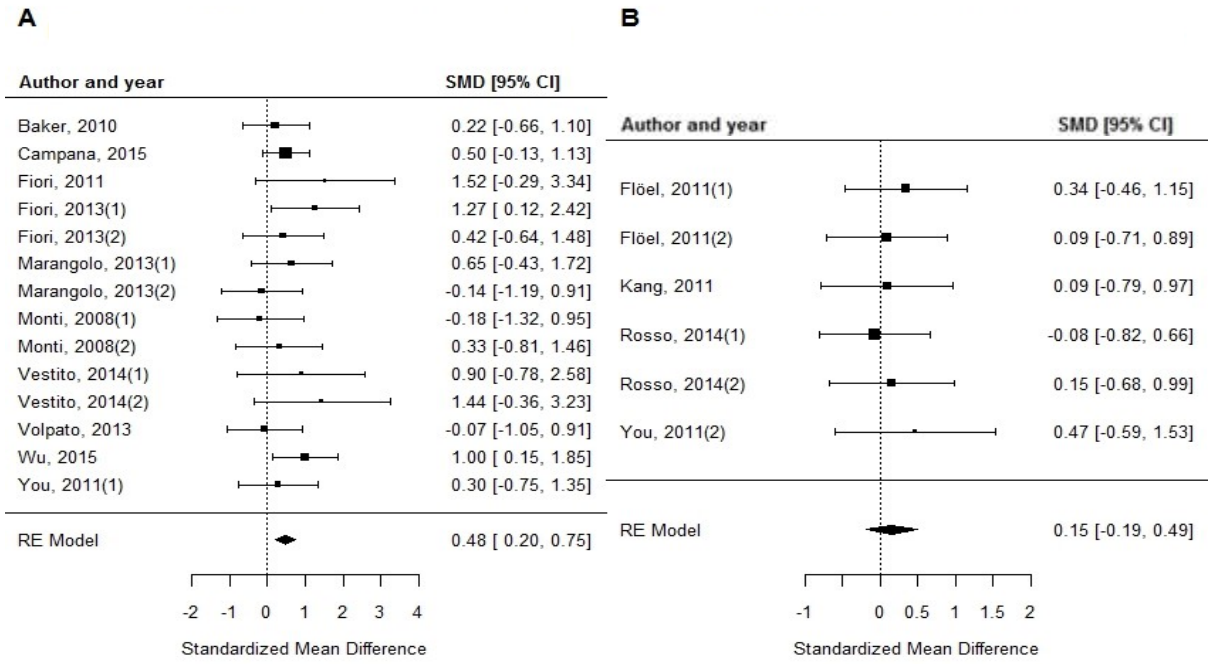

Figure 4. A. Effect size of tDCS stimulation on the left hemisphere vs sham stimulation. B. Effect size of tDCS stimulation on the right hemisphere vs sham stimulation. Forest plot of SMD and 95% CI for tDCS stimulation of any polarity on the left (A) and on the right (B) hemisphere compared to sham stimulation.

2.3.2.4 Effect of site of the brain alone (frontal lobe, temporal lobe)

For this protocol, two conditions were analysed: real tDCS stimulation over the frontal lobe (Figure 5A) and real tDCS stimulation over the temporal lobe (Figure 5B) compared to sham stimulation. Only the latter showed a significant result, with a medium effect size (SMD = 0.58, p = 0.0012).

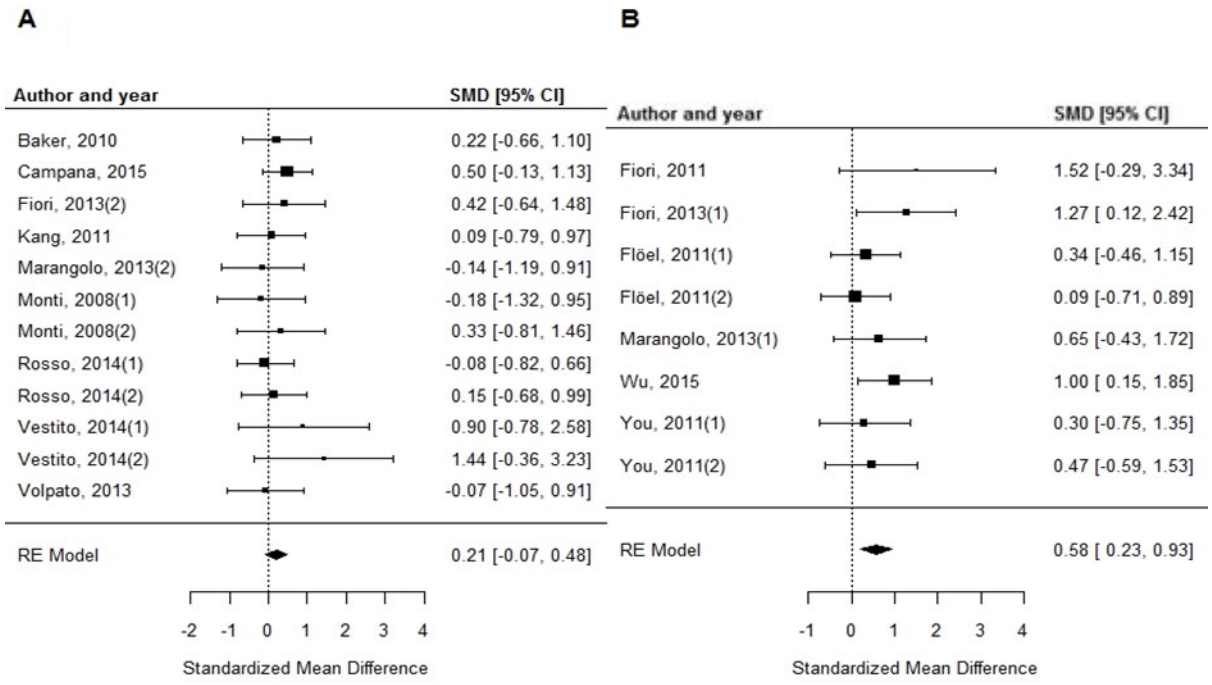

Figure 5. A. Effect size of tDCS stimulation on the frontal lobe vs sham stimulation. B. Effect size of tDCS stimulation on the temporal lobe vs sham stimulation. Forest plot of SMD and 95% CI for tDCS stimulation of any polarity on the frontal (A) and on the temporal (B) lobe compared to sham stimulation.

2.3.2.5 Effect of tDCS polarity and brain hemisphere (combinations of anodal and cathodal tDCS stimulation on the left and right hemispheres)

Four different configurations were identified in the sample for this protocol, but only two reached quorum for analysis: anodal tDCS stimulation on the left hemisphere (Figure 6A), with 13 experiments, and cathodal tDCS stimulation on the right hemisphere (Figure 6B), with five experiments. These correspond to the two main configurations of this protocol reported in the literature (Sandars et al., 2016). The combinations anodal tDCS stimulation on the right hemisphere and cathodal tDCS stimulation on the left hemisphere presented with one experiment each, and therefore were not analysed. Only the condition of anodal tDCS on the left hemisphere compared to sham yielded a significant result with a medium effect size (SMD = 0.49, $p < 0.001$).

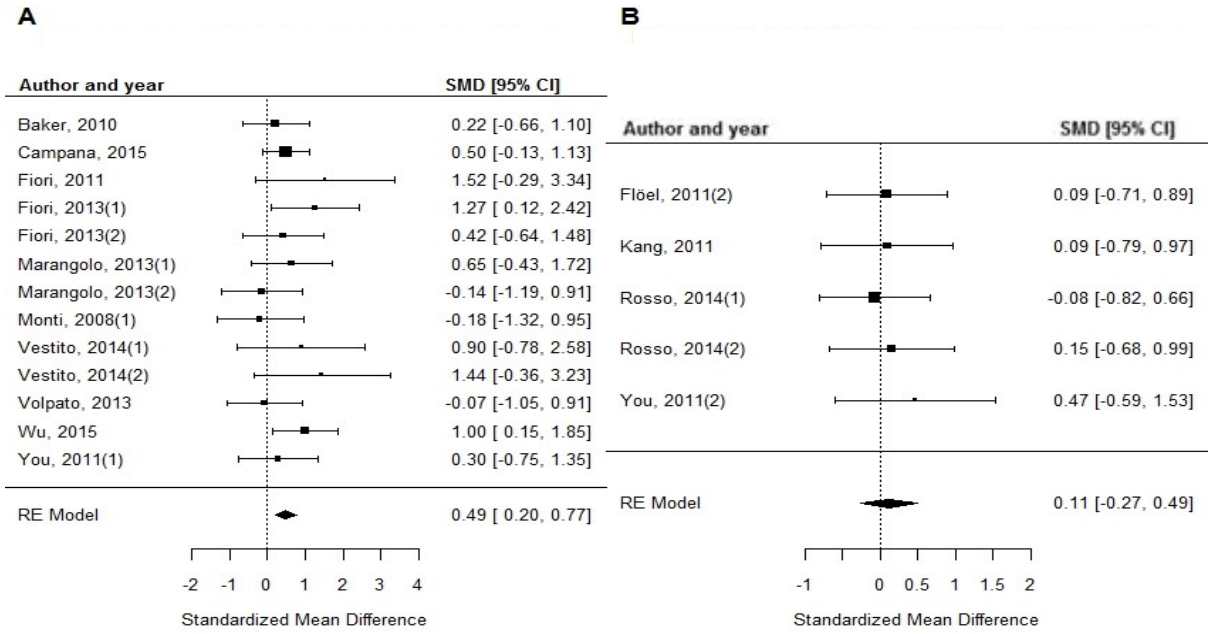

Figure 6. A. Effect size of anodal tDCS stimulation on the left hemisphere vs sham stimulation. B. Effect size of cathodal tDCS stimulation on the right hemisphere vs sham stimulation. Forest plot of SMD and 95% CI for anodal tDCS stimulation on the left hemisphere (A) and cathodal tDCS stimulation on the right hemisphere (B) compared to sham stimulation.

2.3.2.6 Effect of tDCS polarity, brain hemisphere and site of stimulation (combinations of anodal and cathodal tDCS on the frontal and temporal lobes of the left and right hemispheres)

Four different parameter combinations were identified in the sample for this protocol and analysed: anodal tDCS stimulation on the left frontal lobe (Figure 7A), anodal stimulation on the left temporal lobe (Figure 7B), cathodal tDCS stimulation on the right frontal lobe (Figure 7C) and cathodal stimulation on the right temporal lobe (Figure 7D) compared to sham. The parameter combinations of cathodal tDCS stimulation on the left frontal lobe and anodal tDCS stimulation on the right temporal lobe compared to sham, which also occurred in the sample, presented with a single experiment each, and therefore were not analysed. Only the configuration of anodal tDCS

stimulation on the left temporal lobe showed a significant and high effect size (SMD = 0.86, $p < 0.001$). This was the largest effect size among all the analyses performed in the current study.

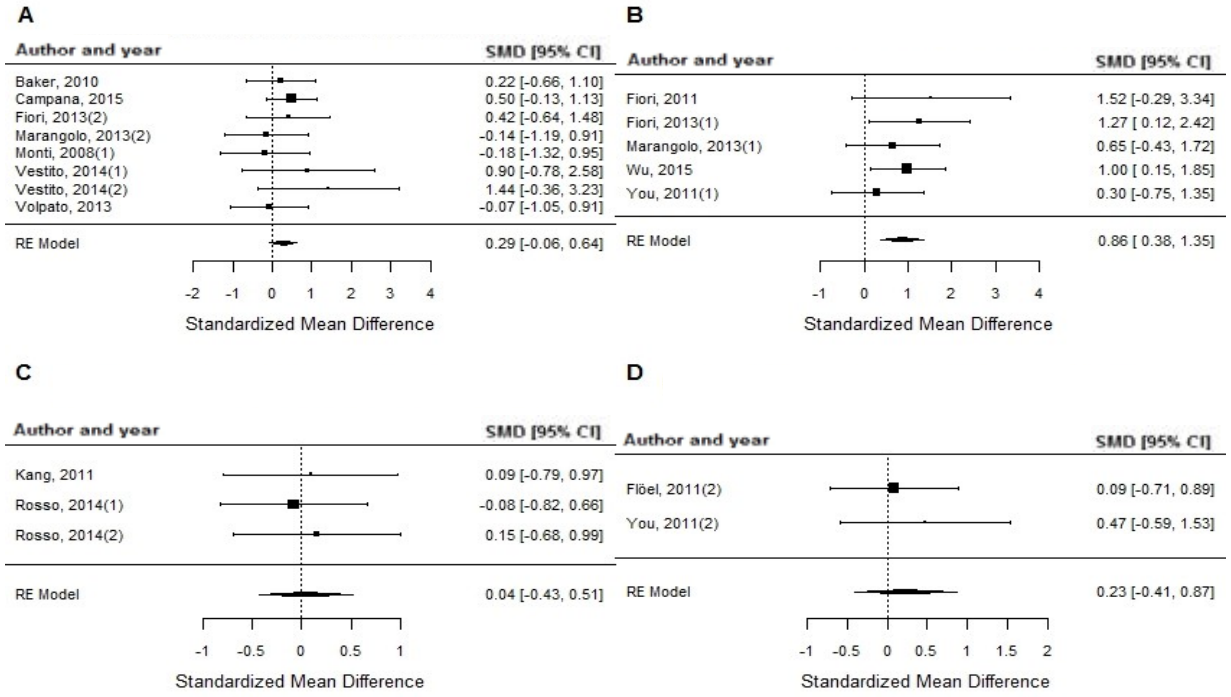

Figure 7. A. Effect size of anodal tDCS stimulation on the left frontal lobe vs sham stimulation. B. Effect size of anodal tDCS stimulation on the left temporal lobe vs sham stimulation. C. Effect size of cathodal tDCS stimulation on the right frontal lobe vs sham stimulation. D. Effect size of cathodal tDCS stimulation on the right temporal lobe vs sham stimulation. Forest plot of SMD and 95% CI for anodal tDCS stimulation on the left frontal lobe (A), anodal tDCS stimulation on the left temporal lobe (B), cathodal tDCS stimulation on the right frontal lobe (C) and cathodal tDCS stimulation on the right temporal lobe (D) compared to sham stimulation.

2.3.2.7 Effect of time of stimulation and task administration (online and offline stimulation)

Two analyses were conducted for this protocol, which aimed to investigate if performance under stimulation could be influenced by the time when tDCS stimulation was applied in relation to that of task administration. Figure 8A shows the effect size of change in performance under online stimulation compared to sham, and Figure 8B shows the outcome of offline stimulation

compared to sham stimulation. A significant result, with medium effect size, only arose for the subsample whose experiments used online stimulation (SMD = 0.47, $p < 0.001$).

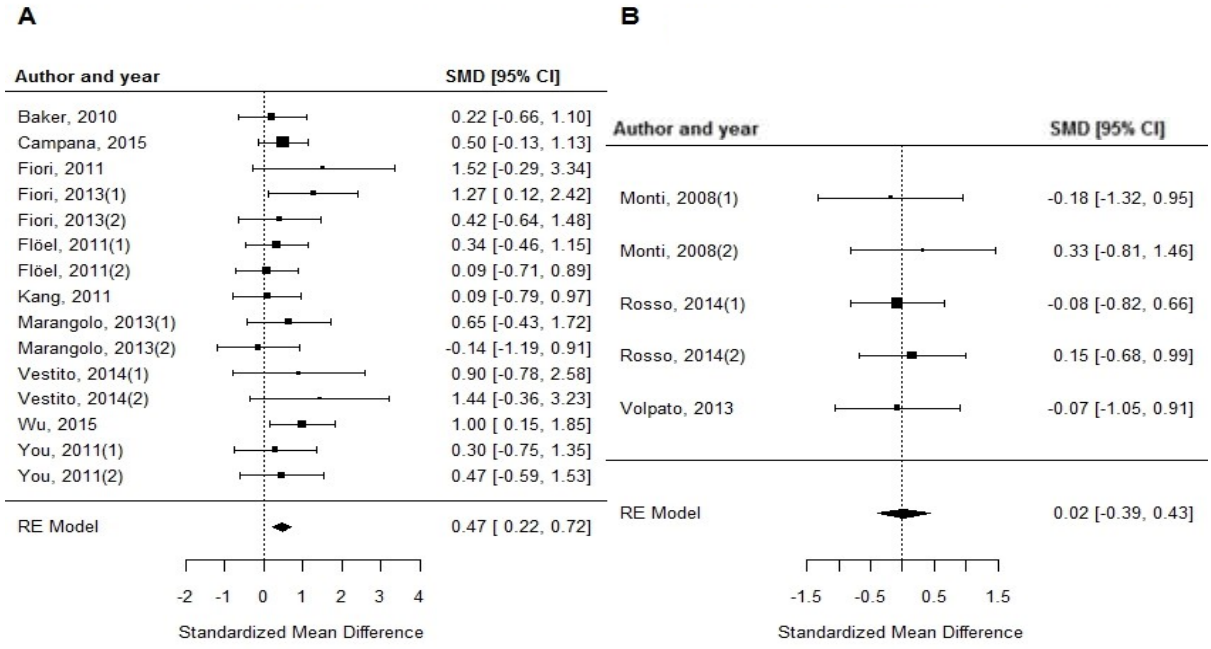

Figure 8. A. Effect size of online tDCS stimulation vs sham. B. Effect size of offline tDCS stimulation vs sham. Forest plot of SMD and 95% CI for online (A) and for offline (B) stimulation compared to sham stimulation.

2.4 DISCUSSION

I meta-analysed studies that applied tDCS for the treatment of aphasic anomia by grouping them according to the most typical tDCS parameters included in their protocols (polarity, brain hemisphere and site of stimulation), as well as their combinations. I called each of these parameter combinations a "protocol", within which as many analyses as data available for the different levels of each parameter allowed were performed. I also performed two analyses that consisted of the grouping of studies using online stimulation and studies using offline stimulation, under the protocol of timing of stimulation and task administration. In this section, I summarised the main

findings per protocol and suggested the underlying factors that modulate the baseline brain activity of participants receiving tDCS that potentially interacted with the typical tDCS parameters I investigated in this meta-analysis, this justifying the relevance that each of these typical parameters showed to have in successful tDCS protocols. The relevance of the target area for the cognitive function of interest (noun naming) and the level of engagement of this area during stimulation were of particular interest for my interpretation of the findings. Last, I discussed the high level of unexplained variability in tDCS studies and how this could potentially be accounted for by uncontrolled experimental and other factors that affect the state of the brain. These may have masked or reduced effects of tDCS in individual studies.

2.4.1 Overview of results

Overall, as predicted, the larger the number of parameters controlled for in the tDCS protocol, the higher the resulting effect size. Indeed, the largest significant effect size in the current study, produced by anodal stimulation of the left temporal lobe (SMD = 0.86, $p < 0.001$), is larger than effect sizes from analyses that controlled for fewer parameters. In line with this trend, the comparison of real tDCS stimulation of any polarity against sham stimulation, with none of the other parameters controlled for, demonstrated a much lower effect size (SMD = 0.35, $p = 0.0015$). This result for real tDCS stimulation against sham stimulation matches a result (SMD = 0.40, $p < 0.001$) that is reported in Shah-Basak et al. (2016). This was not considered of interest in their study as the objective of their particular meta-analysis of brain stimulation and aphasia was not to evaluate the role of tDCS parameters in the effectiveness of stimulation, but to investigate the effects of stroke chronicity and the statistical design of tDCS experiments. In their analysis, neither tDCS polarity, nor brain hemisphere nor site of the brain were controlled for, and most (seven) of

the experiments they included in their sample coincide with experiments included in the current meta-analysis. When comparing real tDCS stimulation against sham stimulation, both the current study and Shah-Basak et al.'s (2016) support tDCS having an effect on performance, although without being informative about the role that each of the typical tDCS parameters might have had.

The results from the analyses, broken down for different types of protocols (which controlled for an increasing number of typical tDCS parameters), therefore, strongly suggest that tDCS is sensitive to protocol differences or specificities. This may seem to be an obvious conclusion (Nitsche et al., 2015); however, consideration for this need in controlling for as many factors as possible in order to tDCS to have an effect on behaviour is often overlooked in the literature, leading to potentially inaccurate interpretation of results. Conclusions about the ineffectiveness of tDCS based on the analysis of broad protocols (which do not reasonably control for a number of parameters) should, therefore, be interpreted rather cautiously (Sandars et al., 2016), since the effects of tDCS in such conditions are likely to be considerably weaker than those yielded by protocols that control for more experimental factors. For example, Elsner et al. (2015)'s recent meta-analysis of tDCS studies in the treatment of aphasia concluded that tDCS has no effect on performance based on their analyses of protocols where only tDCS polarity and brain hemisphere were controlled for. Nonetheless, I am aware that statistical power might also have played a role in the results and is a confounder.

Elsner et al.'s (2015) results for the protocol consisting of the parameters of tDCS polarity and brain hemisphere were different from my own results for the same protocol, which showed a significant result, of medium effect size, for one of the possible analyses, that of anodal stimulation of the left hemisphere. However, the number of studies that Elsner et al. (2015) included in their analyses were remarkably small: half their samples had a single study, the other half had only three

studies. This is likely to have rendered their analyses underpowered (Price & Hamilton, 2015) to detect the small effects that this type of protocol has compared to protocols that also control for site of stimulation. In the current meta-analysis, the analysis that showed significant results (i.e. anodal stimulation of the left hemisphere) included 13 unique experiments. The analysis of cathodal stimulation of the right hemisphere did not show significant results, but it only included five unique experiments. Similarly, the remaining analyses where cathodal stimulation was involved, those where the right hemisphere was stimulated regardless of tDCS polarity, and the analyses of studies that applied offline stimulation, all produced non-significant results, but also all had sample sizes of 6 or less. This is a limitation of the current study and, therefore, my non-significant results based on samples that had less than the ideal minimum of six data points (Price & Hamilton, 2015) should be considered with caution, and so should those by Elsner et al.'s (2015).

Finally, I highlight another significant result in this meta-analysis, that with a subsample of studies that applied online stimulation. This analysis showed a medium effect size (SMD = 0.47, $p < 0.001$), whilst the comparable offline stimulation subsample did not show a significant result. This finding provides hard evidence for the claim that active brain engagement during stimulation is crucial for tDCS to have an effect on behaviour.

2.4.2 tDCS protocol parameters and their role on behavioural outcomes under the brain-state-dependent stimulation perspective

2.4.2.1 Brain hemisphere

In general, tDCS is likely to induce better performance in language functions when applied over the left hemisphere than when applied over the right hemisphere because of the high proportion of the population that exhibits left language dominance (Groen et al., 2012; Springer &

Deutsch, 1993). Although handedness is often chosen as a primary criterion to determine participants' language dominance, it was not chosen for this review, since it has been shown elsewhere not to be a highly accurate indicator of language lateralisation (Bishop, 2013; Mazoyer et al., 2014). Participants in the studies included in this meta-analysis were, instead, assumed to have their language function lateralised to the left hemisphere on the basis of their clinical picture of aphasia following a stroke in the left hemisphere. Despite this, tDCS stimulation of the left hemisphere may not always be the best option to ensure satisfactory results. As outlined earlier, Torres et al. (2013) elucidate three possible models of aphasia recovery that could apply to PWA.

Successful outcomes following stimulation of the damaged left hemisphere, for example, might only arise if sufficient perilesional cortex can assume the missing language functions (Dominguez et al., 2014; Fridriksson, 2010, 2011; Schlaug et al., 2011), or if severity of the language impairment, irrespective of lesion size, is only mild to moderate (Flöel et al., 2011). Otherwise, the right hemisphere may be preferably recruited (Schlaug et al., 2011). In this case, it should be possible to observe improved performance in language functioning when anodal stimulation is applied to the right hemisphere (Flöel et al., 2011) or, in a more commonly used protocol, when cathodal stimulation is applied to a malfunctioning left perilesional area (Monti et al., 2008; Shah-Basak et al., 2015). Results of the analyses for protocols where tDCS polarity and brain hemisphere were controlled for suggest that anodal stimulation has been successfully applied over well-functioning left perilesional regions (Fridriksson, 2010; Sandars et al., 2016; Ulm et al., 2015). The MRI-derived finite element models of tDCS stimulation for stroke by Wagner et al. (2007) suggest that stimulating a well-functioning perilesional area is possible even if the stimulation site and the lesion overlap, because the peak of current density moves towards the lesion borders. My analysis of anodal stimulation over the left hemisphere showed a significant

result of medium effect size (SMD = 0.49, $p < 0.001$). The complementary version of this analysis, where cathodal stimulation was applied to the right hemisphere (where the right language area was thought to be maladaptive) was also expected to show a significant result of similar effect size (Kang et al., 2011; Sandars et al., 2016; Turkeltalb, 2015). However, this protocol produced non-significant results (Flöel et al., 2011; Kang et al., 2011; Rosso et al., 2014; You et al., 2011). Otal et al. (2015) used three of the four studies included in my analysis. Their meta-analysis of cathodal stimulation of the right hemisphere attributed the unexpected result to the low number of participants, the small number of studies and the variable target site of stimulation. I further discuss the role of site of stimulation in the next subsection.

2.4.2.2 Site of stimulation

The most successful choices for site of stimulation are expected to be those that most closely match the features of the specific language impairment, which means that high accuracy in functional targeting needs to be reached (Bikson et al., 2013). The null result for stimulation of the frontal lobe in my sample may reflect a mismatch between the target region and the individual pattern of language deficits. Studies in my sample often reported that participants manifested aphasia following an extensive brain injury which affected both the anterior and the posterior portions of the language networks (e.g., Baker et al., 2010; Fiori et al., 2013; Flöel et al., 2011; Monti et al., 2008). Before tDCS rehabilitation was applied, detailed investigation of these language deficits would ideally have been undertaken to guide the choice of tDCS stimulation site, since the lesion location alone is sufficiently informative for tDCS targeting. However, studies in the literature that have applied tDCS for the rehabilitation of aphasia, such as those in my sample, did not routinely use the pattern of language deficits to guide parameter choices, perhaps because

the relevance of this for determining stimulation outcomes was not appreciated (Crinion, 2016; de Aguiar et al., 2015). I speculate that frontal areas may not be the ideal target for cases of naming impairment that arise from a semantic language deficit. Here, stimulation of the temporal lobe might have been more effective (Saur et al., 2008; Ullman, 2004). Further studies using voxel-based lesion-symptom mapping or related studies with healthy populations might be helpful to clarify the role of frontal and temporal regions in naming. They may help us to disentangle how the interaction between specific types of impairments and stimulation location could produce the results from my analysis of stimulation site.

2.4.2.3 tDCS polarity

It has been clearly noted that anodal stimulation induces the expected changes in performance more often than cathodal stimulation does in studies of cognition, particularly of language (see e.g. Jacobson et al., 2012). My results fall within this trend. Jacobson et al. (2012) conducted a meta-analysis of tDCS studies in the healthy population. They suggested that the null results observed for cathodal stimulation may reflect a neural strategy of compensation that the nodes of the targeted cognitive network implement to prevent a decay in performance. An alternative interpretation is that the inhibition induced by cathodal stimulation fully manifests, but can be beneficial when acting over a brain region that has an abnormally increased inhibitory function, resulting in performance improvement (Monti et al., 2008). Compensation is a known brain strategy to bypass endogenous deficits, such as the cognitive decline in healthy aging (Davis et al., 2008; Langenecker et al., 2004). Similarly, recent evidence in the literature shows that brain compensation may also happen in response to disturbance from exogenous sources, like tDCS cathodal stimulation (Fiori et al., 2014; Friederici et al., 2013; Nozari, Woodard, & Thompson-

Schill, 2014). Friederici et al. (2013), for example, observed that skilled adults drew on a less sophisticated associative learning strategy to overcome the inhibition induced by offline cathodal stimulation of the prefrontal cortex and keep performance unchanged in a lexical learning test. The compensatory strategy was revealed by the presence of a late positive event related potential. Likewise, when Nozari, Woodard and Thompson-Schill (2014) coupled online cathodal stimulation with a non-relevant task for the target area, performance on the subsequent relevant task was also unaffected. The decay in performance observed when cathodal stimulation and a relevant task are simultaneously administered (Fiori et al., 2014; Nozari, Woodard, & Thompson-Schill, 2014) also fits a compensation hypothesis. Such an outcome suggests that the demand imposed on the target area was too high and insufficient time was allowed to properly compensate for the downregulation.

2.4.2.4 Time of stimulation and time of task administration

The relevance of timing of stimulation relative to the time of task administration could be directly modelled in the current study with an objective measure of the effectiveness of online and offline protocols. The results confirmed a prediction that favoured online over offline protocols, especially for older populations, whether they are healthy (Fertonani et al., 2014) or presenting with aphasia (Volpato et al., 2013). This means that online protocols and engaging tasks are particularly important when planning rehabilitation studies for the treatment of aphasia, which affects mostly the elderly. The task presented during stimulation needs to be relevant to induce activity in the stimulated brain area in order to ensure full neuronal engagement (Nozari, Woodard, & Thompson-Schill, 2014). However, the information made available by the studies included in this meta-analysis was not enough to include task relevance as a factor in the analyses.

Nevertheless, the assumption that relevant tasks are important seems at least partly confirmed, since a significant effect of medium size was present for the subsample of online studies. This finding adds to the evidence that the timing of stimulation and task administration are critical to the outcome and potentially a consistent indicator of the brain state.

2.4.3 On the paradox of significant results in the meta-analysis and non-significant results in individual studies

The discrepancy between significant findings from meta-analyses and non-significant results in individual studies included within the meta-analysis is a common outcome that can be explained by two core factors: statistical power and variability in the individual studies (Borenstein et al., 2009). Meta-analyses can reach greater precision than individual studies because they are based on pooling more data (Borenstein et al., 2009); this could help explain the outcome of the current meta-analysis. The studies included, however, may have different variances because there are different sources of variability, for example variance in the experimental design protocol, in the individual pattern of language deficits and in the recovery profile of participants. In this case, the summary statistic from the meta-analysis could differ from the individual studies because it is not representative of any of them but rather constitutes a noisy and meaningless average. Random-effects meta-analysis, such as the one performed in the current study, is the standard strategy to overcome this issue, also weighting studies based on the inverse of the study's variance (Borenstein et al., 2009). This random-effects weighting makes the meta-analysis more robust to detect effects than the individual studies alone were unable to detect. Covariates can also be included in meta-analysis models to partial out known sources of variability when appropriate information is available (Borenstein et al., 2009; Riley et al., 2010).

The current study illustrates a discrepancy between significant results from the meta-analysis and non-significant individual results, as can be seen in Figures 2 through 8. On the one hand, this indicates that the statistical treatment of the data was sufficiently robust to unveil effects of tDCS, which are typically of small effect size. On the other hand, however, these results also show that for individual studies effects of tDCS may fail to be detected because of uncontrolled or unknown sources of variability. My hypotheses and interpretation of the findings aimed to bring into focus factors that potentially account for most of the uncontrolled variability. I discussed the role that the state of the brain has in modulating responses to tDCS, which appears to be much more important than factors such as small variations in tDCS montages (Bikson et al., 2013) or duration of the treatment alone, as the non-significant correlation between duration of treatment and effect sizes in the current study suggests. Recent findings in the literature show considerable promise in advancing our understanding of relevant aspects of the state of the brain (Bikson et al., 2013; de Aguiar et al., 2015; Nozari, Woodard, & Thompson-Schill, 2014). The level of neuronal engagement as a function of the relevance of the task administered, time of stimulation, as well as the profile of post-stroke neuronal reorganisation are highlighted in this particular study. Therefore, I recommend that future brain stimulation studies incorporate the factors known to affect the baseline brain activity, and therefore the outcomes of brain stimulation, when seeking to maximise the chance of producing significant behavioural changes.

2.4.4 Conclusion

Overall, the hard evidence provided by grouping selected studies according to typical parameters of tDCS protocols showed, as predicted, that the larger the number of parameters controlled for, the higher the chance of successful results of stimulation to arise, since it is higher

the chance of meeting tDCS ideal settings for stimulation to have an effect on behaviour. However, not all the combinations with the same number of parameters showed significant results, what is an important indicator that there is more than the typical tDCS parameters to be controlled for in order to tDCS to have an effect on behaviour. My discussion on the factors that can modulate the baseline brain activity and ultimately (re)define the effects of typical tDCS parameters on the outcomes of stimulation (Berryhill & Jones, 2012; de Aguiar et al., 2015; Li et al., 2015; Sandars et al., 2016) showed to be valuable in this regard. I discussed that factors such as the particular language deficit, profile of post-stroke neuronal reorganisation (i.e. which brain regions are recruited to replace damaged functions and how efficiently they perform) and population factors (e.g. age) may have played an important role in the results. I also highlighted that the parameter of time of stimulation and time of task administration seems crucial for successful results to arise, as confirmed by the hard evidence provided by the analysis of online studies and offline studies. The significant results that arose only for the subgroup of online studies supports the claim that active engagement of the brain during stimulation needs to be ensured especially for older adult populations (Fertonani et al., 2014).

Results of the current study suggest that one reason for the variety of non-reproducible findings of tDCS stimulation in cognition may be a failure to consider the state of the stimulated brain area, which is overlooked in most studies. In general, protocols for tDCS experiments should follow brain-state-dependent stimulation principles to be consistent since tDCS parameters and the state of the brain will interact to determine the outcomes of stimulation (Berryhill & Jones, 2012; de Aguiar et al., 2015; Li et al., 2015; Sandars et al., 2016). The findings advance this discussion and support tDCS as a promising tool for rehabilitation of PWA. My discussion aimed to offer novel and valuable insight to motivate further research planned under a brain-state-dependent

stimulation perspective, so that tDCS stimulation can produce more successful and comprehensible outcomes. The conclusions relate specifically to tDCS mechanisms in naming and aphasia, but they may have potential applications more generally to other cognitive functions.

CHAPTER 3:

BACKGROUND AND CURRENT RESEARCH: FRAMEWORKS FOR INTERPRETING tDCS EFFECTS

3.1 INTRODUCTION

In this chapter, the background information and the research interest are presented. In subsection 3.2, I discussed the conceptual frameworks for interpreting and predicting tDCS effects. In subsection 3.3, I presented the particular network and brain areas, language function and tasks that I focused on for the experiments reported in this thesis. For completeness, in subsection 3.4, I presented the expected fMRI signal change associated with each tDCS polarity and with cases of network compensation for the healthy brain and under brain disruption.

3.2 FRAMEWORKS FOR INTERPRETING TDCS EFFECTS

In this section, I first presented the two most conventionally used conceptual frameworks for predicting and interpreting tDCS outcomes, the dual polarity framework and the inhibitory framework. Then, I discussed their extension into a more comprehensive framework, the multi-node framework, which considers two factors thought to be crucial for tDCS outcomes, especially in the cognitive domain: the relevance of the task for the target of stimulation (task load) and the network structure of the brain supporting cognitive functions. These factors are taken into account when making predictions for the experiments conducted in this thesis.

3.2.1 The dual polarity framework

Many tDCS parameters such as electrode positioning, current intensity and current duration have been exhaustively explored elsewhere (DaSilva et al., 2011; Nitsche et al., 2008). However, of these factors none have been shown to be as important as polarity in predicting differential effects of tDCS stimulation on behaviour, i.e., a significant improvement or worsening in

behavioural performance. The dual polarity framework focuses primarily on tDCS polarity in order to make predictions on the direction of behavioural changes induced by tDCS.

Investigation of the effects of tDCS polarity on the cellular level in animals have demonstrated that anodal stimulation shifts the electrical potential of neurons towards depolarisation, whilst cathodal stimulation shifts the electrical potential of neurons towards hyperpolarisation (Bindman et al., 1964; Terzuolo & Bullock, 1956). Behaviourally, the assumption of anodal-excitation-improved performance and cathodal-inhibition-decreased performance has become well established, based primarily on studies in the motor domain (Jacobson et al., 2012; Lang et al., 2004; Nitsche & Paul, 2000). However, this behavioural assumption, as shown in the meta-analysis by Jacobson et al. (2012), is not always met. This is especially the case for studies in the domain of cognition and in particular for language (Jacobson et al., 2012). In the dual polarity framework, the target of stimulation is treated as a single locus that is essential for the task administered but in isolation from other brain areas. This model is likely to be inadequate for cognitive functions which are typically distributed over many brain areas (Jacobson et al., 2012).

3.2.2 The inhibitory framework

The effects of tDCS stimulation on the cellular level, known from research on excitatory neurons in animals (Bindman et al., 1964; Terzuolo & Bullock, 1956), are assumed to be equally valid when the neurons targeted by stimulation are inhibitory in nature. Anodal tDCS modulates neurons electrical potential towards neural depolarisation, whilst cathodal tDCS modulates neurons electrical potential towards neural hyperpolarisation. The expected physiological effect is therefore thought to be such that anodal stimulation causes an increase in cortical inhibition, whilst cathodal

stimulation causes a decrease in cortical inhibition instead. The effects on the behavioural performance in tasks where these neurons are found involved will depend on the role of inhibition to accomplish the task. Studies which use tDCS stimulation to target brain regions specifically involved in inhibition may be classified into two main explanatory mechanisms according to the focus given by researchers when seeking to explain the underlying processes governing inhibitory functioning.

The first mechanism relates inhibitory functions predominantly to the role of inhibitory synapses. Loftus et al. (2015), for example, demonstrated that healthy adults improved their performance in a Stroop task under anodal stimulation of the left DLPFC. One can understand this as an effect of an induced increase in inhibitory activity. Penolazzi et al. (2014), in turn, reported suppression of the retrieval-induced forgetting (RIF) phenomenon caused by cathodal tDCS stimulation of the right dorsolateral prefrontal cortex (DLPFC), assumed to be a result of an induced decrease in inhibition. On the other hand, in cases where pathological increased inhibition is observed, the downregulation induced by cathodal stimulation has been considered to be beneficial (e.g., Monti et al., 2008). Monti et al. (2008), for example, applied cathodal stimulation to the LIFG of participants with aphasia following a stroke. The authors demonstrated improvement in speech production of these participants, and interpreted it as the effect of reducing the increased cortical inhibition that is commonly observed in regions of brain damage.

The second mechanism considers inhibitory functions to be a careful balance between inhibitory and excitatory synapses (Jackson et al., 2015; Krause et al., 2013). In this case, there is a range of possible outcomes for tDCS stimulation, depending on where the imbalance is assumed to be and where tDCS exerts its effect - on the excitatory synapses or on the inhibitory synapses. For example, Weidacker et al. (2016) applied cathodal stimulation to the right DLPFC of

participants with the psychopathic trait of coldheartedness during a task of cognitive control. The authors observed improvement in performance, which they attributed to the effect of cathodal stimulation in reducing the excessive excitatory activity of the target area. Boggio et al. (2007), on the other hand, found anodal stimulation of the left DLPLFC to improve performance of participants with depression in a task of cognitive control. Here one could interpret this as anodal stimulation increasing the activity of inhibitory neurons.

The inhibitory framework takes into account features of the target area together with tDCS polarity in order to make predictions for the effects of tDCS stimulation. This gives it an explanatory advantage in comparison to the dual polarity framework. Crucially, however, predictions and interpretations within this framework are restricted to the investigation of tasks that depend on inhibitory functions. Finally, it should be noted that, just as in the dual polarity framework, the inhibitory framework still treats the target of stimulation as a single locus, essential for the task administered, but in isolation from other brain areas. As remarked in the preceding section, this approach is likely to be inadequate for cognitive functions, which are typically distributed amongst multiple brain areas (Jacobson et al., 2012).

3.2.3 The multi-node framework

As has been raised in the section on the inhibitory framework, there is evidence in the literature to suggest that there may be features of the target area being stimulated, for example the level of neuronal engagement during the task and age-related brain changes, that can interact with tDCS polarity leading to differential effects of stimulation on behavioural outcomes (Bikson et al., 2013; Fertonani et al., 2014; Hartwigsen, 2015; Jacobson et al., 2012; Miniussi et al., 2013; Sergeeva et al., 2014). In the multi-node framework I consider two such factors thought to be

informative where the two simple frameworks are unsatisfactory or insufficient to explain the findings. First, it has been noted in the tDCS literature that predictions based on current frameworks often fail for studies in the cognitive domain (see Jacobson et al., 2012 meta-analysis). Therefore, it is possible that the distributed neuronal network structure that typically underlies cognitive functions have a critical impact on the predictions (Hartwigsen, 2015; Jacobson et al., 2012; Pirulli et al., 2014). Second, the relevance of the task for the target of stimulation and how the network structure of cognitive functions may modulate this factor is likely to have an effect on tDCS outcomes.

The cortical excitability of the target of stimulation determines its susceptibility to respond to brain stimulation such as TMS or tDCS (Miniussi et al., 2013). Cortical excitability can be modulated in a state-dependent manner with the use of appropriate tasks, that will selectively change the level of activation of neuronal populations that respond to the particular task within the target (Bikson et al., 2013; Chiappini et al., 2018; Silvanto et al., 2008). With TMS stimulation, non-linearities between the susceptibility of neuronal populations to respond to stimulation and the level of activation of those neuronal populations can be observed (Silvanto & Cattaneo, 2017). For example, Silvanto et al. (2007) used an adaptation paradigm to modulate neuronal activity specific to some visual attributes, whose perception was altered by TMS. The authors showed that TMS had a selective effect on adapted neurons, i.e., the less active neuronal population, whose excitability was lower compared to non-adapted neurons within the same target. The effect of adaptation was removed by TMS, and perception of adapted attributes was facilitated. Conversely, Cattaneo et al. (2010) used a priming paradigm to pre-condition the processing of letters, which was altered by TMS. The authors showed that TMS had a selective effect on the primed neurons, i.e., on the most active neuronal population, whose excitability was higher compared to non-primed

neurons. The priming effect, where reaction times were smaller for stimuli congruent with the prime, was abolished by TMS. For tDCS stimulation, on the other hand, the relationship between excitability and activation level is assumed to be linear, i.e., tasks administered during stimulation should increase the activation level of the target neuronal population and therefore its excitability, and tDCS is only expected to have an effect on neuronal populations whose excitability is high (Bikson et al., 2013; Fritsch et al., 2010; Miniussi et al., 2013). The tasks chosen for the experiments of this thesis (CP, LD and WN) were assumed to increase the activation level, and therefore the excitability, of the target of tDCS (LIFG or LSTG) to different extents, what should modulate the strength of the response (refer to section 3.2.3.2 for a discussion on functional targeting).

3.2.3.1 Neuronal networks of cognitive functions as investigated by brain stimulation

Cognitive functions are typically supported by neuronal networks of brain areas rather than by single brain areas. Non-invasive brain stimulation has allowed the functional connectivity within cognitive networks to be explored (Bestmann et al., 2008; Hampson & Hoffman, 2010; Hartwigsen, 2015; Pascual-Leone et al., 2000; Stewart et al., 2001). Of particular interest, the study of induced transient cortical downregulation has indicated the adaptive strategies that the brain uses to minimise the effect of the disruption on performance. Compensation by non-targeted brain areas seems to be an accepted mechanism (Bestmann et al., 2008; Hartwigsen et al., 2012; Hartwigsen et al., 2013; Hartwigsen et al., 2016; Pirulli et al., 2014). For example, Hartwigsen et al. (2013) used TMS to downregulate the LIFG before participants performed a speech production task during fMRI. Increased activation of the homologous region in the right hemisphere was observed, suggesting that some degree of contralateral hemispheric compensation took place. It may be

concluded from these findings that compensation could prevent the expected worsening in performance following downregulation from happening. Therefore, as highlighted by Jacobson et al. (2012), the network structure of cognitive functions may be an important aspect to take into account when predicting effects of (cathodal) tDCS for cognitive functions.

3.2.3.2 Relevance of the task and functional targeting

This section focuses on one of the factors that have been shown to interact with tDCS polarity, modulating the effect of the direct current on behaviour and sometimes even reversing predictions based on the dual polarity framework: the relevance of the task for the brain area target of stimulation (task load or specificity of the task to the target). An improved understanding of these mechanisms may help improve predicting the effects of tDCS on behaviour.

Non-invasive brain stimulation has been shown to have a selective effect on neural populations of the target according to their level of neural activity (Bikson et al., 2013; Fritsch et al., 2010; Miniussi et al., 2013; Silvanto et al., 2007; Silvanto et al., 2008). The level of neural activity within the target of brain stimulation is thought to be a function of a combination of factors, such as the specificity of the task to the target neuronal population, task demands, anatomical and physiological states of the brain area and the brain stimulation itself (Miniussi et al., 2013). For tDCS stimulation in particular, the contribution of task characteristics may be crucial (Miniussi et al., 2013). Different from TMS, which can cause neuron depolarisation on the target with high spatial and functional resolution (Silvanto et al., 2008), tDCS is a modulator of the resting membrane potential with low focality that can only induce depolarisation on neurons that are near to the threshold for firing (Miniussi et al., 2013). Tasks that induce high level of neural activity are therefore more likely to cause responses to tDCS to arise than tasks that induce low or no level of

neural activity in the target. Neurons not involved with the task are less likely to fire (Miniussi et al., 2013).

The effect of task load on tDCS-modulated behavioural outcomes has been recently discussed in the tDCS literature under the concept of functional targeting (Bikson et al., 2013). Functional targeting can be understood here as the goodness of fit between the choice of the target brain area being stimulated and its specificity for the task administered (Bikson et al., 2013). At the cellular level, it may be that tDCS has a preferential effect on neuronal populations in a state of ongoing task-induced neural activity, rather than on inactive neurons (Bikson et al., 2013; Fritsch et al., 2010). As the authors (Bikson et al., 2013) remark, active and inactive neuronal populations may be found in the same brain area. Therefore, more specifically, functional targeting refers to the idea of using an appropriate task to induce some proportion of the neuronal population to reach a level of activation needed for tDCS to have an effect. One can assume that different tasks may vary on the amount of neural activation that they are able to induce, which should then be reflected in the magnitude of the effect of tDCS (Hussey et al., 2015; Nozari, Woodard, & Thompson-Schill, 2014; Pope et al., 2015). Note that the authors (Bikson et al., 2013) stress that functional targeting is different from anatomical targeting, because in the latter the choice of site of stimulation is based on the brain structure without consideration of the nuances of functional specificity.

The goodness of fit between task and the targeted neuronal population is expected to be lower for cognitive functions supported by spatially distributed neuronal networks (e.g., language) than for other functions supported by more localised areas of the brain (e.g., motor). In other words, the functional targeting when neuronal networks are involved will likely therefore not be as good a fit as for a single brain area (i.e. efficiency). Targeting efficiency is assumed to be a function of the relevance of the node targeted for the function of interest. For example, it is generally agreed

that CP relies on both the LIFG and (bilateral) STG (Lee et al., 2012; Liebenthal et al., 2013; Watkins & Paus, 2004), but more strongly on the latter, as inferred from observed stronger neural activation (Lee et al., 2012; Liebenthal et al., 2013). The functional targeting, in this case, is therefore considered more efficient if the site chosen for stimulation were to be the STG rather than the LIFG.

3.2.3.3 Timing of stimulation

For completeness, it should also be stated that the timing of stimulation has also been observed to play an important role in the resulting degree of neural activity that tDCS brain stimulation can induce, and therefore, on the corresponding magnitude of behavioural effects. Online stimulation, where time of current delivery and time of task administration overlap, has been shown to be more effective than offline stimulation, where time of current delivery and time of task administration do not overlap (Fertonani et al., 2014; Fritsch et al., 2010). In elderly populations, for example, findings in the literature suggest that online stimulation might be the only temporal modality able to induce brain modulation (Fertonani et al., 2014). This is probably due to the age-related lower level of neuronal excitability and consequent lower propensity of neurons to fire, as cellular studies of ageing in animal brains indicate (Rogers et al., 1981; Turner & Deupree, 1991). Furthermore, the timing of stimulation has also been observed to interact with other task parameters. For example, Nozari, Woodard and Thompson-Schill (2014) showed that performance on working memory tasks was modulated by the interaction of the mode of stimulation (online or offline) and the task load (high or low) to the target brain area. In the next section I elaborate on the potential mechanisms that explain the impact of task load and timing of stimulation on tDCS effects, taking into account the typical underlying neural network structure of cognitive functions.

3.2.3.4 Network compensation

Less efficient functional targeting in cognition potentially explains some of the unexpected results of tDCS stimulation (Friederici et al., 2013; Jacobson et al., 2012; Pirulli et al., 2014) that arise when predictions for cognitive tasks are based on the ideal functional targeting more often achieved in the motor domain. At least two aspects of a less efficient functional targeting might be driving the differences in tDCS effects observed between motor and cognitive domains. First, less neural activity is induced when the functional targeting is less efficient, leading to a lower magnitude of the effect of tDCS in cognition. Second, if a node that is not crucially relevant for the function is downregulated, it may be that the other nodes in the network upregulate to compensate for it in order to maintain overall performance levels. However, if a node that is crucial for the function is downregulated with online stimulation, compensation might be expected to fail (although some degree of self-node compensation could occur if the mode of stimulation were offline). Some findings in the literature (Nozari, Woodard, & Thompson-Schill, 2014; Pope et al., 2015) allow a range of inferences based on different combinations of functional targeting and timing of stimulation to be made for the effects of cathodal and anodal tDCS for neural networks.

The experiments conducted by Nozari, Woodard and Thompson-Schill (2014) are informative in inferring the effects of cathodal tDCS in neuronal networks. Their work studied cathodal stimulation of the pre-frontal cortex whilst manipulating mode of stimulation (online or offline) and cognitive load (high or low) of the stimuli via different task choices. Their findings allow a constrained set of behavioural effects to be predicted, as well as underlying mechanisms to be inferred. The results of Nozari, Woodard and Thompson-Schill (2014) suggest that cathodal stimulation decreased behavioural performance when applied to a target brain area (network node) whose relevance for the task was high, using online stimulation. When the relevance of the target

area or network node for the task was low instead, cathodal stimulation did not alter behavioural performance. In contrast, when the relevance of the target brain area was high for the task, but the mode of stimulation was offline, decrease in performance was not observed.

The concept of functional targeting and of neural network compensation (Bestmann et al., 2008; Hartwigsen et al., 2016; Jacobson et al., 2012) enables an interpretation of Nozari, Woodard, and Thompson-Schill's (2014) behavioural findings. They result from a predictable pattern of effects of cathodal stimulation. If we consider that different nodes in a cognitive network may have different weightings according to their relative contribution in fulfilling the task being administered, then it may be that these weightings can change for compensatory purposes (Hartwigsen et al., 2012; Hartwigsen et al., 2016). In such a multi-node framework, online cathodal stimulation of a particular network node may produce different behavioural outcomes depending on the relevance of the node targeted by stimulation for the task at hand. Considering the relevance of a targeted node in a range from high to low, the efficiency of compensation by the other nodes of the network and the corresponding behavioural effects may vary in the following way. Compensation might fail and consequently a worsening in performance is observed. Or, the level of compensation might be only enough to partially cancel out the decrease in performance that downregulation normally induces, resulting in some worsening of performance, but not as much as if there were no compensation. Or, the level of compensation could be sufficient to produce an apparent null behavioural effect of stimulation. Finally, compensation might be sufficient as to cause the performance to actually increase. With cognitive tasks, cathodal tDCS stimulation may therefore not always result in a decrease in performance as assumed by the dual-polarity framework (Jacobson et al., 2012). Such differential compensations have the potential to explain those findings

in the cathodal tDCS literature in cognition where an increase in performance was observed, often referred to as paradoxical (Jacobson et al., 2012).

Anodal stimulation has been more consistently reported to meet the predictions of the dual-polarity framework (Jacobson et al., 2012) - an increase in performance in response to stimulation. However, some unexpected results can also be found in the literature, such as null results (Fertonani et al., 2014; Jacobson et al., 2012) or an age difference for the effect of offline stimulation (Fertonani et al., 2014). These deviations from the typical improvement in behavioural performance potentially may reflect lower levels of neural activity, for example caused by a lower propensity of neuron firing in the elderly population (e.g. Fertonani et al., 2014) or by insufficient task-induced neural activity (e.g., Hussey et al., 2015; Pope et al., 2015). In the multi-node framework, anodal tDCS stimulation in a cognitive task will therefore most likely either produce an improvement in performance or a null behavioural result, depending on the level of neuronal engagement of the target brain area. Indeed, if neuronal engagement of the target area is not ensured by an appropriate experimental task, anodal tDCS stimulation may not have a facilitatory effect on behaviour. On the other hand, if sufficient neuronal engagement is ensured, stimulation is expected to increase performance with the magnitude of the effect directly dependent on the relevance of the targeted brain area to the task. It should be noted that if the relevance of the targeted area is low for the task of interest, the improvement caused by anodal tDCS stimulation may appear to be a null behavioural result, depending on statistical power. Compensatory strategies seem to be a less plausible underlying mechanism for anodal stimulation. One could speculate, for example, that the upregulation of a particular node that is relevant for the task of interest could be compensated, to some extent, by downregulation of the less relevant nodes involved in that task. However, if this were the case, the effects should cancel out and no improvement should arise. To the best of my

knowledge, network compensation strategies underlying anodal tDCS stimulation effects on performance in cognitive tasks have not yet been explored in such detail.

3.3 TARGET NETWORK AND TASK SELECTION FOR THE EXPERIMENTS

The language domain is known to rely on networks of functionally connected regions, which has been particularly explored in language perception and language production (Goodale & Milner, 1992; Hickok & Poeppel, 2004; Kümmerer et al., 2013; Okada & Hickok, 2006b; Saur et al., 2008; Ungerleider & Mishkin, 1982). Language perception and language production were therefore considered to be prototypical cognitive functions where the presence of an underlying network structure was concerned, enabling the investigation of functional targeting and effects of tDCS in a relatively well-known network. To accomplish this aim, the tasks used in all experiments reported in this thesis were selected as representative of a range from speech perception to speech production: CP, LD and WN.

Also important for the task selection was the fact that phonological processing is present from speech perception to speech production. Phonological processing takes part in the categorisation of acoustic information into linguistic sound units in speech perception, orthographic to sound conversion in reading and encoding of abstract language representations of sounds into acoustic representations in speech production (Burton, 2001). In language disorders such as dyslexia and aphasia, this wide-ranging presence of phonological processing is once more corroborated in findings that suggest that a phonological deficit is always involved (Georgiewa, 1999; Ramus, 2004; van Hees et al., 2013). Therefore, a single network thought to subserve phonological processing across the whole range from speech perception to speech production has

been selected as the target of investigation for this thesis. This network comprised the LIFG, LSTG, RIFG and RSTG.

The LIFG and the LSTG are the typical endpoints of the so-called dorsal stream of phonological processing (Liebenthal et al., 2013; Saur, 2008). This stream corresponds to the sound to articulation representation and is associated with language tasks that do not demand comprehension, such as the processing of words and nonwords (Saur, 2008) and categorical perception of speech (Liebenthal et al., 2013), tasks used in this thesis. Neuroimaging studies have demonstrated that the LIFG and the LSTG are typically activated in tasks that involve phonological processing (Amunts et al., 1999; Burton, 2001; Cornelissen et al., 2009; Indefrey, 2011; Lee et al., 2012; Liakakis et al., 2011; Okada & Hickok, 2006a, 2006b; Rogers et al., 2014; Smalle et al., 2015; Watkins & Paus, 2004; Wheat et al., 2010; Woodhead at al., 2014), and behavioural findings in aphasia and dyslexia seem to support these findings. It has been noticed that some degree of phonological deficit is observed both in language disorders more associated to frontal impairments, such as in frontal aphasia (Blumstein et al., 1977; Braber et al., 2005; Moineau et al., 2005), and in language disorders more associated with posterior impairments, such as in dyslexia (Brunswick et al., 1999; Costanzo et al., 2016a, 2016b; Hoeft et al., 2006).

There is, however, some debate in the speech perception literature questioning the role of the LSTG. On one hand, some studies in speech perception suggest that the LSTG offers no contribution for phonological processing or that the left supramarginal gyrus (LSMG) and the left angular gyrus (LAG) should be considered instead (Blumstein et al., 2005; Dehaene-Lambertz et al., 2005; Turkeltaub & Coslett, 2010). Findings of other studies, on the other hand, do indicate that the LSTG has a role in phonological processing (Altmann et al., 2014; Joanisse et al., 2007; Turkeltaub & Coslett, 2010). It has been suggested that the LSTG activity is sensitive to the level

of active participation in the task of speech perception (Altmann et al., 2014; Nath & Beauchamp, 2012), which could justify the findings in the literature where it did not appeared activated. Furthermore, the LSMG and the LAG have not been consistently found activated in the literature for phonological processing (Turkeltaub & Coslett, 2010). It has been suggested that these two regions might serve a role as mediators to connect the articulatory representation with the perceptual representation in the dorsal stream (Gow, 2012; Rauschecker & Scott, 2009; Turkeltaub & Coslett, 2010). The LSTG has been therefore considered to be involved in phonological processing and ultimately was selected to integrate the target network for the studies of this thesis.

The target network thus comprised the two typical language nodes of the dorsal stream on the left hemisphere (Liebenthal et al., 2013; Saur, 2008), but their right homologues, the RIFG and the RSTG, were also included Right homologues were included because evidence in the literature has found that the right hemisphere performed functions that were originally performed by the left hemisphere to compensate for disturbances which affected the left hemisphere. Right hemispheric compensation has been observed for both endogenous (e.g., aging, dyslexia, aphasia, task difficulty) and exogenous (e.g., brain stimulation) types of disruptions of performance of left hemispheric areas (Davis et al., 2008; Dominguez et al., 2014; Flöel et al., 2011; Gur et al., 2000; Hartwigsen et al., 2013; Meinzer et al., 2009; Sun et al., 2010; Waldie et al., 2013). Therefore, in order to have a network that could accommodate potential need for compensation, the right hemisphere was also included.

Figure 1 summarises the predictions based on the multi-node framework made for the experimental studies in this thesis. It depicts the assumed task load of CP, LD and WN and stimulus types word and nonword for the endpoints of the dorsal pathway of phonological processing, the LIFG and LSTG, as well as the expected effects of tDCS on performance when these nodes are

target of stimulation in the healthy brain. More detail is found in the relevant experimental chapters (5 through 9). Predictions on tDCS effects on performance for disorders where the baseline brain activity differs from that of healthy young adults, i.e., in dyslexia and aphasia in this thesis, are further described in chapters 10 and 11 respectively.

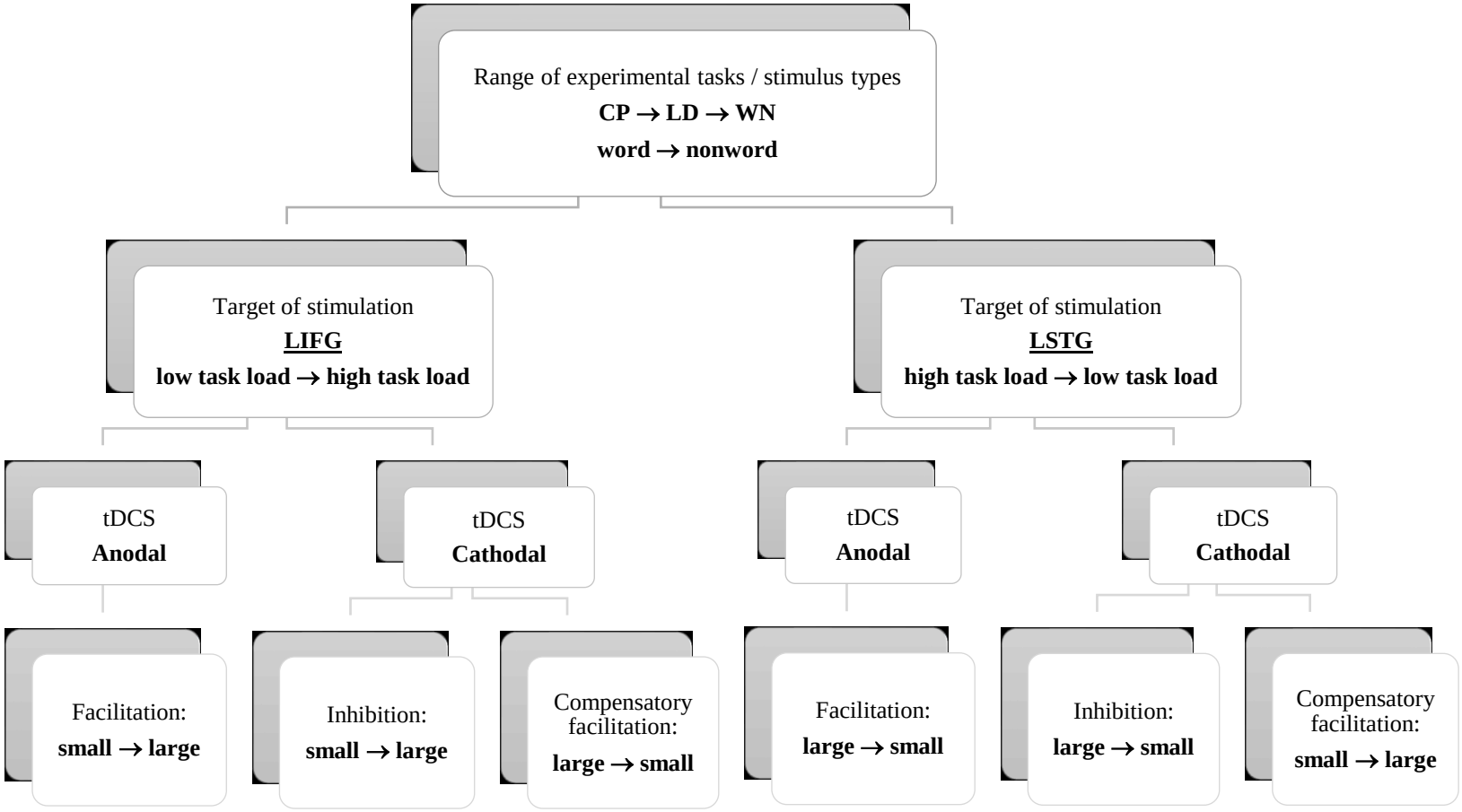

Figure 1. Predicted task load modulation of tDCS effects for the healthy brain

3.4 EFFECTS OF TDCS ON BRAIN ACTIVATION

The tDCS modulates cortical excitability with anodal stimulation increasing it and cathodal stimulation decreasing it (Nitsche et al., 2000). Research combining tDCS and fMRI has shown that this difference in excitability induced by anodal and cathodal stimulation can be indirectly detected through changes in cerebral blood flow (Holland et al., 2011; Holland et al., 2016; Meinzer et al., 2012; Zheng et al., 2011). Zheng et al. (2011) studied the effects of tDCS on blood flow in healthy young adults using arterial spin labelling (ASL) with no concurrent task. A pattern of blood flow responses for anodal and cathodal tDCS was outlined. Anodal stimulation induced a large increase in the blood flow on the target during and post-stimulation (Zheng et al., 2011). Cathodal stimulation induced a modest increase in the blood flow during stimulation, followed by a significant post-stimulation decrease relative to baseline (Zheng et al., 2011). Effects of the direct current were also observed beyond the target region, indicating a network effect of stimulation. A network of brain areas connected to the target was identified, presenting with the same pattern of activation as the target, as shown by a regression analysis (Zheng et al., 2011). Holland et al.'s (2016) findings of the network effects of anodal tDCS with an effective connectivity analysis (with DCM) are consistent with Zheng et al.'s (2011) results. The authors found that anodal tDCS strengthened connections between nodes of the network involved.

It should be noted, however, that these effects of tDCS on blood flow may change in a state-dependent manner. Evidence in the literature suggests that the concurrent presentation of a relevant task during stimulation may introduce a differential effect of tDCS on blood-oxygen-level dependent (BOLD) signal change as compared to the pattern observed for stimulation without a task (Antal et al., 2012; Holland et al., 2011; Meinzer et al., 2012). Specifically, the pattern of BOLD signal change found for tDCS stimulation with a concurrent task is the opposite of that

outlined for tDCS stimulation without a task. As for the pattern of BOLD signal change with no task, tDCS has also been found to have effects both locally on the target and more remotely on non-target areas of the cerebral cortex when a task is concurrently administered. However, the local effects of tDCS are decreased BOLD signal for anodal stimulation (Antal et al., 2011; Holland et al., 2011; Meinzer et al., 2012) and increased BOLD signal for cathodal stimulation (Antal et al., 2012). Although this evidence may appear counterintuitive, Holland et al. (2011) analyse their findings with anodal tDCS during the presentation of a task in terms of neuronal efficiency. The authors explain that the concurrent presentation of a task during anodal tDCS may be critical to maximally facilitate task-induced neurons depolarisation, which results in less synaptic activity needed to reach a threshold. Consequently, the BOLD signal decreases. By inference, the reverse logic should apply to cathodal tDCS. In other words, a decrease in BOLD signal change is linked to improved efficiency of the target to solve the task, while an increase in BOLD signal change is related to decreased performance of the target to solve the task. The expression of the facilitatory or inhibitory effects of tDCS on the BOLD signal parallels that of level of cognitive effort or burden on BOLD signal (Dunst et al., 2014; Engström et al., 2013).

However, in brain conditions where the baseline level of brain activation is abnormal, anodal tDCS seems to act as a regulator (e.g., Costanzo et al., 2016a, 2016b; Dominguez et al., 2014; Meinzer et al., 2013; Schneider & Hopp, 2011). On one hand, when abnormal hyperactivation is involved, the tDCS mechanism has been shown to follow the same pattern observed for healthy populations, i.e., a decrease in brain activation accompanied by improved efficiency of the target to solve the task. This has been observed, for example, in Meinzer et al.'s (2012) study with an elderly population that presented with hyperactivated frontal regions at baseline due to age-associated cognitive decline. Anodal tDCS applied to one of these frontal

regions had the effect of decreasing the BOLD signal relative to baseline. On the other hand, when abnormal hypoactivation is involved, increased behavioural performance after anodal stimulation of brain areas previously identified as hypoactive (e.g., Costanzo et al., 2016a, 2016b, for dyslexia; Dominguez et al., 2014, for aphasia; Schneider & Hopp, 2011, for autism) allows the inference for an induced increase in brain activation. However, as of mid-2018, no simultaneous tDCS/fMRI has been conducted so far in order to test this assumption.

Long-range effects of task-modulated brain stimulation of the cerebral cortex have been particularly observed for downregulation of the target, both with TMS and cathodal tDCS (Hartwigsen et al., 2013; Pirulli et al., 2014). Long-range effects have been observed as hyperactivation of non-target brain regions (Hartwigsen et al., 2013; Pirulli et al., 2014), as opposed to the pattern of small or decreased activation for cathodal stimulation compared to baseline outlined by Zheng et al. (2011) for stimulation without tasks. The long-range effects of task-modulated cathodal tDCS have been suggested to be a mechanism of network compensation (Jacobson et al., 2012; section 3.1.3.4). Compensation seems less plausible for excitatory brain stimulation. However, long-range facilitatory effects of excitatory brain stimulation has already been reported for anodal tDCS, manifested as the strengthening of connections between relevant areas (Baxter et al., 2017; Holland et al., 2016; Meinzer et al., 2012). The literature shows that the effect of tDCS on functional connectivity is not clear-cut, with instances where both anodal and cathodal tDCS are able to enhance connectivity and instances where there is no effect (Amadi et al., 2014; Braxter et al., 2017; Varoli et al., 2018). However, it may be that, at least in cognition, the strengthening of connectivity tends to be larger for cathodal stimulation than for anodal stimulation (Li et al., 2018), especially to support compensatory mechanisms. Specifically, I hypothesised that compensation should be evident through a higher engagement of other network

nodes for the execution of the task induced by inhibitory (cathodal) stimulation (in a low task load condition) than during facilitatory (anodal) stimulation. That is, the demand for compensation was expected to be reflected in a higher strengthening of the connectivity between network nodes than the ordinary overall improvement of network connectivity induced by anodal stimulation. The number of significant correlations between network nodes should differ between tDCS polarity conditions to account for that. In addition, the particular nodes involved in each significant correlation could provide an indication of the nature of compensation involved, for example, if within or inter hemispheric.

CHAPTER 4:

METHODS

4.I INTRODUCTION

In this chapter, methods for all the experiments reported in the studies of this thesis are presented. Studies had an overlapping design in that the same set of tasks and tDCS conditions to investigate the task load modulation of tDCS effects on performance were used. However, they differed in the target of tDCS stimulation (LIFG or LSTG), target population (healthy young and older adults, PWD and PWA), statistical design (within-subjects or between-subjects) and type of performance investigated (behavioural or neural measurements). In the next subsections, the core design across experiments and the particularities that they present are explained. The rationale for the particularities of each experiment were only briefly mentioned in this chapter, where appropriate. They are presented in more detail in the relevant chapters (5 through 11).

4.2 PARTICIPANTS

Participants filled in safety questionnaires for the tDCS and MRI studies, as appropriate, to exclude those with contraindications, such as a history of epilepsy, a medically unstable psychiatric or neurological condition and presence of non-MRI safe metal in the body. Participants gave informed consent before taking part. The study was approved by the Central Ethics Committee of the University of Birmingham.

Because the experiments involved language tasks in English, all participants should be native speakers of English. The specific sub-populations recruited were healthy young adults, healthy elderlies, young self-declared PWD and PWA with a behavioural profile indicative of frontal damage, i.e., with speech production difficulties and spared comprehension (Purves et al., 2001).

Still to meet requirements typical of studies in the language domain, all the participants but those with stroke aphasia had to meet the handedness criterion to be included. That is, only those classified as predominantly right-handed, as assessed by Annet's (1972) handedness inventory, were included. Although handedness is not a perfect predictor of language lateralisation, it has high concordance rate (in the range 88-96% according to Bishop, 2013 and Mazoyer et al., 2014), and therefore, right-handed participants were assumed to be predominantly left lateralised for language. For PWA, stroke on the left side of the brain as a cause of aphasia overrode the handedness criterion.

Furthermore, healthy young and elderly adult participants should not have any declared reading difficulty to be recruited, whilst reading difficulties were expected for PWD (Ramus, 2004). Healthy adults and PWD reading ability was assessed with the TOWRE (Torgesen et al., 1999) and TIWRE (Reynolds & Kamphaus, 2007) sight reading tasks. No control participant was excluded on the basis of poor reading ability. Furthermore, PWD were expected to have cognitive abilities similar to those of matched controls (Ramus, 2004). Cognitive abilities of healthy adults and of PWD were assessed with the picture completion, coding and block design tasks from the WAIS IV battery (Weschler, 2008), and the prediction was met. On the other hand, PWA were expected to have reading and speech production difficulties, and could present some degree of cognitive impairment (Swinburn et al., 2005). PWA language and cognitive abilities were assessed with the Comprehensive Aphasia Test (CAT) battery (Howard et al., 2009; Swinburn et al., 2005). No PWA was excluded on the basis of poor cognitive ability.

4.3 MATERIALS

4.3.1 Tasks

The CP task utilised a standard auditory-perceptual judgment of ten speech sound tokens from a continuum whose endpoints were /ba/ and /da/. Sound tokens were repeatedly presented through headphones, one at a time in randomised order, and a decision made as to which category they belonged to (/ba/ or /da/) by pressing a corresponding button on a hand held button box.

In the LD and WN tasks, words and nonwords (same number of stimuli each) were presented in a random sequence. Each word was displayed on a computer monitor between two vertically aligned bars for 500 ms. The bars always stayed visible on screen to act as visual guides for where to focus attention. Each word or nonword was presented only once per run. In experiments where two runs of the same task were involved, two different, but matched, lists of stimuli were counterbalanced for the two times that the task was presented per participant. Both the LD and the WN task shared the same lists of stimuli. In the LD task, participants judged each target string of letters as either a real word or a nonword and responded using one of two buttons similarly to the CP task. In the WN task, each stimulus was read aloud by the participant and the speech automatically recorded in real time via a microphone.

A rhyme judgment task was also used as a "warming up task" during the initial period of tDCS stimulation to provide online stimulation. The responses for this task were not analysed. It was presented only once per participant, during the initial minutes of brain stimulation, in order to engage the brain areas involved with the tasks of experimental interest, and also as a precautionary measure to ensure enough time for the direct current to start to exert an effect over behaviour (Nozari, Arnold, & Thompson-Schill, 2014). In this task, pairs of words that rhymed and pairs that did not rhyme were presented in a random sequence. Participants should make a decision to judge

if the pair of words presented rhymed or did not rhyme by pressing a corresponding button on a hand held button box. For each pair one of the words was presented above the other in the centre of a desktop computer screen. Two vertical bars were also shown above and below the pair of words. Each word pair was presented for 900ms. The bars always stayed visible on screen. Eighty pairs of words were presented, with an equal number of pairs in each category.

4.3.1.1 Particularities of behavioural experiments

The CP, LD and WN tasks were presented in two runs of equal design. In the CP task, each of ten stimuli were repeatedly presented 15 times each in a randomised sequence (total 150 sounds presented) per run per participant in each of the two times in which the task was run. The inter-trial interval (ITI) was of 1.8 s. In the LD and in the WN task, 80 words and 80 nonwords were presented per run with an ITI of 2 s.

In the WN task, voice responses were recorded via a TASCAM TM-60 battery-powered condenser unidirectional microphone (TASCAM, n.d.). The time of the voice onset to reach a minimal threshold was automatically logged, thereby allowing the calculation of reaction times for analysis. For both LD and CP tasks, participants responded with their right hand on the button box.

4.3.1.2 Particularities of fMRI experiments

The CP, LD and WN tasks had equal design regarding stimulus presentation. Experiments with healthy young adults and PWD (chapters 8, 9, and 10) had two runs of each task to closely match the design of the behavioural experiments. However, to ensure the tolerability of elderly participants with the length of the scanning session, the study with PWA and healthy elderly adults

(chapter 11) had a single run of each task. All the three tasks were matched with 60 stimuli per run and a variable ITI defined by a Poisson distribution with the mean of 9.5 s.

In the CP task, each of ten stimuli were presented randomly and repeatedly for an unequal number of times. From the total number of stimuli presented, the easiest ones, corresponding to the two most extreme tokens in each end of the continuum were presented together 30% of the times, whilst the remaining middle tokens, considered more difficult or demanding to categorise, were presented 70% of the time. Stimuli were delivered through MRI compatible ConFon Electro Dynamic Headphones (MR confon GmbH, n.d.). In the LD and in the WN tasks, 30 words and 30 nonwords were presented per run.

Participants responded with their left hand on the button box in the LD and CP tasks. In the WN task, an MRI compatible Optoacoustics' FOMRI III+ Noise Cancelling microphone (Optoacoustics Ltd., n.d.) was used to record voice responses. However, voice responses were not synchronised with the program that delivered the stimuli to have the voice onset automatically logged in such as in the behavioural experiments. This is because the criterion of reaching a given amplitude threshold for the voice onset to be logged used in the behavioural experiments, run in acoustically isolated room, could not be reproduced in the MRI scanner, where the scanner noise was a confounder. Voice responses were recorded to register participant engagement with the task, but no onset voice information could be obtained to calculate reaction times. The quality of the audiofiles was low. Filtering of the sound waves to obtain the voice responses was unsuccessful, because the audiofiles were very noisy.

4.3.2 Stimuli

Stimuli for the CP task were as per Raizada and Poldrack (2007), who describe them in detail. Briefly, ten 300 ms tokens were created from the continuum of synthesized speech between prototypical /ba/ and /da/ syllables. The stimuli were generated with a SenSyn Klatt synthesizer (Sensimetrics) by manipulating the second and third formants of the endpoints of the continuum.

Words and nonwords for the LD and WN tasks were generated using the VWR R package (Keuleers, 2013), which contains a list of 66,330 English words without spaces or dashes from the CELEX lexical database (Baayen et al., 1995). All words and nonwords were six letters long. Each individual word was sampled from all possible six letter words and had the orthographic neighbourhood density OLD20 score (Yarkoni et al., 2008) calculated. Nonwords were generated using the Wuggy pseudowords generator (Keuleers et al., 2010) and were matched to the words across the range of OLD20 scores. Word frequencies were obtained from the SUBTLEXus database of word frequency for American English (Brysbaert & New, 2009). Words sampled from VWR that happened not to have the frequency known were excluded and replaced. Summary statistics for word frequency count (frequency per million words) were: mean = 503.7; SD = 1966.4; min = 3; max = 22040. OLD20 scores were: words (mean = 1.88; SD = 0.32), nonwords (mean = 1.88; SD = 0.27). An unpaired t-test showed no significant difference between words and nonwords on the OLD20 score.

Another feature of the word and nonword stimuli that is particularly relevant for the WN task is their initial phoneme. Phonemes are detected by voice keys at different times, therefore causing phonetic bias on the reaction times measured for utterances (Kessler et al., 2002). One reason is articulatory, as some phonemes take longer to be initiated by the vocal apparatus. Another important factor is acoustic. Phonemes have different sound pressures and different rise times for

the sound pressure to reach the key voice threshold (that cannot be set too low to avoid being triggered by nonspeech noises). Kessler et al. (2002) found a strong pattern in their data where consonants that are voiceless, as well as plosives, affricates and fricatives take significantly longer to trigger the key voice than voiced consonants, nasal and approximant consonants, and vowels (Kessler et al., 2002). Initial phoneme was not controlled for in the lists of words and nonwords devised for the experiments of this thesis. Since the lists for baseline and online stimulation were different, a potential initial phoneme imbalance could have systematically biased reaction times between baseline and online, introducing a caveat within the session. This caveat was only introduced within session, but not across tDCS sessions, because the same lists, in the same order for baseline and online, were used across all tDCS experimental sessions.

Stimuli for the rhyme judgment task consisted of a subset of McNorgan and Booth (2015)'s. Eighty of their 96 pairs of words were used, sampled according to the same pattern they used: half of the pairs rhymed and half do not, and for each of those categories, half the pairs were orthographically similar. For example, in the rhyming condition, the pair CAGE-RAGE was orthographically similar and the pair GRADE-LAID was orthographically dissimilar. In the non-rhyming condition, the pair STAMP-SWAMP was orthographically similar and the pair THIEF-PLEAD was orthographically dissimilar. McNorgan and Booth (2015) balanced their lists of words by length, frequency and naming accuracy. The length had an average of 4.5 letters and naming accuracy of 100% across all conditions. Frequency varied slightly across conditions, but the difference was not statistically significant.

Stimuli of all the tasks were delivered using the Presentation software (version 18.3, Neurobehavioral Systems) running on Win7 desktop PC. All stimuli were presented on 22" Iiyama CRT monitor in the behavioural experiments or via projector in the fMRI experiments.

4.3.3 tDCS

A neuroConn tDCS device (neuroConn GmbH, n.d.) was used. The target of stimulation was either the LIFG or the LSTG, whose position for placement of the active electrode on the scalp was defined respectively as F5 and Cp5 according to the 10–20 international EEG system (Jasper, 1958). The reference electrode was positioned over the right supraorbicular region in both cases. Positioning was made with the assistance of a standard 10-20 EEG cap. For real tDCS, stimulation had a duration of 20 min; for sham, it lasted for 30 s. In both cases, the direct current was increased to reach the chosen intensity of stimulation with a ramp up of 10 s, and decreased at the end of the stimulation with a ramp down of 10 s. This brief period of stimulation for sham is in agreement with the range typically used in tDCS studies and has not been reported to alter brain function (Nitsche et al., 2008) thereby ensuring sham acts as a satisfactory placebo.

4.3.3.1 Particularities of behavioural experiments

Direct current had an intensity of 1.5 mA and was delivered through the 5 x 7 cm sponge electrodes available in the tDCS kit, which were soaked in saline solution. The resulting current density was of 0.042 mA/cm^2, which is within the range of 0.029 to 0.08 used by most tDCS studies (Nitsche et al., 2008). For the fMRI experiments (see tDCS details in section 4.3.3.2), fMRI-specific 5 x 5 cm rubber electrodes were available in the kit and were used instead of 5 x 7 cm rubber electrodes in order to improve slightly the focality of the direct current (Nitsche et al., 2000). In addition, current intensity was increased by 0.5 mA to augment the likelihood of inducing stronger behavioural effects (Nistche et al., 2000). The resulting current density, of 0.08 mA/cm^2, was higher, also contributing to the likelihood of inducing stronger behavioural effects (Nitsche et al., 2008). This change was implemented in the fMRI studies to help ameliorate the design

difference between the behavioral and the fMRI experiments that could make the effects of tDCS on performance more difficult to detect in fMRI. The main difference was the reduced number of stimuli presented in each fMRI experimental run, with approximately 33% of the number of stimuli presented in the experimental runs of the behavioural studies.

4.3.3.2 Particularities of fMRI experiments

An MRI compatible neuroConn tDCS device (neuroConn GmbH, n.d.) was used. Direct current had an intensity of 2 mA and was delivered through 5 x 5 cm rubber electrodes, as to increase the current density administered in the behavioural experiments and potentially the efficacy of tDCS as a consequence (Angulo-Sherman et al., 2017) where current density is concerned. Ten20 conductive paste was used to reduce scalp electrical resistance in lieu of the saline solution used in the behavioural experiments. This was to avoid drying out of the electrodes over the longer time participants would be wearing them before the tDCS was turned on.

4.4 PROCEDURE

Behavioural experiments were run with a between-subject design, whilst fMRI experiments were run with a within-subject design. tDCS conditions of anodal, cathodal and sham stimulation were counterbalanced across participants and administered in different sessions. Task order was counterbalanced across participants. A single-blind protocol was used, whereby participants were unaware of the stimulation condition.

All participants were given practice for the experimental (CP, LD and WN) and "warming up" (rhyme judgment) tasks prior to the experimental session. Instructions for all the tasks were

displayed on the computer screen and orally reinforced by the researcher conducting the session. Participants were reminded to respond to the stimuli as quickly as possible.

4.4.1 Design of a typical experimental session

CP, LD and WN were administered in a counterbalanced order. In the experiments with healthy young adults and PWD (chapters 5, 6, 8, 9 and 10), these three tasks were presented in two repeats, one for baseline measurements and another one under tDCS stimulation (online run). In the study with PWA (chapter 11), tasks were administered only once in the session, in which the participants were placed under tDCS stimulation. To match the design of the tDCS study for PWA, control data from healthy young adults used in the study reported in chapter 11 consisted of only their online runs.

The session structure consisted of the presentation of the three experimental tasks for baseline, where applicable. The rhyme judgment was then presented at the onset of tDCS. This task was immediately followed by the three experimental tasks, in the same order as presented for baseline, when baseline was administered (Figure 1). Physical effects of the direct current were assumed to be similar for all the tasks, because the effects of the current have been found to be still high for minutes after the end of the stimulation (Mangia et al., 2014).

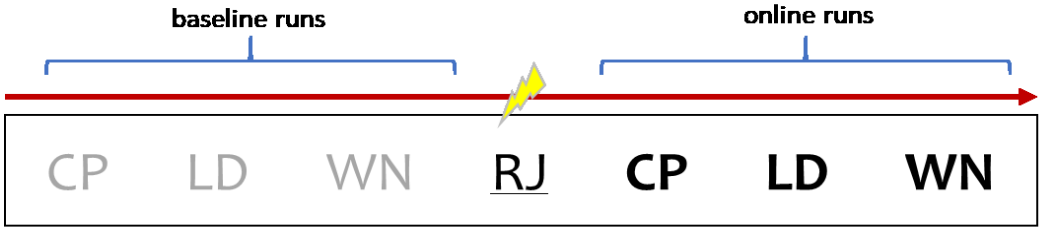

Figure 1. Schematic representation of a typical experimental session. Experimental tasks (CP, LD and WN) are represented in grey for the baseline and in black for the online runs. Thunder ray symbol indicates the onset of the 20 min tDCS stimulation, which overlaps with the onset of the rhyme judgment task (RJ), underlined.

4.4.2 Particularities of fMRI experiments

In the fMRI experiments, the sequence of tasks and the direct current were delivered during the functional resonance magnetic imaging of the participants' brain. Each experimental task (and each repeat where applicable) was presented in a different fMRI scan, whilst the rhyme judgment was presented without scanning. An anatomical scan was also acquired after the sequence of tasks in one of the three sessions of the experiment.

4.4.2.1 MRI acquisition parameters

MRI data were acquired using a 3T Phillips Achieva scanner with a 32 channel head-coil at the Birmingham University Imaging Centre (BUIC). 240 T2*-weighted gradient-echo EPI volumes were acquired per experimental run with the following parameters: repetition time (TR) = 2.5 s, echo time (TE) = 34 ms, flip angle (FA) = 77^{o}, slice thickness = 3 mm, voxel size = 3 mm^{3}, field of view (FOV) = 240 x 130 x 240 mm, acquisition matrix = 80 x 80. Each EPI image consisted of 43 axial oblique slices, enough to cover the whole cortex, that were acquired in sequential descending order. Sparse sampling has been suggested in the literature to be a better type of sequence for speech production (Ulm et al., 2015) and auditory processing (Raizada & Poldrack,

2007) due, respectively, to the minimisation of artefacts caused by articulatory movements and of the interference of scanner background noise in the reception and processing of auditory stimuli. However, a sparse sampling sequence in this experiment would introduce the caveat of sequence variability, preventing comparisons across tasks to be performed. In addition, since acquisition is slower, the time constraint would lead to a decrease in the possible number of stimuli to be presented in a run, with consequent loss in statistical power. The typical non-sparse sampling sequence was therefore preferred and chosen. A pilot study was conducted and demonstrated the feasibility of adopting such sequence for the WN and the CP tasks without major issues. The anatomical scan was acquired as an isotropic structural T1-weighted gradient echo image with 175 sagittal slices, TR = 8.4 ms, TE = 3.8 ms, flip angle of 7° and voxel size of 1 mm^3.

4.5 ANALYSES OF BEHAVIOURAL DATA

4.5.1 Measurements

Reaction times were used as a common measure of processing load across all experimental tasks, enabling comparisons between them to be made. For WN and LD, reaction time is assumed to be an index of operations involved in lexical access (Carreiras et al., 2007). For CP, reaction times reflect the processing load involved in analysing acoustic information and finding the corresponding phonological category. Pisoni and Tash (1974) refer to such measure as a "positive function of uncertainty" in this case, with increased values around the boundary between two categories of the speech continuum.

Accuracy scores are another measure of performance commonly used for LD (Carreiras et al., 2007). These were also analysed for this task. Accuracy in the LD task consisted of a binary score denoting either correct or incorrect responses. For the CP task, the uncertainty in categorising

ba-da stimuli was obtained as a second measure of performance (Vandermosten et al., 2011). Following Vandermosten et al. (2011), the uncertainty was estimated per participant by calculating the slope of the regression line of the logistic regression fitted to the probabilities associated with participants' categorisation of each token. The larger the absolute value of the slope, the greater the consistency in categorising the stimuli, i.e., the smaller the uncertainty (see examples in Figure 2). A custom Matlab script was used to fit individual data and to obtain slopes and intercepts. Corresponding confidence intervals were estimated using a bootstrap method. Slopes whose goodness of fit was unsatisfactory were identified when confidence intervals could not be estimated (Vandermosten et al., 2011) and these values removed from the final data set. The intercepts of the regression lines represented the probability of identifying an endpoint in the speech continuum. Since endpoints are the best prototypes of the two syllables that originated the continuum, the fitted intercepts were not expected to give rise to any uncertainty for categorisation that could be modulated by tDCS. Therefore, intercepts were excluded from further analyses.

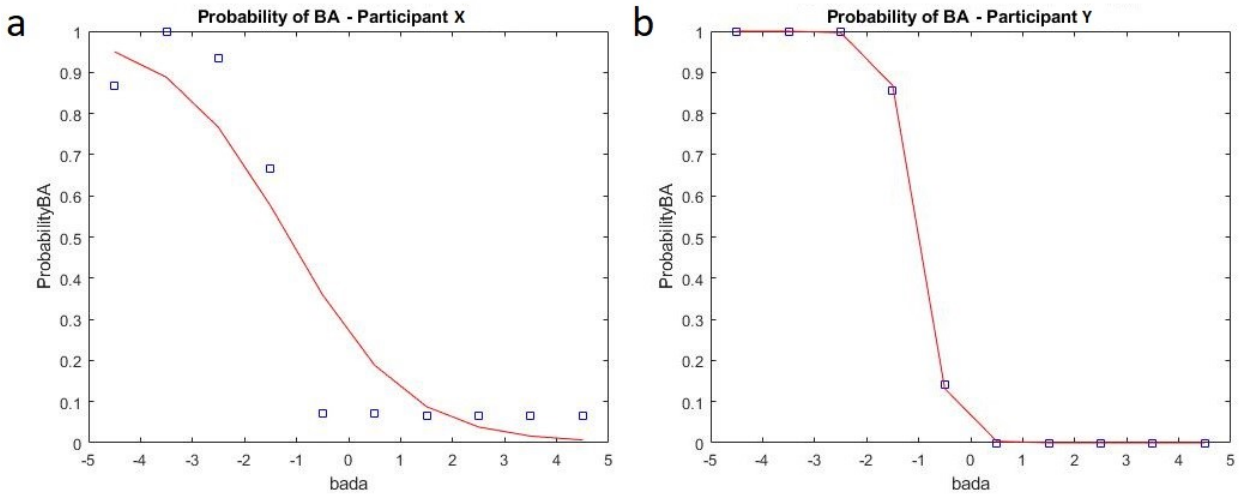

Figure 2. Curves representing the regression line of the logistic regression fitted to the probabilities of categorising each of the 10 tokens from the /ba/ to /da/ continuum as a /ba/. The x-axis displays a range from -5 to 5 that corresponds to the tokens from /ba/ to /da/ in the continuum. The y-axis displays the probabilities of categorising a token as a /ba/. Panels depict examples of baseline data of two participants. The absolute value of the slope for participant X (panel a) is 0.88, and the absolute value of the slope for participant Y (panel b) is 3.77. Participant Y therefore categorised the auditory stimuli with less uncertainty than participant X.

4.5.2 Data analysis

Data were pre-processed in a standard fashion. For the LD and WN tasks, individual trials with reaction times 2.5 standard deviations below and above the mean per participant, run, task and stimulus type were removed. Measures of accuracy for LD and of categorical uncertainty (henceforth accuracy) for CP were analysed with data sets where corresponding reaction time outliers had already been removed. Initial modelling with reaction time and accuracy (of CP) as dependent variables showed a degree of heteroscedasticity and non-Normal distribution of residuals. A log-transformation was therefore applied to these variables before final models were fitted to the data (Vandermosten et al., 2011; Whelan, 2008).

R version 3.3.1 (R Core Team, 2016) was used for data analysis of the behavioural studies. A linear mixed effects model was fitted to the log transformed combined reaction time data of all the tasks. In this model, I included task, with three levels (CP, LD and WN), and run, with two

levels (baseline and under stimulation), as within-subject factors, and brain stimulation, with three levels (anodal, cathodal and sham), as a between-subject factor. A random intercept was included for participants. Further analyses were then conducted. For each of the three tasks, a linear mixed effects model was fitted to the reaction time data, with brain stimulation as a between-subject factor, run as a within-subject factor, and participants as a random effect.

Stimulus type of words and nonwords were also evaluated to investigate if their different load to either the LIFG (chapter 5) or the LSTG (chapter 6) could modulate the responses to tDCS stimulation. A linear mixed effects model with run and stimulus type as within-subject factors, brain stimulation as between-subject factor and participants as a random effect was fitted to the combined reaction time data of LD and WN and also for each task alone. For LD, a subset of the reaction time data was used where only correct responses of the corresponding accuracy data were included. This has had the effect of removing 14% and 18% of the LD reaction time data in the experiments reported, respectively, in chapters 5 and 6.

Accuracy data of CP were also analysed with a mixed effects model. In this model brain stimulation was a between-subject factor, run was a within-subject factor and participants were included as random effects. Accuracy of the LD task was analysed with a mixed effects logistic regression fitted to the binary response variable also with brain stimulation as between-subject factor, run as within-subject factor and participants as random effects, as well as reaction times included as a covariate.

It should be noted that all the behavioural experiments had a design with tDCS stimulation (anodal, cathodal and sham) as a between-subject factor. Each level of the tDCS factor was administered in sessions with two runs of three tasks, the first run being the baseline. Therefore, the baseline measures for the tasks were expected to be different between the tDCS groups. Since

only the amount and direction of change in performance induced by tDCS was of interest, beyond the influence of the relative baseline, the post-hoc contrasts and summary plots reported in chapters of this thesis incorporated the differences between run two (stimulation) and run one (baseline). For clarity, the plots additionally display contrasts per tDCS condition compared to sham, i.e., the difference between a real stimulation and sham (henceforth "anodal tDCS" or "cathodal tDCS"), or comparisons between two real stimulations (henceforth "anodal vs cathodal tDCS"). All contrast analyses were corrected for multiple comparisons using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995).

4.6 ANALYSES OF FMRI DATA

4.6.1 Preprocessing

The FMRIB Software Library (FSL; Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009) was used for preprocessing of functional and structural images, and to analyse the fMRI data. Non-brain tissue was removed from structural anatomical images (T1) with the FSL BET (v.2.1) tool (Smith, 2002). Functional images received regular-down slice timing correction. Images were spatially smoothed with a Gaussian kernel of 4.5 mm (1.5 times one dimension of the isotropic 3 mm^3 voxel). Motion correction of the functional data was performed by using the MCFLIRT tool (Jenkinson et al., 2002) and the ICA-AROMA (ICA-based Automatic Removal Of Motion Artifacts) tool (Pruim, Mennes, Buitelaar et al., 2015; Pruim, Mennes, van Rooij et al., 2015). The MCFLIRT applied rigid body transformation with the middle image as reference. The ICA-AROMA was used to identify and remove motion-related ICA components from the data. Temporal filtering was applied after ICA-AROMA motion correction. The high pass Gaussian weighted filter cut-off was of 50 s.

Multi-stage registration was performed. For all participants except PWA and elderly controls (reported in chapter 11), a 6 DOF affine registration was used to register functional images to individual anatomical space with the FSL FLIRT tool (v.6.0) (Jenkinson & Smith, 2001; Jenkinson et al., 2002). A non-linear registration (warp resolution 10 mm) of each functional image into standard MNI space was then performed with the FSL FNIRT tool (Andersson et al., 2007a, 2007b). However, for PWA, lesion could bias the normalisation transform, especially in the non-linear stage, and cause distortions in the registered images (Brett et al., 2001). For participants with stroke aphasia, the second stage of registration therefore used a 12 DOF affine instead, with the FSL FLIRT tool, to allow for cost-function masking (Brett et al., 2001). For consistency, registration of elderly control images was also performed with an affine transformation in both stages.

4.6.2 Data analyses

4.6.2.1 Whole brain analyses

Whole brain analyses were conducted to investigate the overall brain activation induced by the factors of task, tDCS and population (last two as applicable). They are reported in chapters 7 and 11 for PWA and in Appendices 1 to 3 for healthy young adults and PWD.

Data were analysed with the FSL FEAT v.6.0 tool (Woolrich et al., 2001; Woolrich et al., 2004). A general linear model (GLM) with local autocorrelation correction (using FILM prewhitening; Woolrich et al., 2001) was used to analyse all conditions at the individual level. Each of the functional runs in a session corresponded to one task (either CP, LD or WN), one tDCS condition (either anodal, cathodal or sham for a particular session) and, where baseline measurements were obtained (all experiments except those in aphasia and respective elderly

controls), one repeat (either baseline or online). In the first level of analysis, only task was therefore modelled as factor of interest for each run.

For the LD and the WN tasks, different stimulus types were entered into the design matrix as separate covariates, i.e., words and nonwords were modelled separately. Onset of responses were included in the design matrix as nuisance covariates whenever available (not available for WN). Stimuli presentation and responses had their onset and duration (as described in section 4.3.2. Stimuli) modelled. Button responses were given a notional duration of 100 ms. Time courses associated with each event where onset and duration were modelled were convolved with a double-gamma HRF (Hemodynamic Response Function). Temporal filtering was applied and temporal derivatives were added to the model as separate nuisance covariates in order to improve the model fit. Motion parameters generated by MCFLIRT were also included as nuisance covariates to regress out unwanted influence of motion on performance (Johnstone et al., 2006). T-contrasts were generated for the mean of all stimulus types versus rest for all the tasks. In addition, for the LD and WN tasks, t-contrasts were generated for the mean of each stimulus type, i.e., words and nonwords, versus rest.

Second level analyses were carried out with fixed effect models by participant with the contrast images from the first level analyses as input, i.e., contrast images for the mean across all the stimuli of each task (and mean across stimulus types for LD and WN) per run (baseline where appropriate and online) and tDCS condition (anodal, cathodal and sham). Each task (and stimulus type for LD and WN)/tDCS combination was set up separately as a covariate of interest in the design matrix. For studies where the baseline measurement was available (all the studies, but that with PWA), the difference between the online and the baseline repeat was set up in the design matrix within the covariates for task/tDCS combinations. T-contrasts were set up to perform the

differences between real tDCS (anodal or cathodal) and sham for each task (and stimulus type for LD and WN). To match the second level models for PWA, where baseline was not available, extra models were prepared for healthy young adults with only their online data as input. Output images generated by these extra models were used for group comparisons between PWA and healthy adults as controls.

Group analyses were carried out with random effect models using FLAME stage 1 (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008). Gaussian Random Field Theory thresholding was applied to the statistical maps, with a value of $Z > 2.3$ at the voxel level and $p < 0.05$ at the cluster level, corrected for multiple comparisons. *Z*-value activation maps were produced for each contrast. The second level output images of each participant entered the models as input. Mean t-contrasts (one-sample t tests) were set up to analyse the group mean brain activation for each task (and stimulus type for LD and WN)/tDCS combination from the second levels within a given sample (e.g., PWD or healthy young adults). Two-sample t test contrasts were set up instead to analyse whether two samples, for example PWA or PWD and controls, differed for each task/tDCS combination. For the studies involving PWA, singleton analyses were performed. Each PWA was compared to a group of controls that mostly consisted of healthy young adults, but also counted on few healthy older adults. Although healthy elderly and healthy young adults are assumed to show a similar pattern of baseline brain activity in tasks involving phonological processing (Meinzer et al., 2009), an age covariate was included in the statistical models to regress out any potential age-related brain differences (Peters, 2006).

Group analyses were also performed for baseline. Baseline first level output images of each task (and stimulus type for LD and WN) from the three experimental sessions were used as input for each participant in these analyses. When baseline was not available (for PWA and the elderly),

sham was used instead. T-contrasts were set up to evaluate whether the mean baseline brain activation per task (and stimulus type for LD and WN) alone was different from zero within a given sample or whether it differed between samples.

4.6.2.2 ROI analyses

ROI analyses were conducted to investigate patterns of activation in the target network (which consisted of the LIFG, the LSTG, the RIFG and the RSTG) at baseline and under tDCS stimulation for healthy young adults and PWD (chapters 7 to 10). Due to the small sample size, ROI analyses were not performed for PWA, only whole brain analyses. In the next subsections, data processing and data analyses performed are explained.

4.6.2.2.1 ROI definitions and ROI-based data measurements

As discussed in section 3.3 of chapter 3, the network of interest for the fMRI experiments consisted of the two typical nodes involved in phonological processing, LIFG and LSTG (Burton, 2001; Liebenthal et al., 2013; Saur, 2008), and their right homologues, RIFG and RSTG. Four corresponding ROIs were created with FSL command line tools as a 6 mm radius sphere centred at coordinates of interest in MNI space. Figure 3 shows ROIs corresponding to the targets of stimulation for the experiments in this thesis, the LIFG and the LSTG.

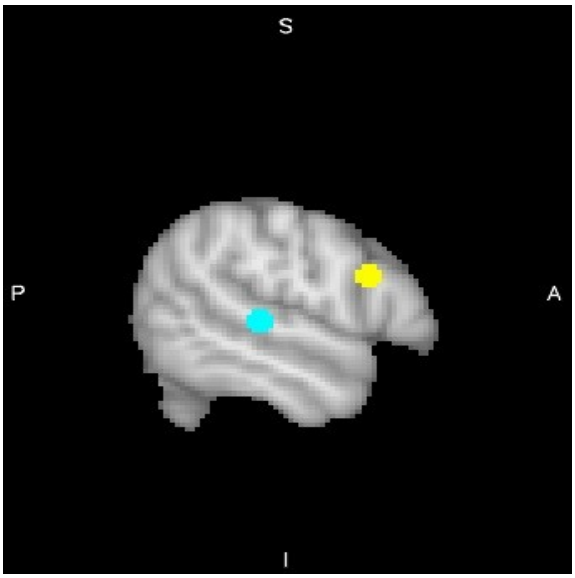

Figure 3. Targets of stimulation in sagittal view: LIFG (yellow) and LSTG (blue).

Coordinates for LIFG and LSTG were obtained from meta-analyses of functional brain activation associated with the CP, LD and WN tasks. These were carried out with the Neurosynth software and database (Neurosynth, 2018; Yarkoni et al., 2011a, 2011b). The search for each task used, respectively, the keywords "speech perception", "lexical decision" and "speech production", and yielded three forward inference statistical maps Benjamini-Hochberg corrected for multiple comparisons with a threshold of 0.01 (see the Neurosynth website and Yarkoni et al., 2011a, 2011b references for further information). By using FSL command line tools, the intersection between the three statistical images was obtained. The resulting image was submitted to a cluster analysis with a *Z* threshold of 2.3. Clusters corresponding to the LIFG and the LSTG in the Harvard-Oxford cortical atlas available in FSL (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006) were identified through their centre of gravity (COG), that is an average of the coordinates within the cluster weighted by intensity. These were then chose as the coordinates for LIFG and LSTG. Coordinates for the right homologues RIFG and RSTG were the same as those

for the left ROIs, but with the sign for the x coordinate reversed. The MNI coordinates for the four ROIs were x = -50, y = 14 and z = 24 (LIFG), x = -58, y = -28 and z = 4 (LSTG), x = 50, y = 14 and z = 24 (RIFG) and x = 58, y = -28 and z = 4 (RSTG).

For each participant, mean percentage signal changes (PSC) were obtained for each condition of interest per ROI with the FSL Featquery tool, based on whole brain analysis contrasts. Conditions of interest were the effect of task (and stimulus type for LD and WN) alone (baseline first level contrasts) or in combination with tDCS (second level contrasts) on brain activation. Contrasts involving the factor tDCS were defined with run 1 (baseline) subtracted from run 2 (online stimulation) and sham subtracted from real tDCS conditions (henceforth "anodal tDCS" or "cathodal tDCS").

4.6.2.2.2 Regression: effects of task and tDCS on mean brain activation per ROI

ROI mean activation measurements (or PSC) were fed into mixed effect linear regressions performed in R version 3.4.2 (R Core Team, 2017) to investigate, whenever applicable, the main effects of the within-subject factors of task, stimulus type (for LD and WN), tDCS and ROI on BOLD signal change, with participants included in the models as random effects. Post-hoc analyses were further set up as appropriate with contrasts to investigate whether each task (and stimulus type for LD and WN) alone (for baseline, chapter 7) or in combination with tDCS (chapters 8 through 10) was significantly different from zero per ROI. All contrast analyses were corrected for multiple comparisons using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995).

4.6.2.2.3 Partial correlation: ROI-based connectivity analyses per task and tDCS combination

Correlational analyses can provide indirect measurement of functional connectivity and have been extensively used for individual level analyses (e.g., Marrelec et al., 2006; Ryali et al., 2012; Sandberg, 2017), especially when precise prior information (e.g. temporal) for the connections between pairs of nodes, usually required to perform effective connectivity analyses, is not available. Partial correlation is therefore deemed to be a reasonable option (Marrelec et al., 2006). Furthermore, as connectivity analyses in this thesis were based on a previously defined network, partial correlation was considered more adequate than seed-based analyses, which are rather exploratory. For these reasons, partial correlation was the analysis of choice to investigate functional connectivity in the studies of this thesis.

Partial correlations using Pearson's *r*, and their level of significance, were calculated for datasets of ROI mean brain activations with the PPCOR R package (Kim, 2015). These analyses were performed to investigate the relationships between each pair of nodes of the target network for the different conditions of task and tDCS to show the most prominent brain activity subserving performance. Datasets for each condition were selected according to contrasts of either task or stimulus type (for LD and WN) alone (for baseline, chapter 7) or in combination with tDCS (chapters 8 through 10).

CHAPTER 5:

TASK LOAD MODULATION OF THE EFFECTS OF tDCS OVER THE LIFG ON BEHAVIOUR FOR PHONOLOGICAL PROCESSING IN HEALTHY YOUNG ADULTS

5.1 INTRODUCTION

In this chapter, I investigated the task load modulation of the effects of anodal tDCS and cathodal tDCS over the LIFG on behavioural performance for tasks that involved phonological processing in healthy young adults. In other words, I investigated the impact of modulating the efficiency of the functional targeting on the effects of tDCS. Functional targeting was modulated by the administration of three tasks that ranged from speech perception to speech production during tDCS stimulation of a single target, the LIFG. The tasks selected, CP, LD and WN, were assumed to increasingly engage the LIFG (c.f. Figure 1 in chapter 3 for an overview of predictions on task load modulation of the effects of tDCS over the LIFG).

Predictions are described in the next subsections by task and stimulus type (for LD and WN). Some of these predictions, in the current and in the remaining experimental chapters of this thesis, foresee the possibility of a null result to arise, which may appear unusual. Therefore, I will briefly discuss what the potential null results mean in the context of this thesis, explaining the underlying theoretical motivation. It is well accepted that no statistical approach can prove that a non-significant finding corresponds to the absence of effect (Harms & Lakens, 2017). Lack of power to detect an effect is another possibility, and a non-significant result brings insufficient evidence to disambiguate between the two possibilities. In this thesis, theoretical reasons, in the context of the multi-node framework (see Chapter 3), offer support for the prediction of potential null effects of tDCS, as well as their potential underlying reasons. However, it should be noted that this is a tentative approach, since statistically, a non-significant result does not allow definitive conclusions on the reasons behind a null finding.

In the context of the multi-node framework, the magnitude of effects of tDCS depends on task load (c.f. Figure 1 in chapter 3 for an overview of predictions). As outlined in Figure 1 of

Chapter 3, the facilitatory effect of anodal tDCS and the inhibitory effect of cathodal tDCS increase with task load. Therefore, with all other factors held constant, facilitation (with anodal tDCS) or inhibition (with cathodal tDCS) when the task load is low should have a smaller effect than when the task load is high. Thus, a null finding when anodal tDCS or cathodal tDCS is applied to a target in a condition of low task load could be a potential result (in spite of having sufficient statistical power to detect a small effect) as opposed to a successful detection of a larger effect in conditions of high task load.

Mechanisms behind a potential null finding for cathodal stimulation in a condition of low task load can be, however, slightly more complex due to the possibility of a network compensation to take place. Cathodal tDCS is assumed to cause inhibition that, in turn, translates into a decrease in performance from baseline. However, when cathodal tDCS is applied to a node under a condition of low task load there is room for compensation by other network nodes. Compensation is assumed to be facilitatory, i.e., to cause an increase in performance from baseline. Therefore, it is likely that the performance observed for cathodal stimulation in a condition of low task load represents a summation of effects with opposite directions: cathodal tDCS inducing decrease in performance and compensation by other network nodes inducing increase in performance. In the event that these two effects of opposite directions have a similar magnitude, they could cancel out, amounting to a near zero effect identical to a null finding. If any of the two effects of opposite direction is much stronger than the other and the resulting effect size is large enough to be detected, results will have a winner direction that will be either deteriorated or improved performance. Improved performance is more likely to be the winner direction, since downregulation of a node in a condition of low task load is expected to have a small effect.

5.1.1 CP

I used CP as a prototypical speech perception task. This task was expected to engage the LIFG the least (Lee et al., 2012; Rogers et al., 2014; Smalle et al., 2015; Watkins & Paus, 2004), because the role of the LIFG in speech perception is considered minor compared to the role of the LSTG, a region that is important in the processing of linguistic auditory information (Chang et al., 2010; Leonard & Chang, 2014). The role of the LIFG in speech perception processing is usually associated with access to motor codes of phonemes (Meister et al., 2007; Watkins & Paus, 2004). The speech perception task, therefore, was assumed to have the smallest efficiency of functional targeting amongst the three tasks used in this study. For this task, the LIFG was considered to be a network node of low relevance. Predictions for tDCS effects on behavioural performance for CP were that cathodal stimulation of the LIFG task would induce some level of compensation. An apparent null result of stimulation or an improvement in performance was therefore expected. Anodal stimulation was expected to cause performance to improve. However, given that the task-induced level of neural activity was assumed to be modest, the behavioural improvement induced by anodal stimulation could be as small as to appear to be a null result.

5.1.2 LD

A LD task was used as an intermediate task in the range from speech perception to speech production. Overt speech production is not involved in this task, but it shares some features with the WN. For example, some studies suggest that the LIFG has a somewhat modulatory effect on early visual word recognition (Deng et al., 2012), a processing step common to both LD and WN. More specifically, magnetoencephalography (MEG) studies have shown LIFG activity at around 130 ms of word presentation (Cornelissen et al., 2009; Wheat et al., 2010; Woodhead at al., 2014).

Phonological processing in the LIFG would also be similar for tasks involving silent reading and reading aloud particularly where orthographic to phonemic conversion is concerned (Burton, 2001). However, articulatory decoding in speech production would implicate a higher load for the LIFG (Fiez et al., 1995), and seems to be a key factor to differentiate the task load in the LIFG between the two tasks (LD and WN). On this basis, LD was assumed to be an intermediate task in the range from speech perception to speech production, but more shifted towards speech perception. The LIFG can therefore be considered to be a network node of low relevance for LD but of somewhat higher relevance than for CP. The efficiency of the functional targeting was assumed to be low. Predictions for tDCS were similar to those for CP. Cathodal stimulation of the LIFG was expected to induce some level of compensation that could lead to apparent null results or to an improvement in performance. Compensation was expected to be lower for LD than for CP because the room for compensation is smaller when the task load is higher. Anodal stimulation was expected to cause performance to improve. The task-induced level of neural activity of the LIFG was assumed to be higher than for CP, and therefore the improvement caused by anodal stimulation was likely to be larger than that for CP, but smaller than that for WN.

5.1.3 WN

The WN was a task of speech production and therefore expected to engage LIFG the most, because the LIFG is canonically associated with speech production and articulatory planning (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011). The LIFG was therefore considered to be a network node of high relevance for speech production, and the efficiency of the functional targeting assumed to be the largest amongst the three tasks used in this study. Predictions for tDCS effects on behavioural performance were that cathodal stimulation

would cause performance to worsen, because the downregulation of a relevant network node is not expected to be satisfactorily compensated by other, less relevant, nodes in the language network. Anodal stimulation was expected to induce significant behavioural improvement, because the task-induced neural activity was assumed to be high.

5.1.4 Words and nonwords

The efficiency of functional targeting with word and nonword stimuli during tDCS stimulation of the LIFG was also investigated. Nonwords were expected to be more demanding for the LIFG (Heim et al., 2005; Nosarti et al., 2010; Xiao et al., 2005), and hence to show more efficient functional targeting than words. It is generally thought that nonwords rely comparatively more on a more phonological or sublexical-dependent processing pathway, whilst words rely more on a lexical-dependent pathway (Binder et al., 2003; Fiebach et al., 2002; Forster & Chambers, 1973; Levy et al., 2009; Marshall & Newcombe, 1973; Patterson & Shewell, 1987). The difference in processing load between the stimuli of words and nonwords could also be attributed to a stimulus frequency effect. Processing of words that are infrequent in the lexicon is naturally more demanding, nonwords being an extreme case (Nosarti et al., 2010). Therefore, the LIFG was considered to be a more relevant node for nonwords than for words, and the efficiency of the functional targeting assumed to be greater for nonwords. It would seem likely therefore that cathodal stimulation should always worsen performance for both word and nonword stimuli, but with a stronger effect for nonwords. However, depending on the actual degree of compensation that takes place, it may be that for words an apparent null effect or even an improvement in performance could be observed. Anodal tDCS stimulation was expected to increase performance for both word types. Since the level of task-induced neural activity was assumed to be higher for

nonwords, effects of anodal stimulation were expected to be larger for nonwords. Increase in performance for words was expected to manifest behaviourally as either a small performance increase or as an apparent null result.

An inhibitory component in the processing of words and nonwords, which would be regulated by the LIFG, also needs to be considered. In tasks of word recognition, the presentation of a word (either visually or auditorily) activates plausible phonological, orthographic and semantic neighbours (Dufour & Frauenfelder, 2009; Johnson & Pugh, 1994; Schnur et al., 2009; Vitevitch, 2007). The competing neighbours have been shown to either facilitate or disturb the selection of the target word (Schnur et al., 2009). Hence word recognition is expected to involve some level of inhibition of the inappropriate candidates. The LIFG has been identified to be crucial in selecting a target amongst competing alternatives in tasks of word recognition (Mirman & Graziano, 2013; Snyder et al., 2007) across different domains of competition (e.g., phonological, semantic) (Snyder et al., 2007). Consequently, one could infer that inhibitory synapses take part in the neural basis of word recognition and predictions on the effects of tDCS brain stimulation for tasks involving word recognition (such as LD and WN) should take the inhibitory framework into account if the area stimulated is the LIFG.

According to the approach of the inhibitory framework that considers inhibitory functions to rely predominantly on the key role of inhibitory synapses, anodal stimulation increases inhibition and cathodal stimulation decreases it. The effect on performance depends on the role of inhibition for the task. Here I assume that inhibition is directly related to the ability of suppressing inadequate candidates, facilitating the selection or retrieval of the appropriate word. Therefore anodal tDCS could be expected to enhance the LIFG ability to suppress inadequate competing candidates. For words, this would be beneficial. For nonwords, on the other hand, this would probably be

detrimental, since the stimuli themselves could be considered inadequate candidates because they cannot be found in the lexicon. Cathodal tDCS was expected to show the reverse pattern, i.e., whilst decreasing the inhibitory role of the LIFG, poorer performance in the processing of words and increased performance in the processing of nonwords should be observed. An alternative explanatory mechanism under the inhibitory framework, on the other hand, considers inhibitory functions to rely on the right balance between inhibitory and excitatory synapses (Jackson et al., 2015; Krause et al., 2013). The tDCS is assumed to have an effect on either the inhibitory or the excitatory synapses as to solve the imbalance. In word selection, the main source of imbalance is probably the hyperexcitation of competing non-target words. Cathodal stimulation should therefore reduce the hyperexcitation of competing non-target words and facilitate the processing of words. If anodal stimulation were applied, the effect should be over inhibitory synapses as to increase their ability to reduce the hyperexcitation of the non-target words.

For the LD task in particular, a model of word selection has been proposed that can account for observed behavioural differences in the processing of words and nonwords (Grainger & Jacobs, 1996). According to Grainger and Jacobs (1996) multiple read-out model of orthographic processing in visual word recognition, a correct response in a task that requires word recognition depends on the appropriate word representation to reach a critical level of activation. However, LD needs an additional mechanism to solve the task, which has time from stimulus onset as an extra-lexical regulator (Grainger & Jacobs, 1996). In this model there is a temporal threshold that corresponds to an individual time limit for the identification of a stimulus in the lexicon with the appropriate level of activation. If the intra-lexical criteria are met within the given temporal limit, a positive response for word is made. Otherwise, at timeout the stimulus is classified as a nonword. With this model, I would predict that the facilitatory effect of anodal tDCS would be to extend the

temporal threshold, thus allowing more time for the search of a stimulus in the lexicon before the decision for nonword is made. Conversely, cathodal tDCS would shorten the temporal threshold, resulting in nonword decisions being made more quickly than a decision for word, since the time available for the inter-lexical criterion check would be reduced.

5.2. METHODS

Methods are as described in chapter 4 Methods. For the current study, 63 young healthy adults who met the inclusion criteria that was described in chapter 4 were recruited. Sixty (mean age: 20.6 years, SD: 2.13, 45 females) were included in the sample; three were excluded due to technical problems with the recording of responses. All three experiments (CP, LD and WN) were performed by all participants in the sample (n = 60), in counterbalanced order, as an experimental design with a within-subject factor of task, a within-subject factor of run (baseline and online) and a between-subject factor of tDCS stimulation (anodal, cathodal and sham, for which the sample split in subgroups of 20 participants each). This sample of participants was unique to the study reported in the current chapter.

5.3 RESULTS

First, I give an overview of the effects of task load on tDCS performance by showing the results from the model fitted to the combined reaction time data of all the tasks. Further exploration was then conducted by task, and the results are presented following the range from speech perception to speech production, i.e., from CP to LD to WN. Last, I present results of the analyses where effects of tDCS on words and nonwords are compared.

The first analysis looked at the effects of factors of task, brain stimulation and run within session on behavioural performance (reaction times). A 3 x 3 x 2 (task x brain stimulation x run) linear mixed effects model was fitted to the combined reaction time data of the CP, LD and WN tasks and showed significant interactions of task and brain stimulation ($F(4,51901) = 81.04$, $p < 0.001$) (Figure 1), task and run ($F(2,51901) = 14.01$, $p < 0.001$) and brain stimulation and run ($F(2,51901) = 7.43$, $p < 0.001$).

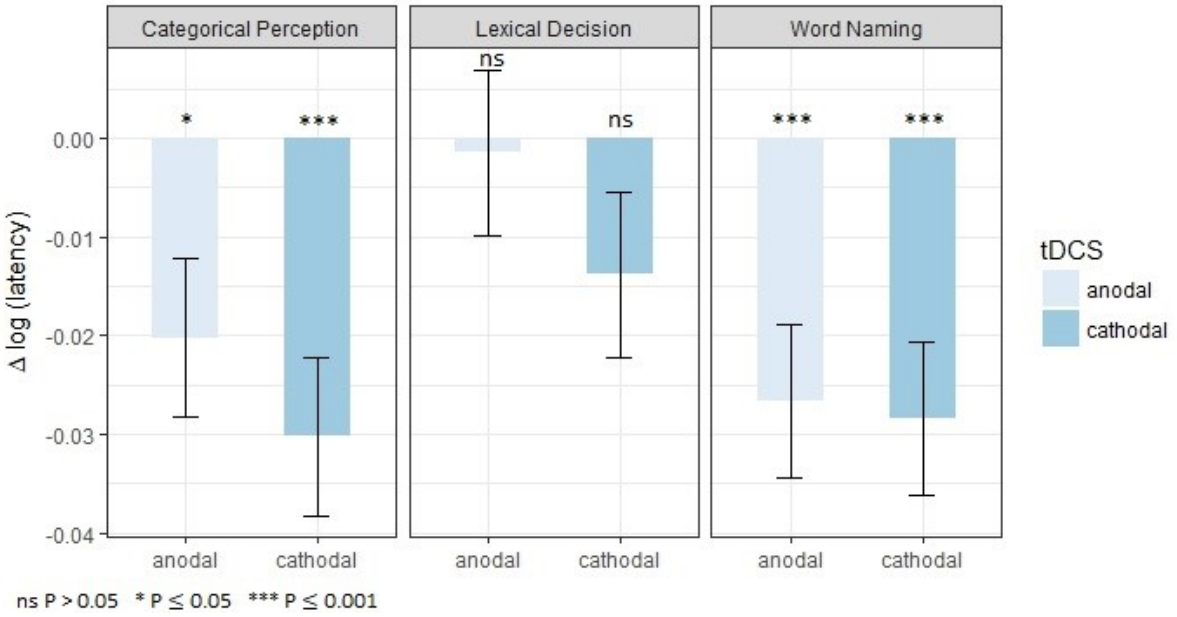

Figure 1. Delta RT latency per task and tDCS polarity. The x-axis displays the tDCS stimulation polarities compared to sham. The y-axis displays the contrast estimates (logarithmic scale). Error bars represent the contrast estimate ± the pooled standard error.

5.3.1 CP

5.3.1.1 Latency

A 3 x 2 (brain stimulation x run) linear mixed model was fitted to the reaction time data of the CP task. tDCS was found to play a modulatory role in behavioural performance, as indicated by a significant brain stimulation by run interaction ($F(2,17393) = 8.39$, $p < 0.001$).

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) showed a significant decrease in reaction times in the CP task caused by both anodal tDCS ($t(17393) = -2.69$, $p = 0.01$) and by cathodal tDCS ($t(17393) = -4.02$, $p < 0.001$), with a stronger effect for the latter (Figure 1, panel 1, and Table 1).

Table 1. Contrast analyses for latency of CP

Contrast	Estimate	SE	df	*t*	*p*
Anodal vs Sham	-0.02	0.01	17393	-2.69	0.01
Cathodal vs Sham	-0.03	0.01	17393	-4.02	< 0.001
Anodal vs Cathodal	0.01	0.01	17393	1.32	0.19

5.3.1.2 Accuracy

Accuracy in CP was also modulated by the action of direct current. The 3 x 2 (brain stimulation x run) linear mixed model fitted to the accuracy data showed a significant interaction of brain stimulation and run ($F(2,52) = 4.18$, $p = 0.02$).

Post hoc contrast analyses (Benjamini-Hochberg corrected) indicated that anodal stimulation was driving this effect (see Figure 2 and Table 2). Anodal stimulation significantly decreased participants' consistency in disambiguating the acoustic information of the stimuli into

well-defined phonemic categories ($t(52) = -2.89$, $p < 0.01$). Cathodal stimulation did not exert a significant difference on accuracy ($t(52) = -1.32$, $p = 0.096$).

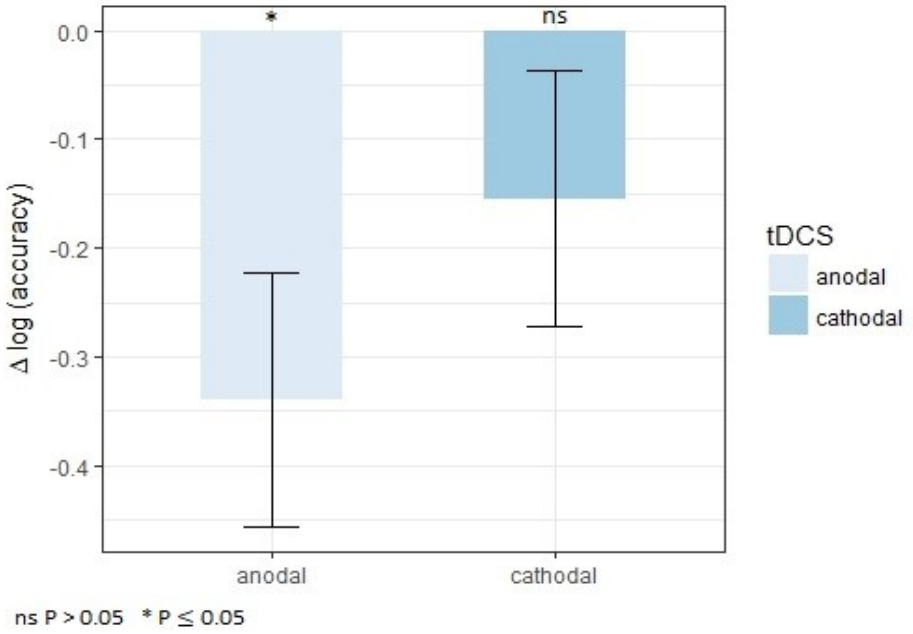

Figure 2. Delta accuracy in CP per tDCS polarity. The x-axis displays the tDCS stimulation polarities vs sham. The y-axis displays the contrast estimates (logarithmic scale). Error bars represent the contrast estimate ± the pooled standard error.

Table 2. Contrast analyses for accuracy of CP

Contrast	Estimate	SE	df	*t*	*p*
Anodal vs Sham	-0.34	0.12	52	-2.89	0.02
Cathodal vs Sham	-0.16	0.12	52	-1.32	0.19
Anodal vs Cathodal	-0.18	0.12	52	-1.55	0.19

5.3.2 LD

5.3.2.1 Latency

A 3 x 2 (brain stimulation x run) linear mixed model was fitted to the reaction time data of LD task. No significant effect of tDCS was found on behavioural performance for this task.

Neither the contrast of anodal tDCS stimulation nor the contrast of cathodal tDCS stimulation versus sham showed significant results for the LD task (Figure 1, panel 2, and Table 3).

Table 3. Contrast analyses for latency of LD

Contrast	Estimate	SE	df	*t*	*p*
Anodal vs Sham	0.00	0.01	15950	-0.39	0.70
Cathodal vs Sham	-0.02	0.01	15950	-1.84	0.20
Anodal vs Cathodal	0.01	0.01	15950	1.46	0.22

5.3.2.2 Accuracy

A 3 x 2 (brain stimulation x run) mixed effects logistic regression was fitted to the accuracy data of the LD task with reaction times included as a covariate. No significant effects were found in this analysis. Contrast analyses (Benjamini-Hochberg corrected) similarly showed no significant effects for both anodal and cathodal stimulation (Figure 3 and Table 4).

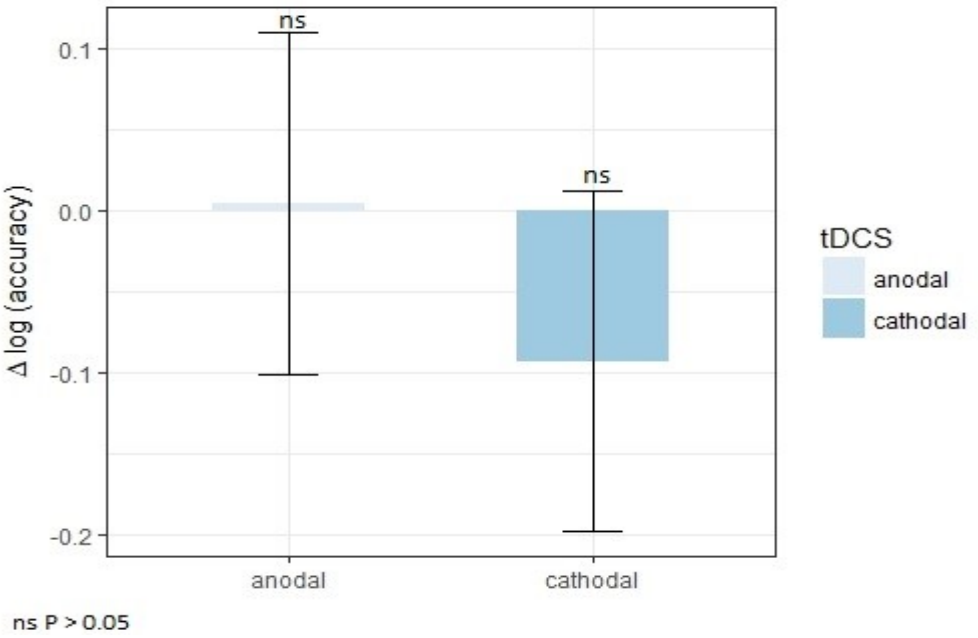

Figure 3. Delta accuracy in the LD task per tDCS polarity. The x-axis displays the tDCS stimulation polarities. The y-axis displays the contrast estimates on logit scale. Error bars represent the contrast estimate ± the pooled standard error.

Table 4. Contrast analyses for accuracy of LD

Contrast	Estimate	SE	df	*z*	*p*
Anodal vs Sham	0.00	0.11	NA	0.04	0.97
Cathodal vs Sham	-0.09	0.11	NA	-0.89	0.56
Anodal vs Cathodal	0.10	0.11	NA	0.91	0.56

5.3.3 WN

A 3 x 2 (brain stimulation x run) linear mixed model was fitted to the reaction time data of the WN task. tDCS was found to influence behavioural performance, with a significant brain stimulation by run interaction ($F(2,18444) = 8.79$, $p < 0.001$).

Contrast analyses (Benjamini-Hochberg corrected) showed that both anodal tDCS and cathodal tDCS caused performance to improve significantly (t(18444) = -3.74, p < 0.001 and t(18444) = -3.50, p < 0.001, respectively) (Figure 1, panel 3, and Table 5).

Table 5. Contrast analyses for latency of WN

Contrast	Estimate	SE	df	*t*	*p*
Anodal vs Sham	-0.03	0.01	18444	-3.74	< 0.001
Cathodal vs Sham	-0.02	0.01	18444	-3.50	< 0.001
Anodal vs Cathodal	0.00	0.01	18444	-0.22	0.83

5.3.4 Analysis of words and nonwords

A 2 x 2 x 3 x 2 (task x stimulus type x brain stimulation x run) linear mixed effects model was fitted to the combined reaction time data of the LD and the WN tasks to analyse the lexicality effect. Results of this analysis suggest that the effect of lexicality is relevant for performance, as revealed by the significant three-way interaction between stimulus type, brain stimulation and run (F(2,34439) = 4.54, p = 0.01).

Two separate 2 x 3 x 2 (stimulus type x brain stimulation x run) linear mixed effects models were then independently fitted to the LD and the WN reaction time data. The three-way interaction was only significant for LD (F(2,15944) = 5.48, p < 0.01). Figure 4 depicts the changes in reaction times in response to tDCS for words and nonwords in the LD and WN tasks.

Contrast analyses (Benjamini-Hochberg corrected) for the LD data revealed a significant decrease in reaction times for words versus nonwords induced by anodal tDCS stimulation (t(15944) = -2.58, p = 0.04). Decrease in reaction times for nonwords induced by cathodal tDCS

stimulation was significantly larger than that induced by anodal tDCS stimulation (t(15944) = -3.20, p = 0.01). Details for all contrasts are shown in Table 6.

Contrast analyses (Benjamini-Hochberg corrected) for the WN data showed that both anodal tDCS stimulation (t(18438) = -3.78, p < 0.01) and cathodal tDCS stimulation (t(18438) = -3.23, p < 0.01) similarly cause reaction times of words to decrease. No significant effects of tDCS were found for nonwords. Details for all contrasts are shown in Table 7.

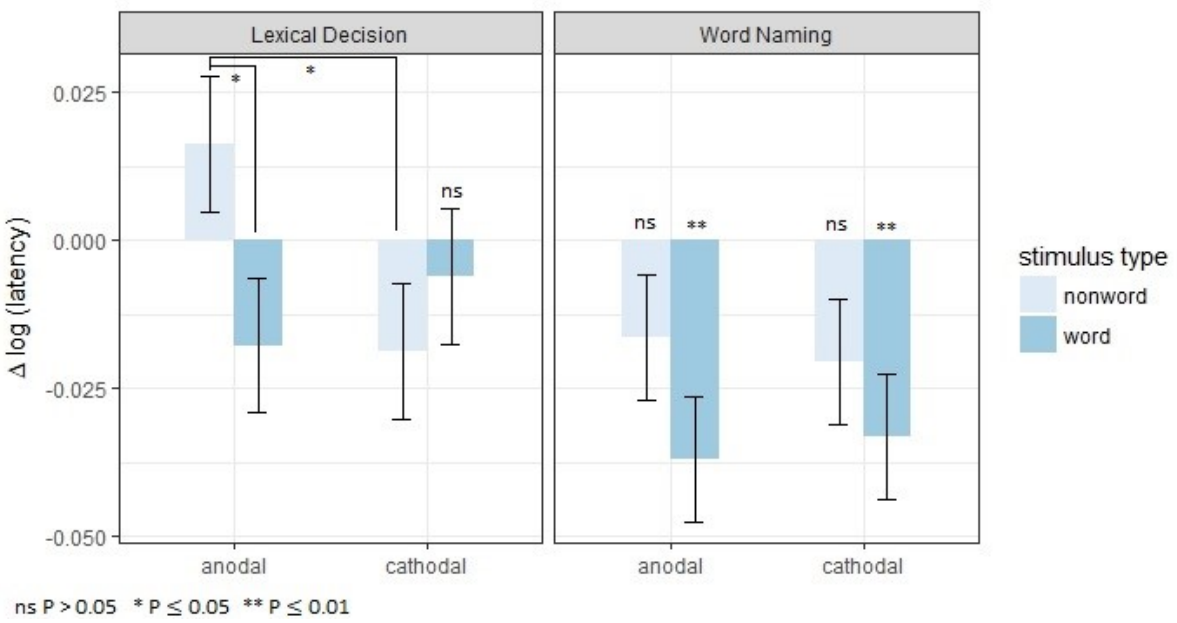

Figure 4. Delta RT latency for words and nonwords per task and tDCS polarity. The x-axis displays the tDCS stimulation polarities vs sham. The y-axis displays the contrast estimates (logarithmic scale). Error bars represent the contrast estimate ± the pooled standard error.

Table 6. Contrast analyses for latency of words and nonwords in LD

Contrast	Estimate	SE	df	*t*	*p*
Word: Anodal vs Sham	-0.02	0.01	15944	-2.13	0.09
Word: Cathodal vs Sham	-0.01	0.01	15944	-0.95	0.39
Word: Anodal vs Cathodal	-0.01	0.01	15944	-1.15	0.33
Nonword: Anodal vs Sham	0.02	0.01	15944	1.53	0.20
Nonword: Cathodal vs Sham	-0.02	0.01	15944	-1.65	0.20
Nonword: Anodal vs Cathodal	0.04	0.01	15944	3.20	0.01
Word vs Nonword: Anodal vs Sham	-0.04	0.02	15944	-2.58	0.04
Word vs Nonword: Cathodal vs Sham	0.01	0.02	15944	0.49	0.62

Table 7. Contrast analyses for latency of words and nonwords in WN

Contrast	Estimate	SE	df	*t*	*p*
Word: Anodal vs Sham	-0.04	0.01	18438	-3.78	< 0.01
Word: Cathodal vs Sham	-0.03	0.01	18438	-3.23	< 0.01
Word: Anodal vs Cathodal	-0.01	0.01	18438	-0.53	0.68
Nonword: Anodal vs Sham	-0.02	0.01	18438	-1.63	0.20
Nonword: Cathodal vs Sham	-0.02	0.01	18438	-1.93	0.14
Nonword: Anodal vs Cathodal	0.00	0.01	18438	0.31	0.75
Word vs Nonword: Anodal vs Sham	-0.02	0.01	18438	-1.52	0.20
Word vs Nonword: Cathodal vs Sham	-0.01	0.01	18438	-0.92	0.48

5.4 DISCUSSION

Findings from the current study suggest that the relevance of the task for the target of tDCS stimulation as well as the network structure underlying the particular cognitive task can help predict tDCS effects in behavioural performance. I have demonstrated that modulating the relevance of the cognitive task for a particular target brain area that is part of a larger distributed network, such as the LIFG is for language, can cause differential effects of tDCS stimulation. I discuss next how well the multi-node framework, which takes these factors into account, the dual polarity framework and the inhibitory framework were supported by the data of the current study.

Before summarising and interpreting the results, I review my earlier predictions. Under the multi-node framework, responses to tDCS can be modulated by the relevance of the task for the node targeted by stimulation. CP was the task in the range from speech perception to speech production considered to have the lowest relevance for the LIFG. LD was considered to have higher relevance for the LIFG than for CP. WN was considered to have the highest relevance for the LIFG. Predictions based on the multi-node framework were therefore that cathodal stimulation of the LIFG during CP and LD would be compensated by more relevant nodes in the network. Since the task load in LIFG for CP was smaller than that for LD, compensation for the former could be stronger. The expected behavioural results of compensation were an apparent null effect of stimulation or an improvement in performance. Cathodal stimulation of the LIFG during WN, on the other hand, was expected to decrease performance due to the inability of less relevant nodes to compensate. Anodal stimulation under the multi-node framework was assumed to improve performance as a function of the task-induced neural activity. Therefore, improved behavioural performance was expected for all the tasks, with an increasing trend for the magnitude of the effect from speech perception to speech production. Words and nonwords were expected to respond to tDCS stimulation in opposite directions, much like the endpoints of the speech perception to speech production range of tasks used in this study. Words were considered less relevant for the LIFG than nonwords were. Predictions on the behavioural effects of tDCS stimulation for words were the same as those made for the CP task. Predictions for nonwords matched those made for WN.

The dual-polarity framework does not take into account the potential differential effects of task load and task-induced neural activity to make predictions. Therefore, there was a single prediction, rather than a range of possibilities, for each polarity of tDCS in this framework. Cathodal stimulation of an area considered involved with the task was expected to worsen

performance, for all tasks, and for both words and nonwords, whilst anodal stimulation was expected to improve performance for all tasks and both word types. Finally, the inhibitory framework appears suitable to explain mechanisms of word selection, which are particularly relevant for the task of LD. Word selection may be assumed, on one hand, to predominantly rely on inhibitory synapses to suppress activated competing non-target words. Anodal stimulation in this case should facilitate word processing by enhancing the LIFG ability to inhibit inappropriate words. Cathodal tDCS, in turn, should decrease the inhibitory function and weaken suppression of non-target words. The effect of tDCS over inhibitory neurons for nonwords should have the reverse pattern. Alternatively, one could consider that word selection is accomplished by a careful balance between inhibitory and excitatory synapses that direct current stimulation could modify. For example, if competing non-target words were in a state of hyperexcitation then cathodal stimulation would have the effect of decreasing such hyperexcitation, facilitating word selection. Anodal stimulation might induce a similar outcome by increasing the activity of inhibitory synapses.

5.4.1 CP

Both anodal tDCS and cathodal tDCS of the LIFG caused a behavioural performance improvement in the CP task with decreased reaction times. Such an outcome is inconsistent with the dual-polarity framework, where cathodal stimulation is always expected to decrease performance. It is also inconsistent with the inhibitory framework whereby differential outcomes would be expected between anodal and cathodal tDCS. However, this result does fit the multi-node framework, corroborating the assumption that the LIFG is a network node of low relevance for the task (Lee et al., 2012; Rogers et al., 2014; Smalle et al., 2015; Watkins & Paus, 2004). In particular, the improved behavioural performance observed in the data following cathodal tDCS supports the

concept of compensation by more relevant nodes of the language processing network. Such cathodal tDCS-induced improvement indicates a level of compensation strong enough to go beyond the level of only cancelling out the effect of the decrease in performance that cathodal stimulation might be expected to induce. The effect of improvement in performance caused by anodal stimulation also matches the predictions of the multi-node and dual-polarity frameworks.

For the accuracy results, anodal stimulation of the LIFG led to a decrease that was unexpected under both the multi-node and the dual-polarity frameworks. However, this outcome is likely due to a speed-accuracy trade-off and is consistent with the task instructions, which prioritised speed over accuracy (Standage et al., 2014). That is, once time to accomplish the task improved, accuracy scores were very likely to respond in the opposite direction. The different effects of anodal and cathodal stimulation on accuracy (decrease and null effect, respectively) whilst their effect on speed was the same (improvement) could be justified by the assumption that cathodal stimulation of the LIFG during CP induced some degree of compensation by more relevant nodes of the same network. Such compensation was only enough to cancel out the effect of the decrease of performance in the LIFG. However, since a non-significant result brings insufficient evidence to disambiguate between lack of statistical power to detect a small effect or absence of an effect, no definitive conclusions can be drawn from this result. Anodal stimulation on the other hand was not expected to induce any compensation, and thereby the decrease in accuracy caused by the speed-accuracy trade-off could be seen more clearly.

Outcomes of anodal tDCS and cathodal tDCS of the LIFG for latency and accuracy show a trend where the effect of cathodal stimulation is stronger than that induced by anodal stimulation. This may be due to which network nodes are involved in the task. Cathodal stimulation of a node of low relevance, such as the LIFG in CP, would induce compensatory excitation of other network

nodes of higher relevance. Anodal stimulation of the LIFG, on the other hand, would directly induce excitation in the node itself.

5.4.2 LD

Results for both reaction times and accuracy in LD did not reach significance. However, trends in the data, as well as the separate analysis where words are compared to nonwords (section 5.4.4), hint at possible underlying processing mechanisms. In particular, the null results observed here might be an effect of averaging over words and nonwords, whose pattern of response to tDCS go in opposite directions (see section 5.4.4).

The null results measured for LD were unexpected under the dual-polarity framework. Here anodal tDCS should have improved performance and cathodal tDCS decreased performance. It is also inconsistent with the inhibitory framework that considers inhibitory functions to rely predominantly on inhibitory synapses, and would predict a reverse pattern of results. The multi-node framework, on the other hand, may offer at least a partial account. Performance decrease induced by cathodal stimulation of a network node of low relevance for the task, as the LIFG is assumed to be for LD (Carreiras et al., 2007; Deng et al. 2012), was expected to be compensated by other networks nodes of higher relevance. An apparently null effect of stimulation was a possible result arising from network compensation that was only sufficient to cancel out the effect of local node decrease. Note that, in comparison to CP, the LIFG was assumed to be a node of higher relevance for LD, thereby having a comparatively smaller room for compensation. A null result obtained for LD following cathodal stimulation is therefore plausible. On the other hand, with the same logic, anodal stimulation of the LIFG was expected to improve performance more for LD than for CP given that the effects of anodal tDCS are a positive function of task-induced

neural activity (Fritsch et al., 2010; Hussey et al., 2015; Miniussi et al., 2013; Pope et al., 2015). The apparent null effect of anodal stimulation in the LD task is therefore weaker than expected, and might indicate that the assumed relevance of the LIFG in LD is incorrect. It may be that other, perhaps anterior, brain areas (Carreiras et al., 2007) share similar relevance.

5.4.3 WN

Improved behavioural performance (decreased reaction times) was observed in WN following both anodal tDCS and cathodal tDCS. Taken together, this is inconsistent with the dual-polarity framework, where cathodal stimulation is always expected to decrease performance, with the multi-nodal framework for the cathodal stimulation if the target is considered to be a relevant node for the task at hand and with the inhibitory framework which focus on inhibitory synapses only, whereby differential outcomes between the stimulation polarities would be expected.

The improved performance in WN induced by anodal tDCS fits both the multi-node and the dual-polarity frameworks. The LIFG is known to be of high relevance for speech production (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011), and therefore the task-induced neural activity was assumed to be high enough for tDCS to have an effect on behaviour. The effect of cathodal tDCS, on the other hand, was unexpected under the multi-node framework. Increased performance following cathodal tDCS is a possible outcome under the multi-node framework, provided that satisfactory compensation has taken place. However, the LIFG was assumed to be a network node of high relevance for speech production, and therefore compensation by less relevant nodes was expected to fail, leading to an inevitable decrease in performance. The improved performance under cathodal stimulation observed in these data, therefore, indicates that

some degree of satisfactory compensation of the LIFG by other relevant nodes of the language network may have occurred.

These results in WN, where both anodal and cathodal stimulation improve performance, appear to better fit an inhibitory framework that views inhibitory functions as a result of a precise balance between excitatory and inhibitory synapses. Direct current stimulation would have an effect on either inhibitory or excitatory synapses as appropriate to ensure satisfactory accomplishment of the task. Cathodal stimulation might have had a dampening effect on excitatory synapses underlying activation of non-target words, whilst anodal stimulation might have had an effect on inhibitory synapses, leading to a more efficient suppression of non-target competing words. Both mechanisms could lead to a beneficial effect on performance.

5.4.4 Words versus nonwords comparison

The results showed that words and nonwords differentially modulated the effects of anodal tDCS and cathodal tDCS on behavioural performance. Cathodal tDCS produced a significant improvement for words in the WN task, whilst nonwords under the same polarity had non-significant results. This corresponds to the predictions of the multi-node framework, where the detrimental effect of cathodal on performance should be larger for nodes to which the task load is higher. However, for all three frameworks the findings in the WN and in the LD tasks diverged from predictions to some extent.

Inconsistent results to the dual-polarity framework occurred whenever cathodal stimulation caused improved performance or an apparent null effect, since a decrease was expected. Here, for example, cathodal stimulation improved performance for words in the WN task, an unexpected finding for this framework. Inconsistent results to the approach of the inhibitory framework that

considers that inhibitory functions rely primarily on the role of inhibitory synapses were apparent whenever anodal and cathodal stimulation produced similar results, such here for both words and nonwords in WN. Inconsistent results to the multi-node framework are shown by a reverse effect of stimulation for most of the predictions based on task load. Task-induced neural activity was assumed to be higher for nonwords than for words, since the former is thought to be more demanding for the LIFG (Heim et al., 2005; Nosarti et al., 2010; Xiao et al., 2005). Therefore, anodal tDCS was expected to benefit performance more in processing of nonwords than in processing words, whilst compensation of the detrimental effect of cathodal tDCS should happen more satisfactorily for words. However, most findings exhibited the opposite pattern. For example, in LD anodal tDCS significantly decreased reaction times more for words than for nonwords. Results of this study also showed a trend where cathodal stimulation decreased reaction times (improved performance) of nonwords more than anodal stimulation did, when some level of performance decrease was expected. In the WN task, anodal tDCS significantly improved performance for words, while nonwords had a non-significant effect in the same direction under the same stimulation polarity.

It is perhaps worth noting that the particular profile of responses to tDCS observed in the LD task can be satisfactorily accounted for by the multiple read-out model of orthographic processing in visual word recognition (Grainger & Jacobs, 1996). In this model, judgment of a stimulus as being either a word or a nonword is dependent on a participant-specific covert time limit for the search of the item in the internal lexicon among competing non-target activated words. If the word is identified in the lexicon before the time limit expires, the decision is for word. But if the time limit expires before the item can be found, the decision is for nonword. Predictions of the effects of tDCS considering this model were that anodal would increase the time limit, so that more

words could be more successful retrieved before the expiry of the time limit forced a nonword decision. Cathodal would decrease the time limit, and therefore more decisions for nonword would probably be made. The results of this study are consistent with these predictions. Anodal tDCS caused reaction times to decrease for words and to increase for nonwords, as can be seen in Figure 4. Since time to decide for nonwords was much longer, decisions for words could also be done more efficiently, with time enough to meet the required inter-lexical criteria. Figure 4 also depicts a trend for cathodal tDCS, where decisions for nonword appear to be faster than decisions for word. In line with these findings, Figure 3 shows a trend for the effects of tDCS on accuracy in LD where cathodal tDCS decreases performance, potentially due to the higher time constraint for word identification in the lexicon induced by this polarity of stimulation.

In general it may be that the comparison of words and nonwords appears to be better explained by nuances of the inhibitory framework, which predicts different results for the WN and the LD task. The profile of responses to tDCS observed in the WN task is consistent with the idea that inhibitory functions rely on the right balance between excitatory and inhibitory synapses, and that tDCS can have an effect on either as appropriate. This accounts for the improved performance induced by both anodal and cathodal stimulations. The profile of responses also reveals how efficient this attempt to reach the right balance can be depending on the stimulus type. Overall, processing of words significantly improved under tDCS, whilst processing of nonwords showed non-significant results. This is probably because nonwords are processed similarly to non-target competing words, since they cannot be found in the lexicon. Therefore, tDCS-induced enhancement of non-target suppression benefits the processing of words, but worsens the processing of nonwords.

CHAPTER 6:

TASK LOAD MODULATION OF THE EFFECTS OF TDCS OVER THE LSTG ON BEHAVIOUR FOR PHONOLOGICAL PROCESSING IN HEALTHY YOUNG ADULTS

6.1 INTRODUCTION

In this chapter, the second behavioural tDCS study is reported. This study had the same design as that described in chapter 5, but with a different target of tDCS stimulation: the LSTG. The aim of this study was to investigate the task load modulation of the effects of anodal tDCS and cathodal tDCS over the LSTG on behavioural performance for tasks that involved phonological processing in healthy young adults. I used the CP, the LD and the WN tasks, which were representative of the range from speech perception to speech production. These tasks were assumed to decreasingly engage the LSTG. Findings were therefore expected to reverse the pattern of findings of the study reported in chapter 5 where the LIFG was the target of stimulation (c.f. Figure 1 in chapter 3 for an overview of predictions on task load modulation of the effects of tDCS over the LSTG).

6.1.1 CP

The CP was used as a prototypical speech perception task. The LSTG is considered to be a highly relevant region for the processing of linguistic auditory information (Chang et al., 2010; Leonard & Chang, 2014). CP was therefore expected to engage the target the most (Lee et al., 2012; Liebenthal et al., 2013) compared to the other tasks selected for this study. In other words, CP was expected to have the most efficient functional targeting, because the LSTG was a node of high relevance for the task. Predictions for the effects of stimulation were that anodal tDCS over the LSTG would improve performance in CP, because facilitation was assumed to have a direct relationship with task load, which was high. Cathodal stimulation should dampen performance, since the downregulation of a node of high relevance for the task was expected to be robust, as well as the attempt of compensation by other nodes, inefficient.

6.1.2 LD

A LD task was chosen as an intermediate task in the range from speech perception to speech production. This is because this task presents some features of both ends of the range, but not the most prototypical, such as overt articulation of the speech production end. Particularly, as alluded to in chapter 5, the lack of overt articulation, which is one of the most demanding features in speech production (Fiez et al., 1995), would suggest that LD is more similar to a speech perception task than to a speech production task. Therefore, the LSTG was considered to be a network node of high relevance for LD, although of smaller relevance than for the prototypical speech perception task of CP. The functional targeting was assumed to be efficient, although less efficient than for CP. Predictions for the effects of tDCS on performance were therefore similar to those for the CP task. Anodal tDCS of the LSTG was expected to improve performance, since the level of neuronal engagement during the stimulation would be high. However, the improvement could appear as a null result, especially if the neuronal engagement were lower than that expected for CP. Cathodal stimulation was expected to decrease performance, because compensation of a relevant node by less relevant nodes was likely to be insufficient to avoid performance to deteriorate. However, since the LSTG node is less important for LD than it is assumed to be for CP, compensation could be more efficient. Behavioural apparent null result of stimulation or even enhanced performance were possible outcomes.

6.1.3 WN

WN was used as a prototypical task of speech production. This task was expected to engage the LSTG the least compared to the other tasks in the range of speech perception to speech production used in this study. This is because the LSTG is more strongly associated with speech

perception (Chang et al., 2010; Leonard & Chang, 2014), whilst the LIFG is more strongly associated with speech production instead (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011, Liakakis et al., 2011). The functional targeting was assumed to be the least efficient, since the LSTG was considered to be a node of low relevance for the task. Predictions for the effects of tDCS on behaviour for WN were that anodal stimulation would induce improvement in performance. However, since the target was a node of low relevance for the task, the level of neuronal engagement during stimulation would consequently be low, which could result in modest improvement or apparent null effect of anodal tDCS. Cathodal tDCS of the LSTG was expected to induce some level of compensation by other nodes which were more relevant for the task. Consequently, improved performance should be observed if compensation went beyond cancelling out the effect of cathodal tDCS downregulation; an apparent null result should be observed otherwise.

6.1.4 Words and nonwords

Words were assumed to rely more on the LSTG than nonwords (Okada & Hickok, 2006a), reversing the pattern observed for words and nonwords for the LIFG (Heim et al., 2005; Nosarti et al., 2010; Xiao et al., 2005). As alluded to in chapter 5, this is generally thought to be the case because words are considered to rely primarily on a lexical-dependent pathway of processing, whilst nonwords would rely more on a phonological-dependent pathway (Binder et al., 2003; Fiebach et al., 2002; Forster & Chambers, 1973; Levy et al., 2009; Marshall & Newcombe, 1973; Patterson & Shewell, 1987). Some also defend that differences in processing of words and nonwords are actually due to a frequency effect; nonwords would be the most infrequent stimuli, and therefore the most demanding of a phonological or sublexical-dependent pathway (Nosarti et

al., 2010). Given these assumptions, the LSTG was considered to be a network node of higher relevance for words than for nonwords. The functional targeting was therefore assumed to be more efficient when words were presented during tDCS of the LSTG than when nonwords were presented.

Predictions for the effects of tDCS on performance were that anodal tDCS would improve performance for both stimulus types, but more for words. Improvement would depend on the level of neuronal engagement during the stimulation, with an apparent null result or a significant enhanced performance as possible outcomes. Cathodal tDCS was expected to decrease performance for both stimulus types, but more for words. Since the LSTG is considered to be a node of higher relevance for words than for nonwords, compensation of cathodal tDCS downregulation by other nodes was expected to be more successful for nonwords. Depending on the degree of compensation achieved, possible outcomes were deterioration in performance in case of insufficient compensation, apparent null result of stimulation if compensation was only enough to cancel out the downregulation or enhanced performance if compensation was sufficiently strong.

6.2 METHODS

Methods are as described in chapter 4 Methods. For the current study, 60 young healthy adults (mean age: 19.02 years, SD: 1.19, 54 females) who met the inclusion criteria described in chapter 4 were included in the sample. All three experiments (CP, LD and WN) were performed by all participants in the sample (n = 60), in counterbalanced order, as an experimental design study with a within-subject factor of task, a within-subject factor of run (baseline and online) and a between-subject factor of tDCS stimulation (anodal, cathodal and sham, for which the sample split

in subgroups of 20 participants each). This sample of participants was unique to the study reported in the current chapter.

6.3 RESULTS

The first analysis was run with the combined reaction time data of all tasks to investigate the claim that task load modulates the effect of tDCS on performance. Further analyses were then conducted by task. Analyses are presented in the order of the speech perception to speech production range, i.e., first CP, then LD and WN. For the last two tasks analysis of the effects of tDCS for words and nonwords was also carried out and is presented in the last subsection.

In the first analysis reaction time data of all tasks (CP, LD and WN) were combined and the effects of the factors of task, brain stimulation and run within session were investigated. A 3 x 3 x 2 (task x brain stimulation x run) linear mixed effects model was fitted to the data and significant interactions of task and brain stimulation ($F(4,51276) = 97.48$, $p < 0.001$) (Figure 1), task and run ($F(2,51276) = 11.89$, $p < 0.001$), brain stimulation and run ($F(2,51276) = 6.34$, $p < 0.01$) and task, brain stimulation and run ($F(4,51276) = 6.42$, $p < 0.001$) arose.

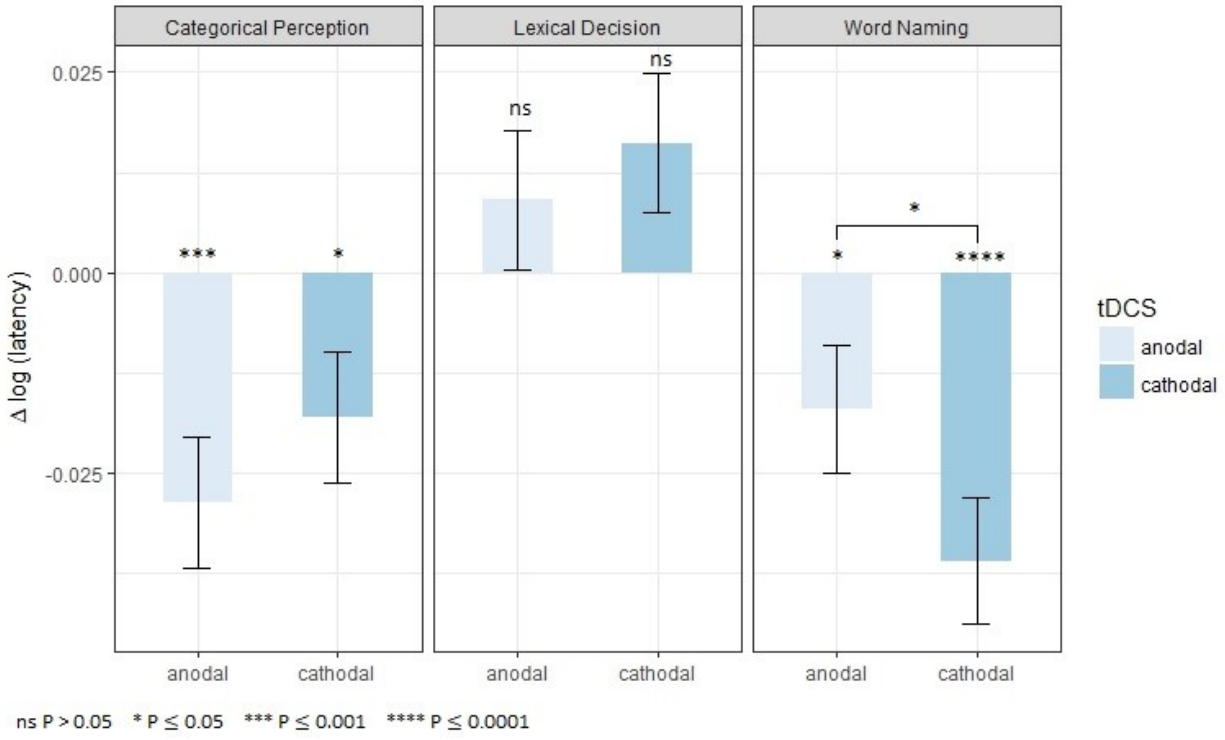

Figure 1. Delta latency per task and tDCS polarity. The x-axis displays the tDCS stimulation polarities compared to sham. The y-axis displays the contrast estimates (logarithmic scale). Error bars represent the contrast estimate ± the pooled standard error.

6.3.1 CP

6.3.1.1 Latency

Latency outcomes in CP suggest that tDCS had an effect on performance for this task. The 3 x 2 (brain stimulation x run) linear mixed model fitted to the reaction time data showed a significant brain stimulation by run interaction ($F(2,17427) = 8.01$, $p < 0.001$).

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) showed that both anodal tDCS ($t(17427) = -3.96$, $p < 0.001$) and cathodal tDCS ($t(17427) = -2.51$, $p = 0.01$) induced a significant decrease in reaction times, with a stronger effect for the former (Figure 1, panel 1, and Table 1).

Table 1. Contrast analyses for latency of CP

Contrast	Estimate	SE	df	*t*	*p*
Anodal vs Sham	-0.03	0.01	17427	-3.96	< 0.001
Cathodal vs Sham	-0.02	0.01	17427	-2.51	0.02
Anodal vs Cathodal	-0.01	0.01	17427	-1.44	0.15

6.3.1.2 Accuracy

Accuracy outcomes suggest that tDCS stimulation of the LSTG has no effect on the consistency with which participants disambiguate sounds from a continuum intro well-defined phonemic categories. The 3 x 2 (brain stimulation x run) linear mixed model fitted to the accuracy data showed no significant effect of the direct current. Post hoc contrast analyses (Benjamini-Hochberg corrected) confirmed that neither anodal tDCS nor cathodal tDCS had a significant effect on accuracy for the CP task (Figure 2 and Table 2).

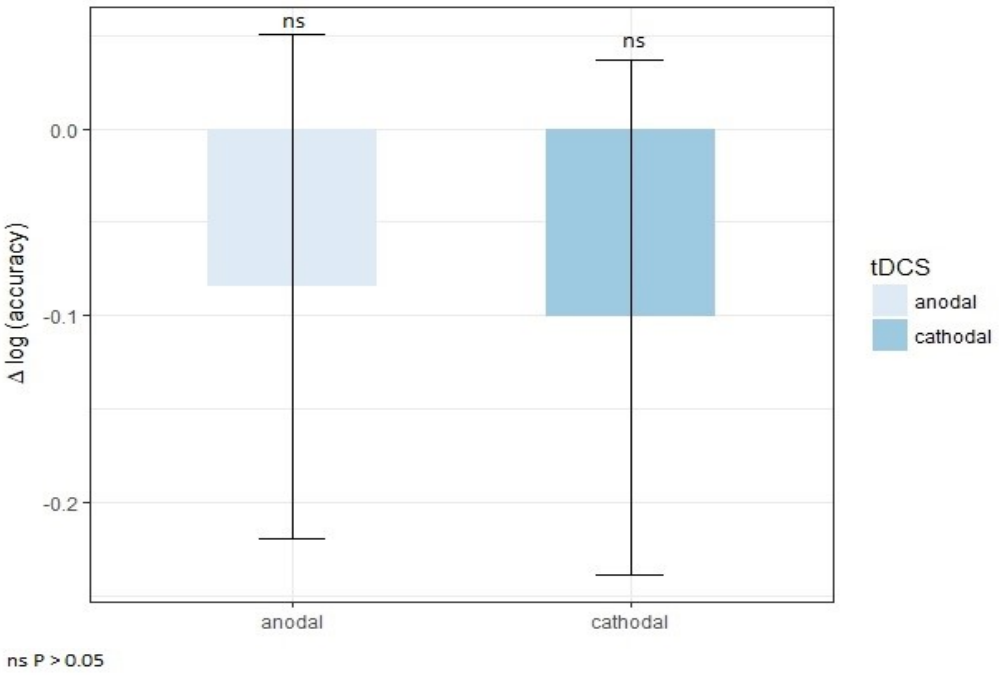

Figure 2. Delta accuracy in CP per tDCS polarity. The x-axis displays the tDCS stimulation polarities vs sham. The y-axis displays the contrast estimates (logarithmic scale). Error bars represent the contrast estimate ± the pooled standard error.

Table 2. Contrast analyses for accuracy of CP

Contrast	Estimate	SE	df	*t*	*p*
Anodal vs Sham	-0.08	0.14	51	-0.62	0.80
Cathodal vs Sham	-0.10	0.14	51	-0.73	0.80
Anodal vs Cathodal	0.02	0.14	51	0.12	0.90

6.3.2 LD

6.3.2.1 Latency

Latency outcomes suggest that tDCS of the LSTG has no effect on behavioural performance in LD. A 3 x 2 (brain stimulation x run) linear mixed model fitted to the reaction time data showed no significant effect of the direct current for this task. Post hoc contrast analyses (Benjamini-Hochberg corrected) corroborated this finding, showing that neither anodal tDCS nor cathodal tDCS had a significant effect on reaction times for the LD task (Figure 1, panel 2, and Table 3).

Table 3. Contrast analyses for latency of LD

Contrast	Estimate	SE	df	*t*	*p*
Anodal vs Sham	0.01	0.01	15236	0.79	0.43
Cathodal vs Sham	0.01	0.01	15236	1.78	0.22
Anodal vs Cathodal	-0.01	0.01	15236	-1.00	0.43

6.3.2.2 Accuracy

Results suggest that tDCS of the LSTG has no effect on accuracy in the LD task. The 3 x 2 (brain stimulation x run) mixed effects logistic regression fitted to the accuracy data with reaction times included as a covariate showed no significant results. Post-hoc contrast analyses (Benjamini-Hochberg corrected) similarly showed non-significant effects of anodal tDCS and cathodal tDCS (Figure 3 and Table 4).

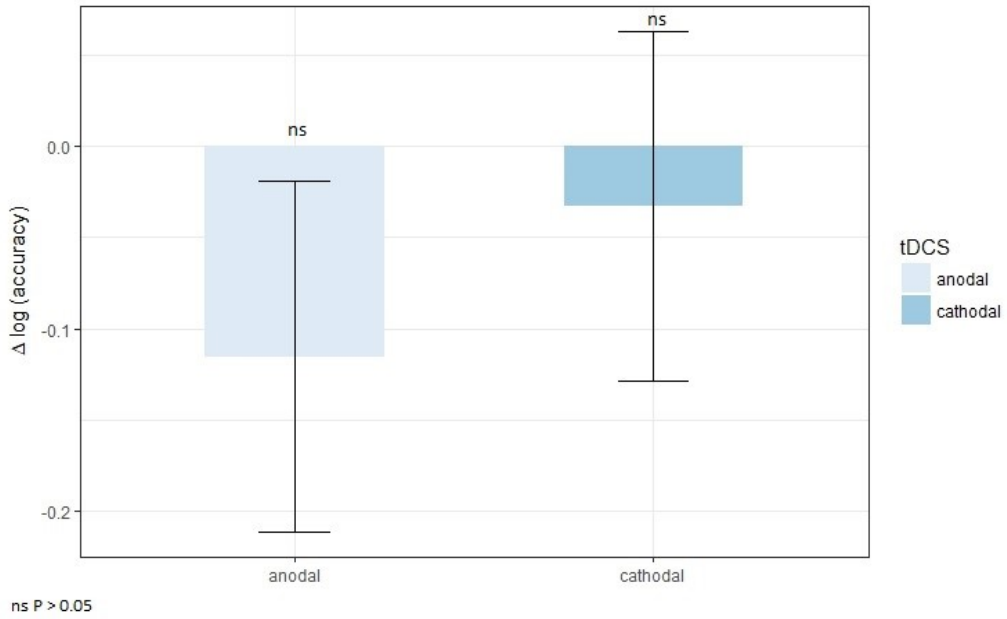

Figure 3. Delta accuracy in the LD task per tDCS polarity. The x-axis displays the tDCS stimulation polarities. The y-axis displays the contrast estimates on logit scale. Error bars represent the contrast estimate ± the pooled standard error.

Table 4. Contrast analyses for accuracy of LD

Contrast	Estimate	SE	df	*z*	*p*
Anodal vs Sham	-0.12	0.10	NA	-1.20	0.58
Cathodal vs Sham	-0.03	0.10	NA	-0.34	0.73
Anodal vs Cathodal	-0.08	0.10	NA	-0.86	0.58

6.3.3 WN

Latency outcomes in the WN task suggest that tDCS of the LSTG modulates performance. The 3 x 2 (brain stimulation x run) linear mixed model fitted to the reaction time data showed a significant interaction of brain stimulation by run ($F(2,18499) = 11.61$, $p < 0.001$).

Post-hoc contrast analyses (Benjamini-Hochberg corrected) showed significant decrease in reaction times (improved performance) for both anodal tDCS ($t(18499) = -2.38$, $p = 0.02$) and cathodal tDCS ($t(18499) = -4.82$, $p < 0.001$). Cathodal tDCS decreases reaction times significantly more than anodal tDCS ($t(18499) = -2.44$, $p = 0.02$) (Figure 1, panel 3, and Table 5).

Table 5. Contrast analyses for latency of WN

contrast	estimate	SE	df	t	p
Anodal vs Sham	-0.02	0.01	18499	-2.38	0.02
Cathodal vs Sham	-0.04	0.01	18499	-4.82	< 0.001
Anodal vs Cathodal	0.02	0.01	18499	2.44	0.02

6.3.4 Analysis of words and nonwords

The effect of stimulus type (words or nonwords) on behavioural responses to tDCS stimulation of the LSTG was analysed with a 2 x 2 x 3 x 2 (task x stimulus type x brain stimulation x run) linear mixed effects model fitted to the combined reaction time data of the LD and the WN tasks. The three-way interaction between stimulus type, brain stimulation and run was non-significant. Two 2 x 3 x 2 (stimulus type x brain stimulation x run) linear mixed effects models were also separately fitted to reaction data of each of these tasks. Similarly, the three-way interaction between stimulus type, brain stimulation and run was non-significant for both tasks (Figure 4). However, post-hoc contrast analyses revealed some significant effects of stimulus type and tDCS polarity for the LD and the WN tasks.

For the LD task, contrast analyses showed a significant increase in reaction times (decreased performance) for words caused by cathodal stimulation ($t(15230) = 2.80$, $p = 0.04$) (all contrasts are shown in Table 6).

For the WN task, contrast analyses showed a significant decrease in reaction times (improved performance) caused by cathodal stimulation for both words ($t(18493) = -3.20$, $p < 0.01$) and nonwords ($t(18493) = -3.71$, $p < 0.01$). Cathodal tDCS decreased reaction times for nonwords significantly more than anodal tDCS did ($t(18493) = -2.47$, $p = 0.04$) (all contrasts are shown in Table 7).

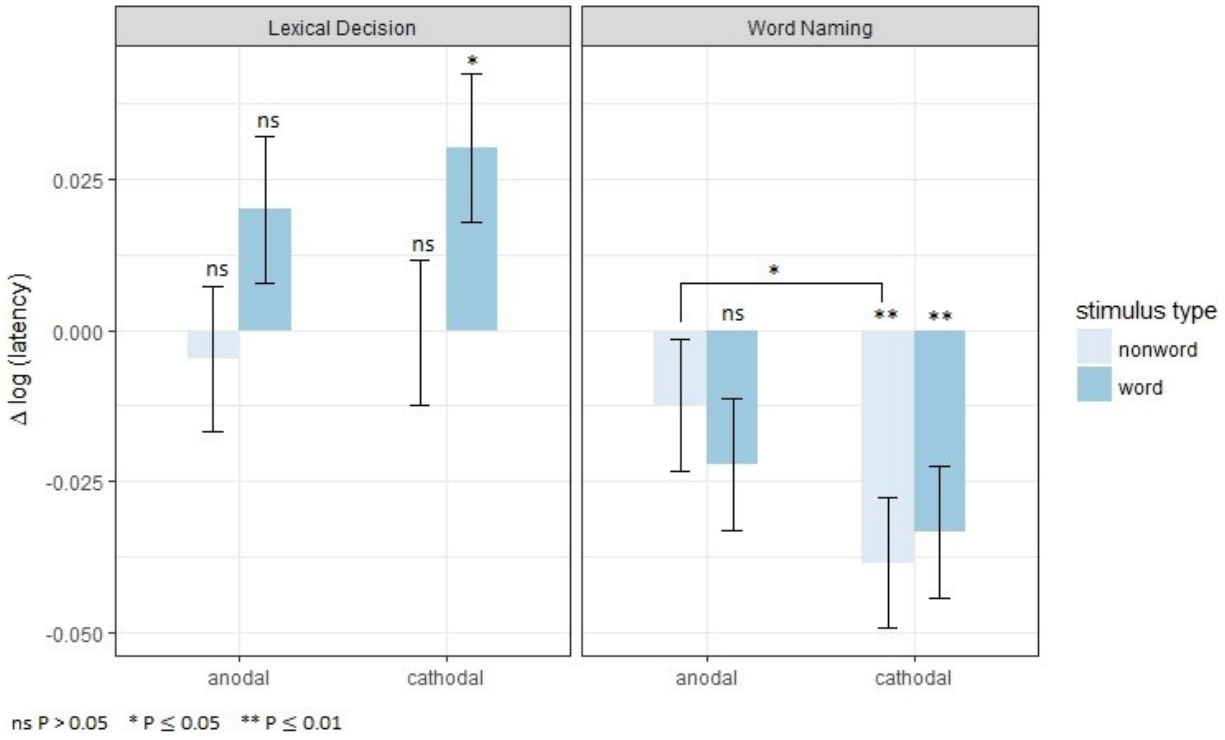

Figure 4. Delta latency for words and nonwords per task and tDCS polarity. The x-axis displays the tDCS stimulation polarities vs sham. The y-axis displays the contrast estimates (logarithmic scale). Error bars represent the contrast estimate ± the pooled standard error.

Table 6. Contrast analyses for latency of words and nonwords in LD

Contrast	Estimate	SE	df	*t*	*p*
Word: Anodal vs Sham	0.02	0.01	15230	1.59	0.30
Word: Cathodal vs Sham	0.03	0.01	15230	2.80	0.04
Word: Anodal vs Cathodal	-0.01	0.01	15230	-1.22	0.36
Nonword: Anodal vs Sham	0.00	0.01	15230	-0.44	0.85
Nonword: Cathodal vs Sham	0.00	0.01	15230	-0.25	0.85
Nonword: Anodal vs Cathodal	0.00	0.01	15230	-0.20	0.85
Word vs Nonword: Anodal vs Sham	0.02	0.02	15230	1.45	0.30
Word vs Nonword: Cathodal vs Sham	0.03	0.02	15230	2.17	0.12

Table 7. Contrast analyses for latency of words and nonwords in WN

Contrast	Estimate	SE	df	*t*	*p*
Word: Anodal vs Sham	-0.02	0.01	18493	-2.16	0.06
Word: Cathodal vs Sham	-0.03	0.01	18493	-3.20	< 0.01
Word: Anodal vs Cathodal	0.01	0.01	18493	1.04	0.40
Nonword: Anodal vs Sham	-0.01	0.01	18493	-1.24	0.34
Nonword: Cathodal vs Sham	-0.04	0.01	18493	-3.71	< 0.01
Nonword: Anodal vs Cathodal	0.03	0.01	18493	2.47	0.04
Word vs Nonword: Anodal vs Sham	-0.01	0.01	18493	-0.66	0.59
Word vs Nonword: Cathodal vs Sham	0.01	0.01	18493	0.36	0.72

6.4 DISCUSSION

Findings from this second behavioural experiment also suggest that consideration of the factors of task load and the network structure that underlies cognitive functions helps to predict the effects of tDCS on behaviour. I particularly have demonstrated that modulation of the relevance of the task for the target LSTG, which is a node in a network that also includes the LIFG for the processing of CP, LD and WN, had differential effects for the behavioural outcomes induced by the direct current. In this section, I discuss the suitability of the multi-node framework, which takes task load and network structure of cognitive functions into account, and of the dual polarity framework to interpret tDCS outcomes in light of the findings of the current study. The inhibitory framework was considered to be unsuitable, because the role of the LSTG in the experimental tasks is not assumed to involve inhibitory functions. Therefore, the inhibitory framework will not be further discussed.

According to the multi-node framework, effects of tDCS on behaviour are modulated by the relevance of the task for the area target of stimulation (task load). In the current study, CP was a prototypical speech perception task, and therefore was considered to be the task that engaged the LSTG the most. The LD task, next in the range, was also considered of high relevance for the

LSTG, but somewhat of smaller relevance than the CP task. The WN task, on the speech production endpoint of the range, was considered to have the lowest relevance for the LSTG. The LSTG was also assumed to be more relevant for the stimulus type word than for the stimulus type nonword. Predictions for the effects of tDCS were that anodal tDCS of the LSTG would improve performance for all the tasks, but the degree of improvement would depend on the level of task-induced neuronal engagement of the target. Therefore, improvement was expected to be larger for the CP task than for the LD or WN, and larger for words than for nonwords. In all cases, outcomes could vary from an apparent null result of tDCS to a significant increased performance depending on the degree of current-induced improvement. Cathodal tDCS was expected to downregulate the target with outcomes varying from deteriorated performance to improved performance (if successful compensation took place). Deterioration should occur as a direct function of task load, whilst compensation was expected to be negatively related to task load. The more important the node was considered to be for the task or stimulus type, the more detrimental the downregulation was expected to be and less successful the compensation. Therefore, a larger decrease in performance was expected for CP than for LD or WN. The LSTG was considered to have more room for successful compensation for WN than for the other tasks. Similarly, for words a decreased performance was expected, whilst for nonwords increased performance due to satisfactory compensation was comparatively more likely.

For the dual-polarity framework, task load has no relevant modulatory influence on the effects of tDCS on behavioural performance. Rather, tDCS has a single predicted outcome per tDCS polarity. Anodal stimulation should improve performance in all cases, whilst cathodal tDCS should decrease performance. Therefore, according to this framework, anodal tDCS of the LSTG

should result in enhanced performance for all the tasks and stimulus types used in this study, whilst cathodal should induce deteriorated performance.

6.4.1 CP

Both anodal tDCS and cathodal tDCS of the LSTG caused significant improvement in CP performance with decrease in reaction times. This contradicts predictions of the dual polarity framework, for which cathodal stimulation should cause performance to deteriorate. However, the multi-node framework can accommodate these results better. In Figure 1, panel 1, and in Table 1, it can be noticed that anodal tDCS of the LSTG decreased reaction times to a greater degree than cathodal tDCS of the LSTG did. I recall that the LSTG was assumed to be a network node of high relevance for CP (Lee et al., 2012; Leonard & Chang, 2011; Liebenthal et al., 2013). Therefore, the LSTG was expected to largely benefit from anodal tDCS-induced excitation showing improved performance, as it did. Under cathodal tDCS, the LSTG should show decrease in performance, because compensation by less relevant network nodes was expected to be inefficient. However, findings showed improved performance, suggesting that compensation of a node of high relevance for the task was much more efficient than expected. Nonetheless, the improvement caused by cathodal stimulation was smaller than that caused by anodal stimulation. This difference between the two tDCS polarities suggests that cathodal tDCS downregulation took place, was compensated beyond the level of cancelling out its effects, but was not as efficient as to produce facilitatory effects as large as those induced by anodal tDCS.

The tDCS showed no significant effect on accuracy in CP, a result predicted neither by the dual polarity nor by the multi-node frameworks. However, as alluded to in chapter 5, this finding probably reveals a speed-accuracy trade-off that is consistent with the task instructions, which

prioritised speed over accuracy (Standage et al., 2014). Therefore, participants are likely to have focused on their speed performance more than on their accuracy performance, generating outcomes for reaction times and accuracy that were in opposite directions.

6.4.2 LD

Neither reaction times nor accuracy showed to be significantly modulated by tDCS in LD. This contradicts predictions based on the dual polarity framework, according to which anodal tDCS should improve performance and cathodal tDCS should decrease performance. The multi-node framework, on the other hand, can offer a better account for these results. The LSTG was assumed to be relevant for LD (Carreiras et al., 2007; Deng et al. 2012), but as a node of intermediate relevance compared to its role for CP or WN. LD was assumed to be rather shifted to the speech perception end of the range due to the lack of overt articulation. As a node of intermediate relevance for the task, it could be that the LSTG was not able to achieve sufficient task-induced neuronal activation to react to either anodal or cathodal tDCS with a significant response. However, the trend observed in the CP task where performance induced by cathodal stimulation is worse than that induced by anodal stimulation (see section 6.4.1) seems to also apply here, supporting the assumed shift of LD towards the speech perception end. Although the average result across stimulus types of words and nonwords is non-significant (Figure 1, panel 2), the trend reaches significance when stimulus types are separately analysed (see Figure 4, panel 1).

6.4.3 WN

Both anodal tDCS and cathodal tDCS of the LSTG caused performance to improve (with decreased reaction times) in the WN task. This contradicts the dual polarity prediction for cathodal

tDCS, according to which performance was due to decrease. However, the profile of responses is well accounted for by the multi-node framework. As can be seen in Figure 1, findings for the WN task presented the reverse pattern of findings for the CP task, with cathodal tDCS inducing better performance than anodal tDCS for WN. This is consistent with the positioning of CP and WN on opposite ends of the range from speech perception to speech production, and consequently with the different task loads that each of these tasks poses for the LSTG. The LSTG was assumed to be a node of comparatively lower relevance for WN than for CP. The WN would rely more strongly on the LIFG, canonically associated with articulatory planning and speech production (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011). As a node of low relevance for the task, the LSTG was expected to present modest improvement induced by anodal tDCS, with a significant effect or even an apparent null result as possible outcomes. Cathodal tDCS, on the other hand, was expected to induce satisfactory compensation by nodes which were more relevant to the task, with the likely outcome of a significantly large improvement in performance. These behavioural predictions were met by the findings in the WN task.

6.4.4 Words versus nonwords comparison

Findings suggest that effects of tDCS on behavioural performance are differentially modulated by stimulus type of words and nonwords. In the LD task, cathodal tDCS of the LSTG significantly decreased performance (increased reaction times) for words. This finding meets the dual polarity framework prediction for cathodal tDCS, where decreased performance was expected. In the WN task, cathodal tDCS of the LSTG significantly improved performance (decreased reaction times) of both words and nonwords, whilst anodal tDCS had no significant effect. The effect of cathodal tDCS on nonwords was significantly different from that of anodal tDCS on

nonwords. Cathodal tDCS-induced improvement in performance reverses the dual polarity prediction that determines decreased performance as the effect of this tDCS polarity.

The multi-node framework can offer a more comprehensive explanation for these findings, although still partial. The LSTG was assumed to be a node more relevant for words than for nonwords (Heim et al., 2005; Nosarti et al., 2010; Xiao et al., 2005). Therefore, cathodal tDCS of the LSTG was more likely to decrease performance for words, since compensation by less relevant nodes was expected to be unsatisfactory. On the other hand, nonwords were more likely to present improved performance or an apparent null result of stimulation, because satisfactory compensation by more relevant nodes was expected to take place. The cathodal tDCS-induced decrease in performance for words in the LD task meets this prediction. The null result observed for nonwords might be due to compensation that was only enough to cancel out the effect of downregulation.

I recall that the LSTG was considered to be a node of intermediate relevance for the LD task, and therefore was expected to have less room for compensation than in the case where the LSTG was a node of lower relevance, such as for the WN task. This difference in node relevance between tasks potentially explains the differences in the degree of responsiveness of words and nonwords to tDCS between the two tasks. For example, the significant improved performance induced by cathodal tDCS for nonwords in the WN task suggests that compensation of downregulation of the LSTG by more relevant nodes was more satisfactory than that in the LD task, which showed a null result (this is a tentative and theoretically motivated interpretation of a null result that should, nevertheless, be considered cautiously, since no definitive conclusions can be drawn from non-significant results). However, some degree of compensation seems to have happened also for words, whose performance improved under cathodal stimulation. This result was unexpected, but might be explained by the overall larger room for compensation into play due to

the task. On the other hand, the degree of improvement caused by anodal tDCS of a node of low relevance for the task was expected to be small, and this might explain the null results of anodal tDCS for words and nonwords in the WN task. In the case of the LD task, null effects of anodal tDCS might be due to the intermediate relevance that the LSTG has for the task. Because of that, the LSTG was expected to be less responsive to the direct current than it would be under a higher task load, such as in the CP task.

CHAPTER 7:

TASK LOAD MODULATION OF BRAIN ACTIVATION FOR PHONOLOGICAL PROCESSING IN HEALTHY YOUNG ADULTS, PWD AND PWA

7.1 INTRODUCTION

In this chapter, I investigated the baseline task load modulation of brain activation in PWD, PWA and healthy young adults. The same language tasks used in the behavioural studies were used for this fMRI study.

As discussed in chapter 3, phonological processing is a language function that is present in all the three experimental tasks, namely CP, LD and WN. These tasks represented a range from speech perception to speech production, and were chosen with the aim of covering both the speech perception and the speech production ends of phonological processing.

In terms of the underlying brain areas that subserve phonological processing during the performance of these tasks, two canonical regions were expected to be activated: the LIFG, associated with the production end of phonological processing, and the LSTG, associated with the perceptive end (Liebenthal et al., 2013; Saur, 2008). CP, LD and WN were expected to increasingly recruit and activate the LIFG, whilst decreasingly recruit and activate the LSTG. Similarly, for the LD and WN tasks, the stimulus type word was expected to depend more on the LSTG than on the LIFG, whilst the stimulus type nonword should show the reverse pattern (Binder et al., 2003; Fiebach et al., 2002; Forster & Chambers, 1973; Levy et al., 2009; Marshall & Newcombe, 1973; Patterson & Shewell, 1987).

For consistency with the fMRI studies of this thesis where tDCS stimulation was applied, the right homologues (RIFG and RSTG) of the two canonical regions of the dorsal pathway of phonological processing were also included in the ROI analyses reported in this chapter. In the tDCS studies and in the studies where participants had a phonological processing deficit, these two non-canonical regions were expected to play a complementary or compensatory role. In the baseline experiments, the burden of exogenous perturbation was absent. However, the inclusion of

the right homologues in the analyses would allow to investigate their role on phonological processing, that was assumed to be more onerous in cases of language disorders (Flöel et al., 2011; Waldie et al., 2013) and potentially also to be more onerous due to task difficulty to some degree (Gur et al., 2000).

7.2 METHODS

Methods are as described in chapter 4 with the following adjustments. Only run 1 (baseline) data were used, and therefore tDCS was not included as a factor in the statistical models. However, since for older participants baseline runs were not collected, data from their sham session was used instead. Pooled baseline data across young healthy participants from the studies where the LIFG (chapter 8) and the LSTG (chapter 9) were targeted formed the healthy young adult group in the current study (n = 40, mean age: 21.48 years, SD: 2.86, 17 females). Six PWD (mean age: 20 years, SD: 1.94, 3 females) and 2 PWA (JW – age: 51 years, female, and MB – age: 56 years, male) in the current study met the inclusion criteria described in chapter 4 and are the same PWD and PWA recruited, respectively, for the studies in chapters 10 and 11. All three experiments (CP, LD and WN) were performed by healthy young adults (n = 40), PWD (n = 6) and PWA (n = 2), in counterbalanced order across participants, with task as a within-subject factor. For healthy young adults, whole brain analyses and ROI analyses for each experiment had a within-subject design. For PWD, analyses were performed both within the group, with a within-subject design (ROI analyses and within group whole brain analyses) and between PWD and controls (whole brain analyses) with group as a between-subject factor (controls were the same healthy young adult group of the current study, n = 40). PWA were compared to controls (same healthy young adults, n = 40, plus 2 healthy older adults, age 65, female, and age 63, male) using whole brain analyses with

group as the between-subject factor. Due to the small sample size, ROI analyses were not performed for PWA.

PWD were recruited based on a self-reported formal diagnosis of developmental dyslexia. PWD's performance on cognitive tasks (on selected tasks from the WAIS IV battery, c.f. Chapter 4) and on reading tasks (TIWRE and TOWRE, c.f. Chapter 4) compared to performance of controls was consistent with the self-informed formal diagnosis. Unpaired t-tests showed no significant difference between PWD and controls on the cognitive tasks, as expected. However, PWD had significantly lower performance on the reading tasks than controls. This was particularly noticeable from their accuracy ($t(5.70) = -6.24$, $p < 0.001$) and reading speed ($t(39) = 3.49$, $p < 0.01$) performance on the task of phonemic decoding, which is highly demanding on phonological processing.

PWA with a frontal profile of aphasia were recruited on the basis of a clinical picture that showed difficulties in speech production with preserved speech comprehension caused by a stroke event on the left hemisphere. PWA gave a self-reported formal diagnosis of the stroke event without precise reference to the brain hemisphere or site. Stroke on the left hemisphere could be inferred for both PWA from their motor sequels, such as reduced arm and leg mobility, on the right side of the body. The T1 images of the PWA confirmed a brain injury on the frontal lobe in the left hemisphere that included the IFG. The clinical picture of aphasia with speech production difficulties characterised by the presence of phonological deficits and preserved comprehension was confirmed by the CAT battery for JW. JW performed above the cut-off score for healthy population in the language comprehension part of the test. A mild difficulty was observed in the expressive language part of the test, where JW performed below the cut-off score for healthy population in the repetition section. The decreased performance in repetition was particularly

noticeable in JW's performance on the repetition of nonwords, which is a task that strongly demands phonological processing. Participant MB was not available to perform the CAT assessment.

7.3 RESULTS

7.3.1 Whole brain analyses

Whole brain analyses were conducted with task, stimulus type (for the LD and WN tasks) and population as factors where appropriate. Overall, in healthy young adults and in PWD, tasks and stimulus types induced activation on the brain areas typically reported in the literature, including the LIFG and the LSTG (see Figures 1 through 10). The hypoactivation of the temporal lobe expected for PWD (Brunswick et al., 1999; Georgiewa et al., 1999; Hoeft et al., 2006; Ruff et al., 2003) was also observed, as can be appreciated by comparing the Figures of healthy young adults to those of PWD across tasks and stimulus types (Figures 1 and 2 for CP, 3 and 4 for LD, 5 and 6 for WN, 7 and 8 for words and nonwords in LD, 9 and 10 for words and nonwords in WN). Results for healthy young adults and PWD can be seen in Appendix 1. For PWA, significant brain activation was found across tasks and stimulus types for the contrast controls > PWA. These results are reported in the current chapter.

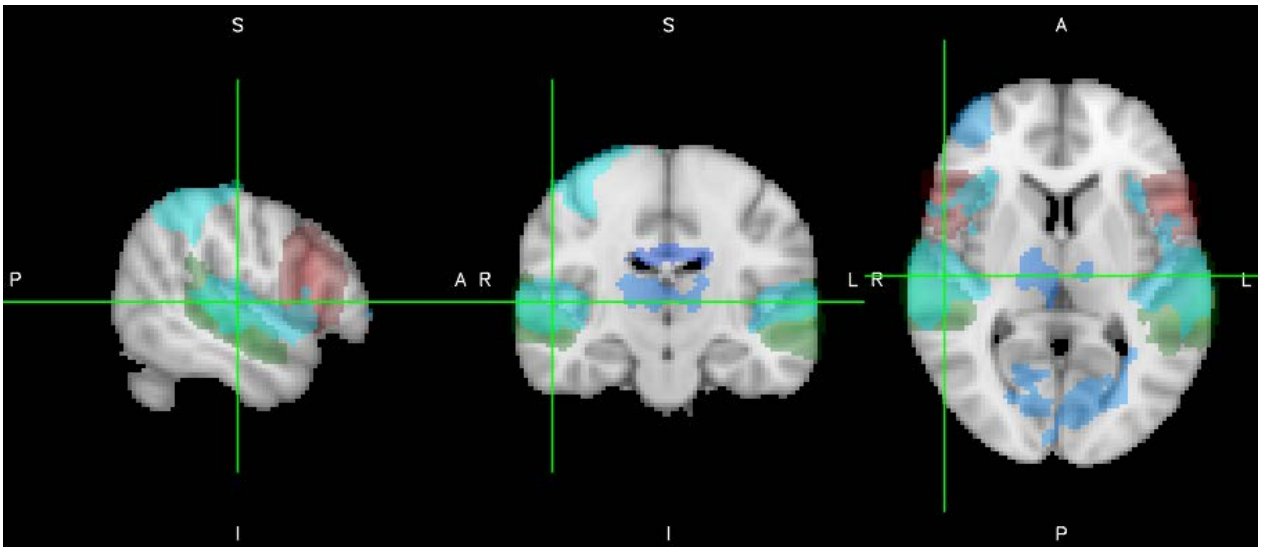

Figure 1. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast CP > rest in healthy young adults, represented in blue. Crosshair is on the highest cluster peak, the Right Heschl's Gyrus. Activated brain areas include some portion of the LIFG and RIFG, represented in transparent red, and some portion of the LSTG and RSTG, represented in transparent green.

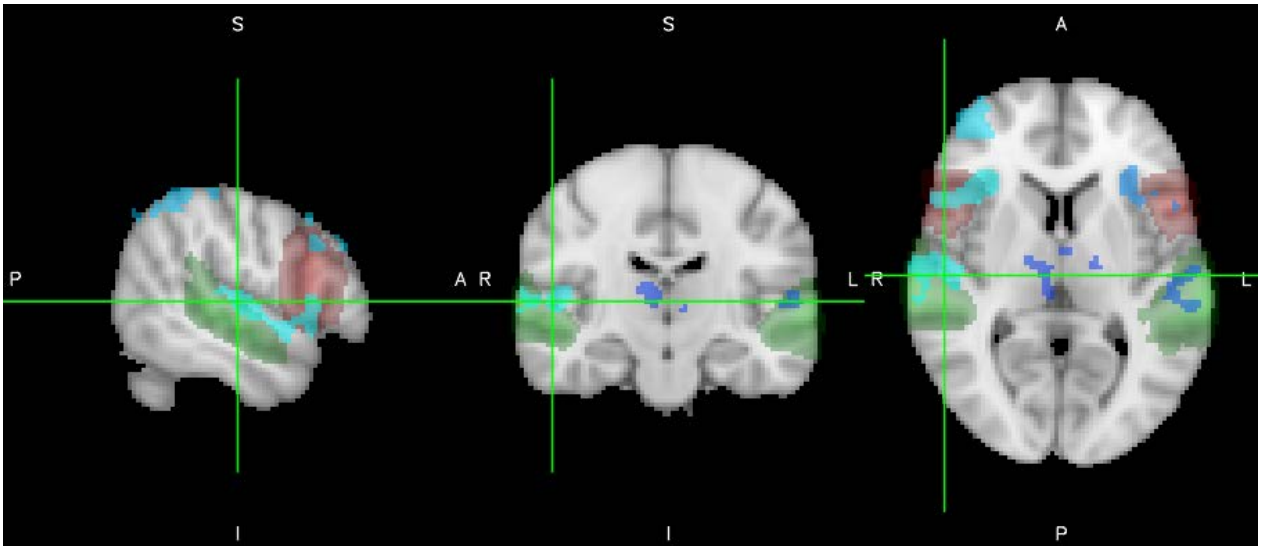

Figure 2. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast CP > rest in PWD, represented in blue. Crosshair is on the Right Heschl's Gyrus. Activated brain areas include some portion of the LIFG and RIFG, represented in transparent red, and some portion of the LSTG and RSTG, represented in transparent green.

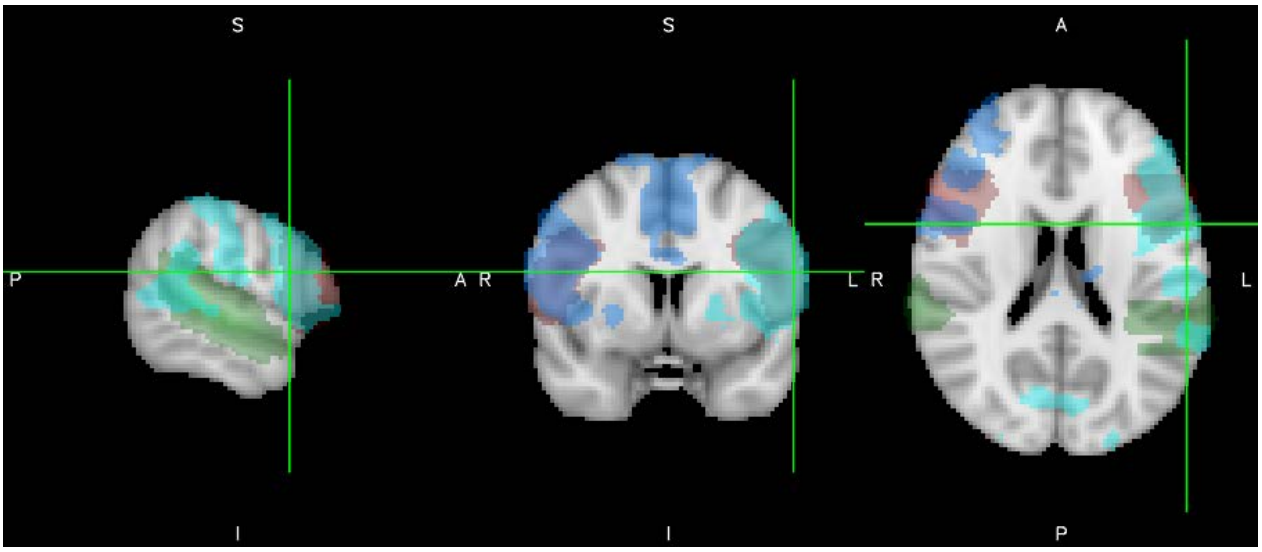

Figure 3. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast LD > rest in healthy young adults, represented in blue. Crosshair is on one of the highest cluster peaks, the Left Precentral Gyrus. Activated brain areas include some portion of the LIFG and RIFG, represented in transparent red, and some portion of the LSTG, represented in transparent green.

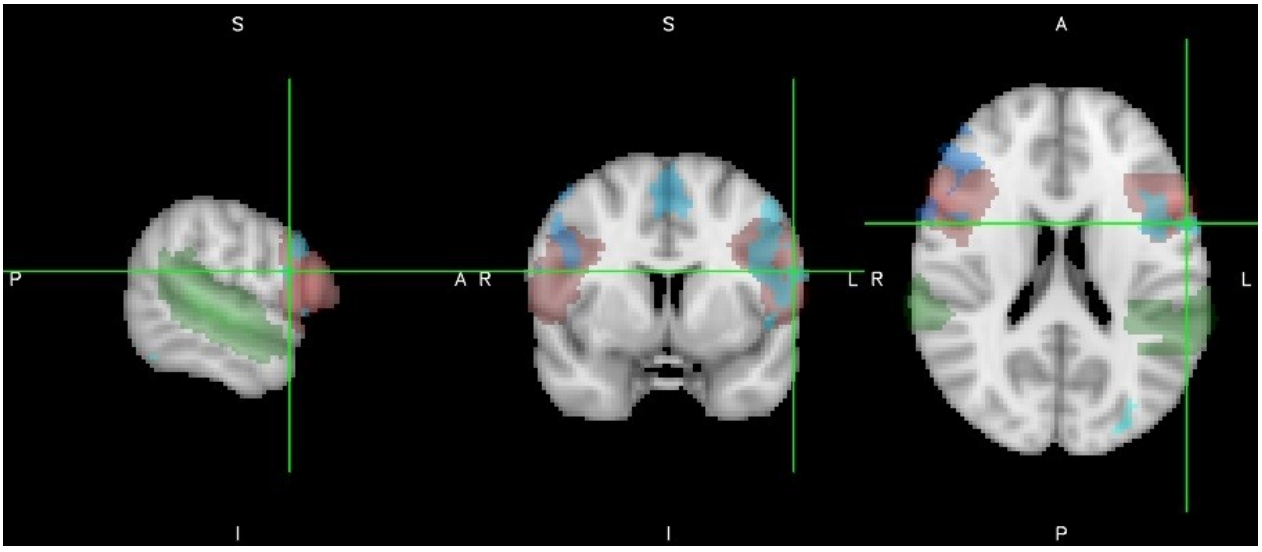

Figure 4. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast LD > rest in PWD, represented in blue. Crosshair is on the Left Precentral Gyrus. Activated brain areas include some portion of the LIFG and RIFG, represented in transparent red, but not of the LSTG or RSTG, represented in transparent green.

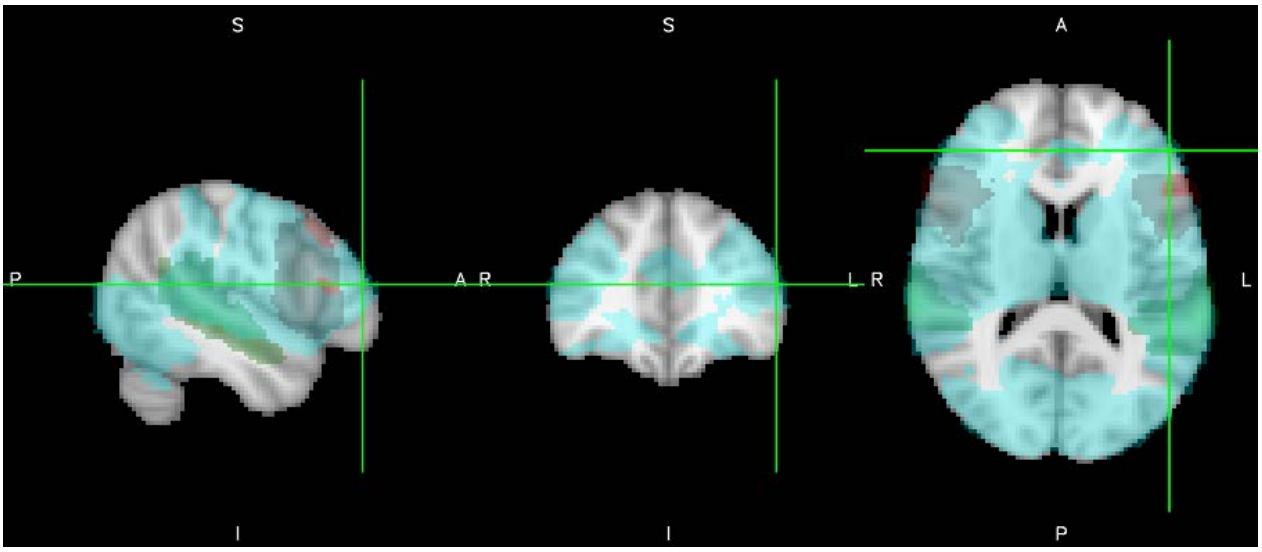

Figure 5. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast WN > rest in healthy young adults, represented in blue. Crosshair is on the Left Frontal Pole. Activated brain areas include virtually all the LIFG and RIFG, represented in transparent red, and the LSTG and RSTG, represented in transparent green.

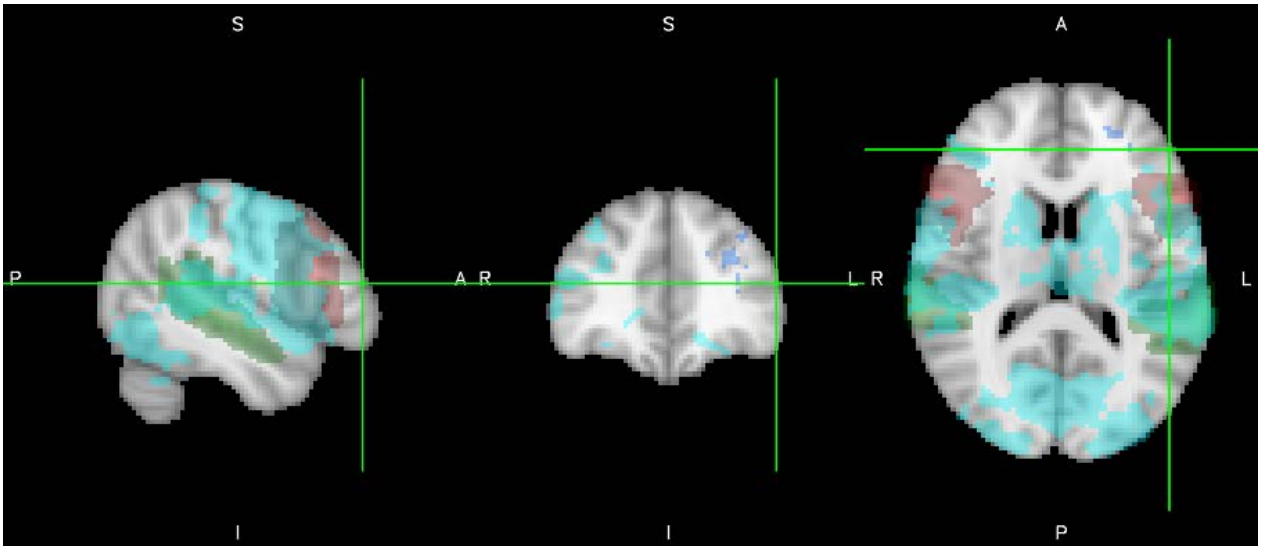

Figure 6. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast WN > rest in PWD, represented in blue. Crosshair is on the Left Frontal Pole. Activated brain areas include virtually all the LIFG and RIFG, represented in transparent red, and the LSTG and RSTG, represented in transparent green.

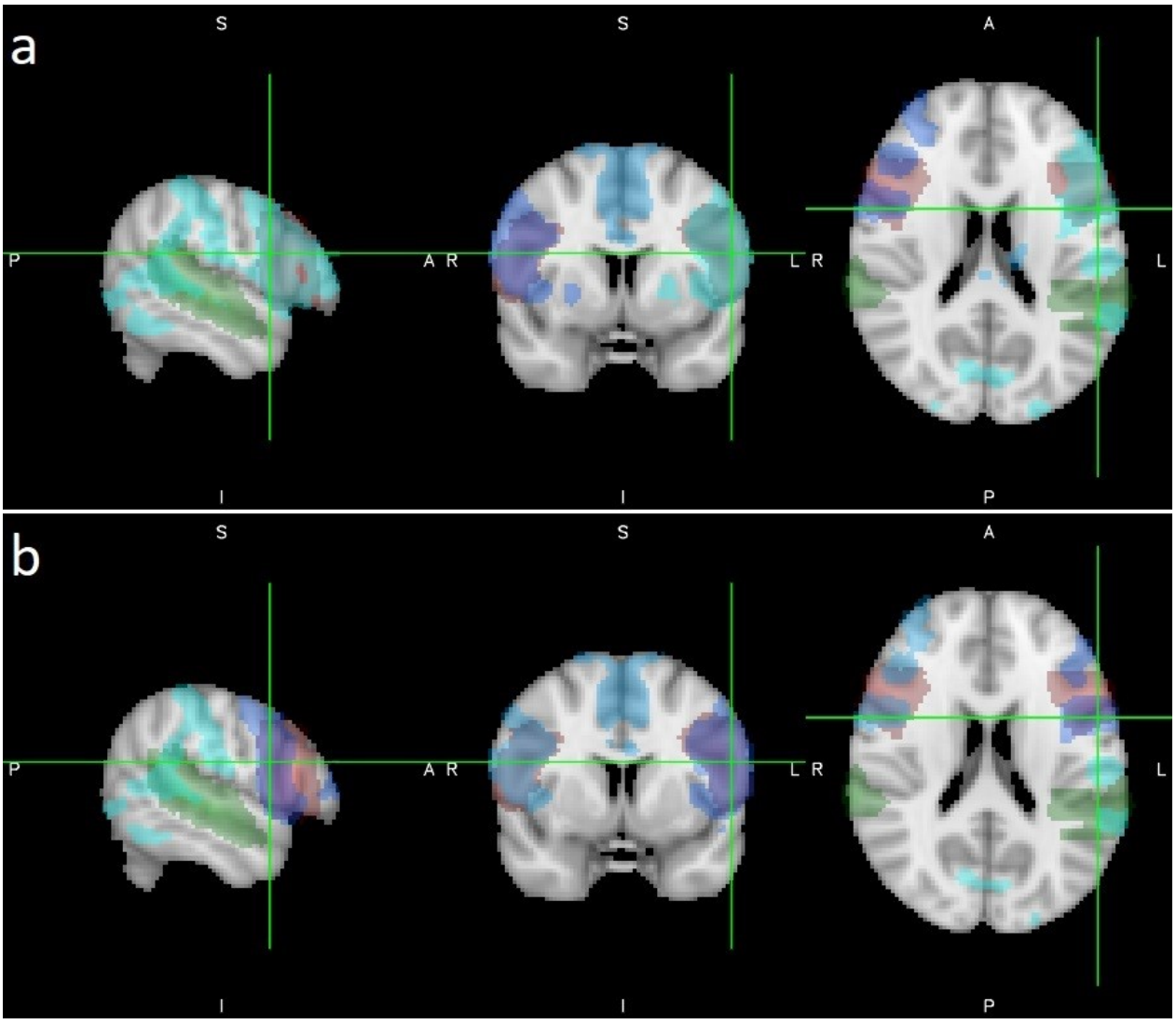

Figure 7. Brain activation clusters (Z > 2.3, p_{corr} < 0.05) represented in blue for the contrast words > rest (a) and nonwords > rest (b) in LD for healthy young adults. Crosshair is on the Left Precentral Gyrus for both (a) and (b). Activated brain areas include some portion of the LIFG and RIFG, represented in transparent red, and of the LSTG, represented in transparent green.

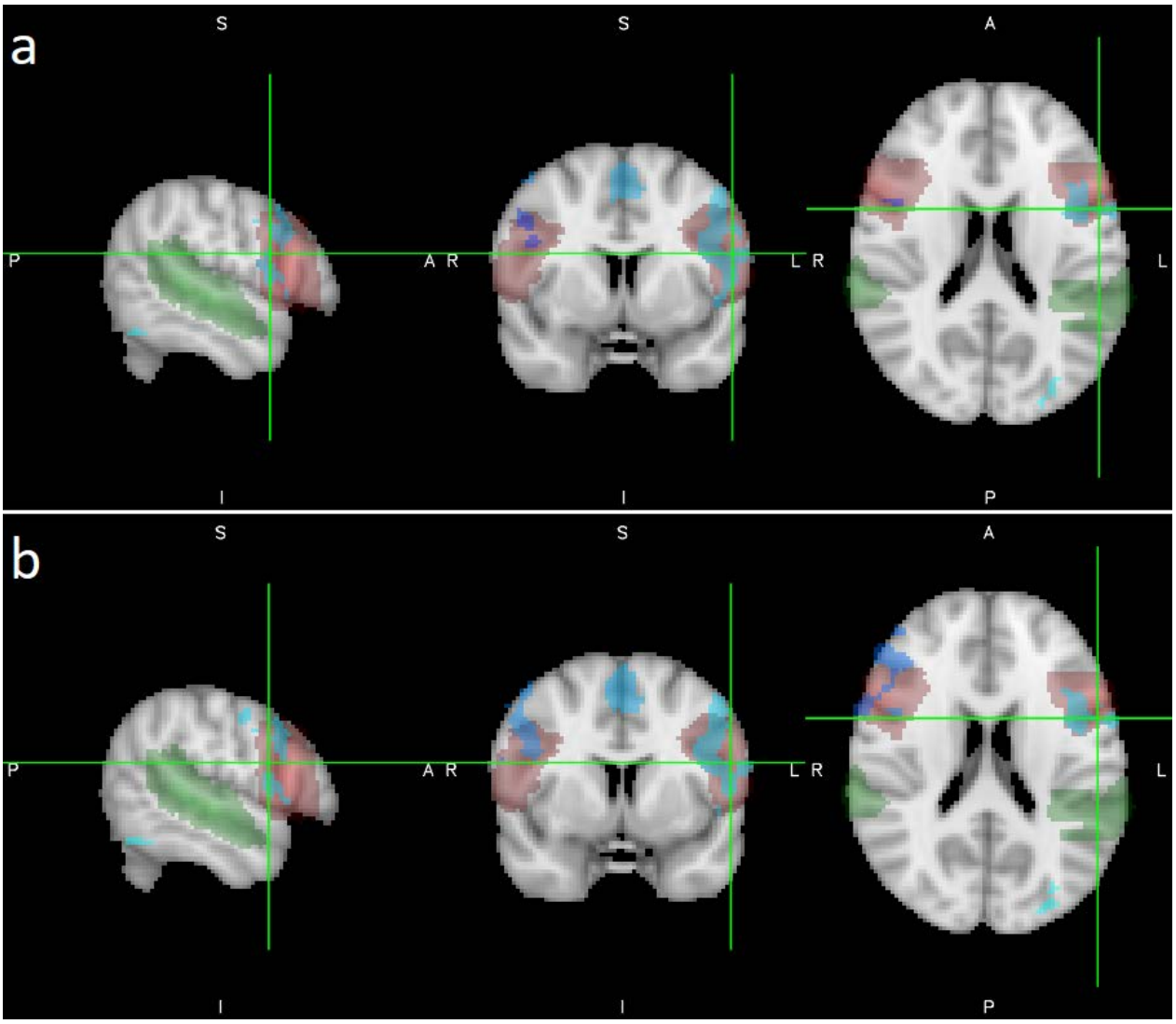

Figure 8. Brain activation clusters (Z > 2.3, p_{corr} < 0.05) represented in blue for the contrast words > rest (a) and nonwords > rest (b) in LD for PWD. Crosshair is on the Left Precentral Gyrus for both (a) and (b). Activated brain areas include some portion of the LIFG and RIFG, represented in transparent red, but not of LSTG and RSTG, represented in transparent green.

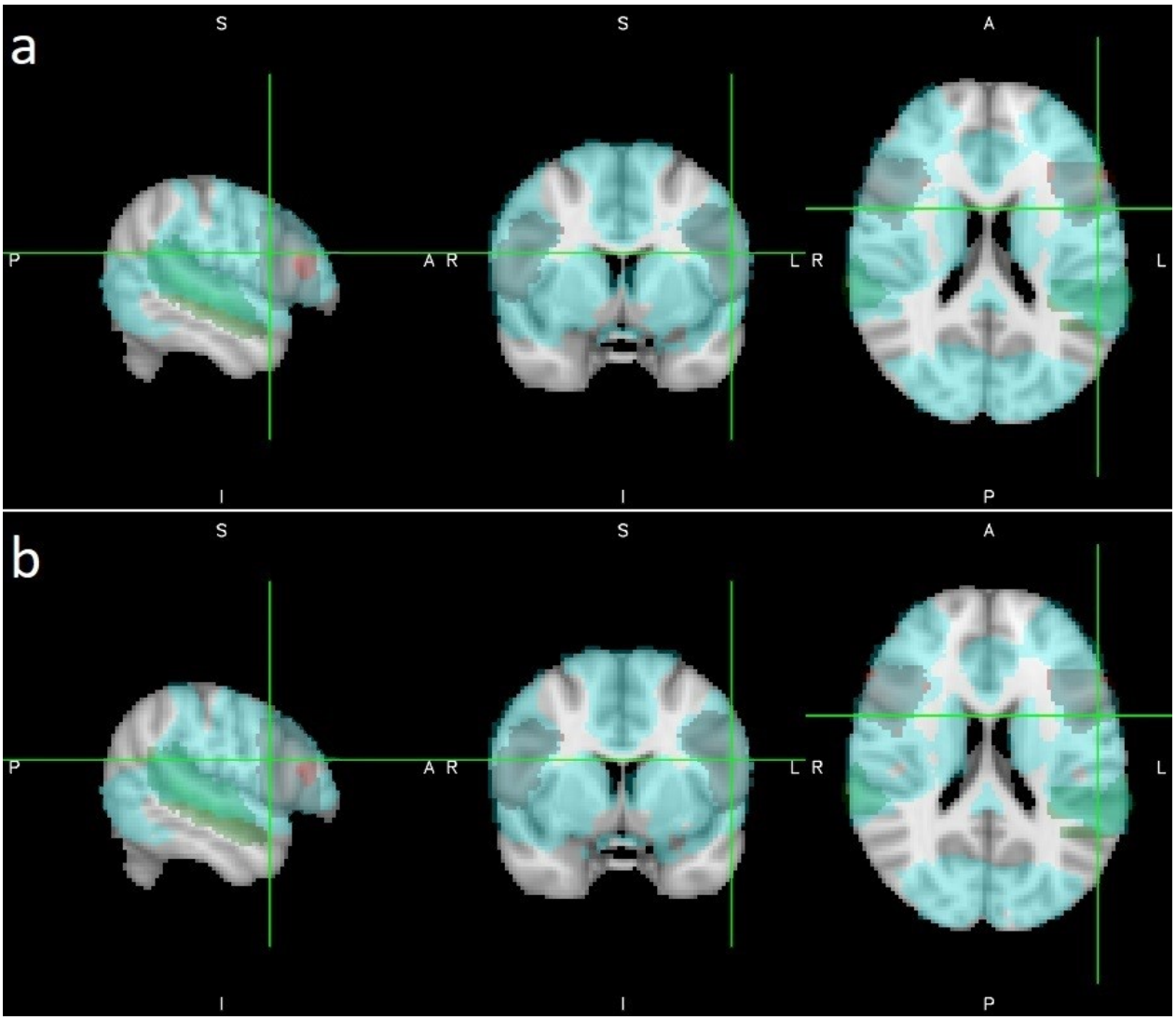

Figure 9. Brain activation clusters (Z > 2.3, p_{corr} < 0.05) represented in blue for the contrast words > rest (a) and nonwords > rest (b) in WN for healthy young adults. Crosshair is on the Left Precentral Gyrus for both (a) and (b). Activated brain areas include virtually all the LIFG and RIFG, represented in transparent red, and LSTG and RSTG, represented in transparent green.

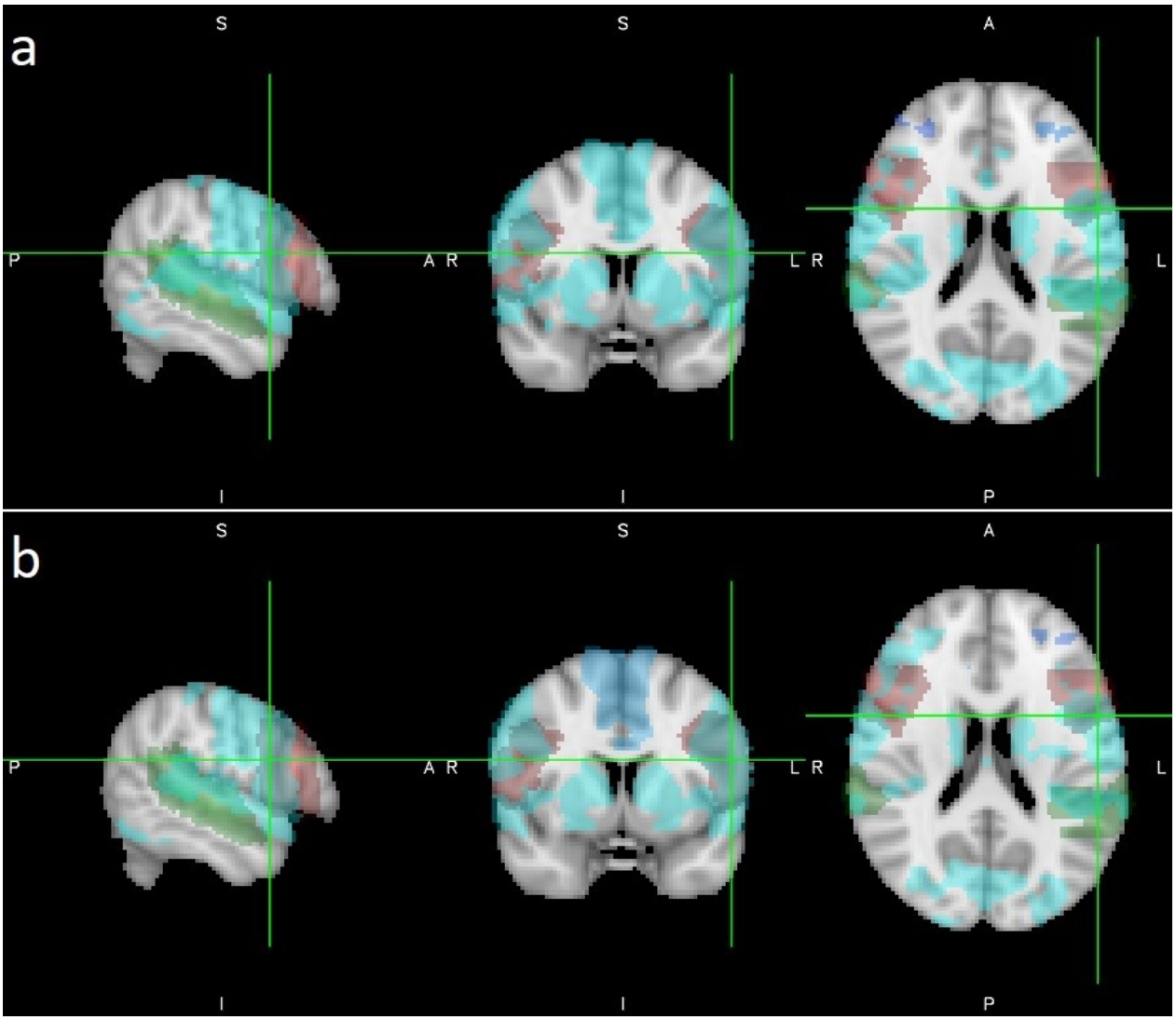

Figure 10. Brain activation clusters (Z > 2.3, p_{corr} < 0.05) represented in blue for the contrast words > rest (a) and nonwords > rest (b) in WN for PWD. Crosshair is on the Left Precentral Gyrus for both (a) and (b). Activated brain areas include some portion of the LIFG and RIFG, represented in transparent red, and of the LSTG and RSTG, represented in transparent green.

7.3.1.1 CP for PWA

No significant result was observed for the whole brain analysis of CP for JW or MB.

7.3.1.2 LD for PWA

Only MB showed significant results in the whole brain analyses of LD. Results suggest that brain activation in MB for the processing of LD was weaker than that of controls in frontal and temporal areas of both left and right hemispheres. Table 1 and Figure 11 show brain areas where the contrast controls > MB was significant.

Table 1. Cluster peaks of activated cortical regions for the contrast controls > MB in LD

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
Frontal Pole	R	2524	48	46	6	4.64
Superior Frontal Gyrus	R	841	4	38	52	4.02
Cingulate Gyrus, anterior division	L	418	-4	28	14	3.91
Temporal Occipital Fusiform Cortex	R	1099	28	-56	-12	3.87
Temporal Occipital Fusiform Cortex	L	377	-30	-52	-20	3.59
Temporal Pole	L	983	-38	8	-20	3.5

T-contrast with Z > 2.3, $p_{corr} < 0.05$.

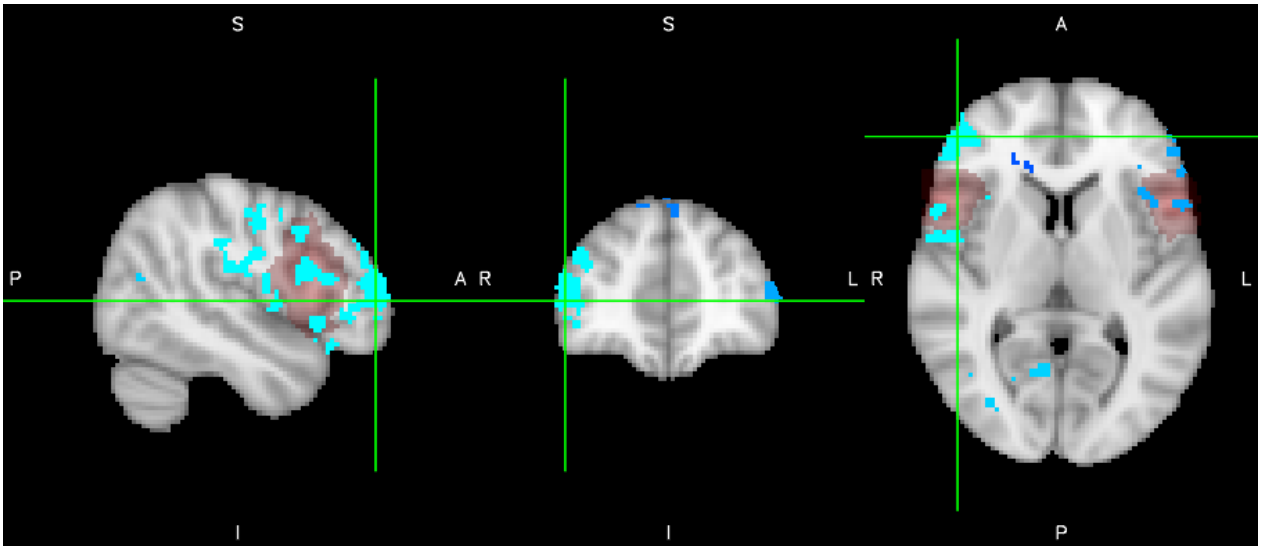

Figure 11. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast controls > MB in LD, represented in blue. Crosshair is on the highest cluster peak, the Frontal Pole. Activated brain areas include some portion of the LIFG and the RIFG, represented in transparent red.

7.3.1.3 WN for PWA

Only JW showed significant differences in cortical activation from controls for WN. Results indicate that right frontal and temporoparietal activity in JW is lower than right frontal activity in controls at baseline (Table 2 and Figure 12).

Table 2. Cluster peaks of activated cortical regions for the contrast controls > JW in WN

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
Supramarginal Gyrus, posterior division	R	1223	38	-44	18	4.46
Insular Cortex	R	974	24	-20	12	4.17
Suplementary Motor Cortex	R	1184	12	-2	58	4.15
Frontal Operculum Cortex	R	703	46	18	4	3.69

T-contrast with Z > 2.3, $p_{corr} < 0.05$.

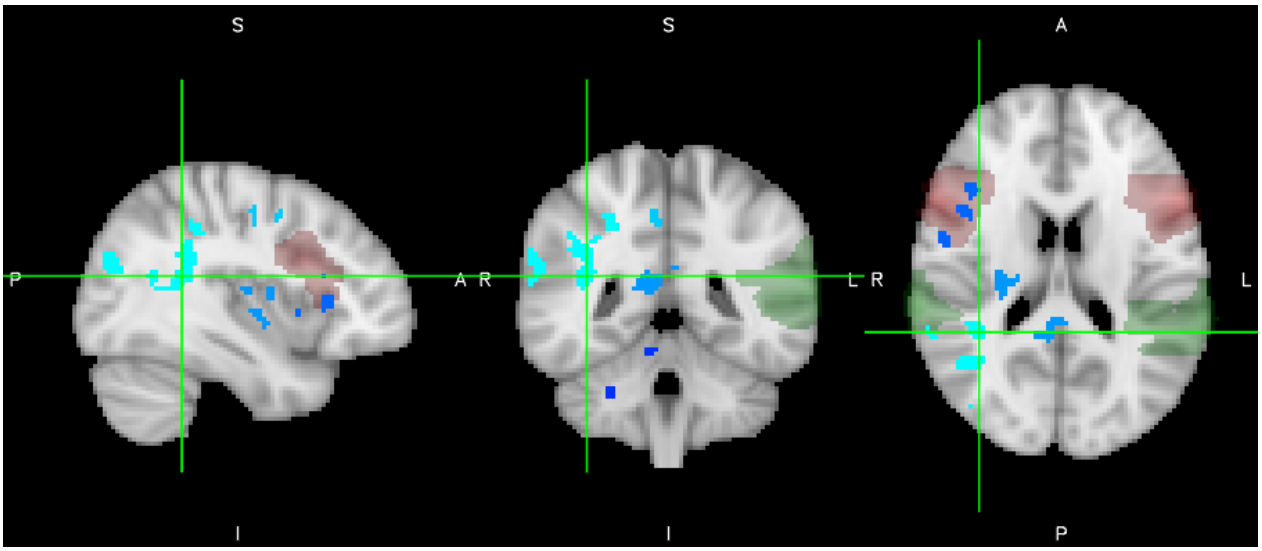

Figure 12. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast controls > JW in WN, represented in blue. Crosshair is on the highest cluster peak, the Supramarginal Gyrus, posterior division. Activated brain areas include some portion of the RIFG and RSTG, represented respectively in transparent red and transparent green.

7.3.1.4 Analysis of words and nonwords in LD for PWA

Only MB showed significant results in whole brain analyses for the stimulus types words and nonwords in LD. Cortical areas that showed lower activation for MB than for controls are listed in Table 3 and shown in Figure 13.

Table 3. Cluster peaks of activated cortical regions for the contrast controls > MB in words and nonwords of LD

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
words						
Frontal Pole	R	982	48	46	6	3.9
Superior Frontal Gyrus	R	344	4	38	52	3.83
Frontal Orbital Cortex	L	607	-28	22	-14	3.69
Temporal Occipital Fusiform Cortex	R	867	28	-56	-12	3.53
nonwords						
Frontal Pole	R	709	48	46	6	4.52
Superior Frontal Gyrus	L/R	748	0	54	32	3.89
Temporal Occipital Fusiform Cortex	R	672	26	-56	-14	3.63
Cingulate Gyrus, anterior division	L	314	-4	26	12	3.6
Insular Cortex	L	757	-34	18	0	3.57
Poscentral Gyrus	R	395	64	-12	18	3.53
Temporal Occipital Fusiform Cortex	L	320	-30	-52	-20	3.32
Precentral Gyrus	R	474	58	0	40	3.11

T-contrasts with $Z > 2.3$, $p_{corr} < 0.05$.

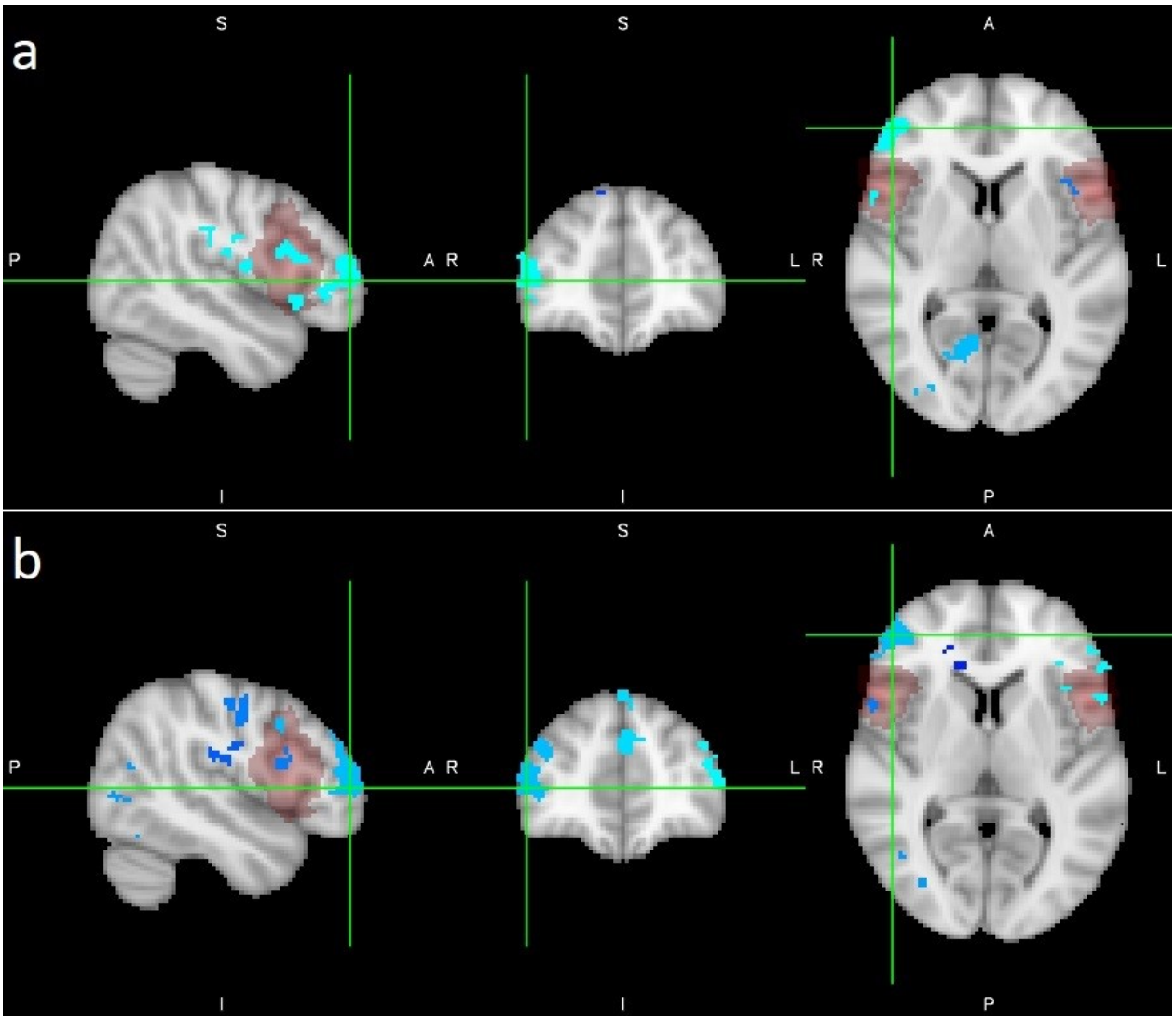

Figure 13. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast controls > MB in words (a) and nonwords (b) of LD, represented in blue. Crosshair is on the highest cluster peak, which is the Frontal Pole for both (a) and (b). Activated brain areas include some portion of the LIFG and RIFG, represented in transparent red.

7.3.1.5 Analysis of words and nonwords in WN for PWA

Only JW showed significant differences in cortical activation from controls in the stimulus types of words and nonwrds in WN. Cortical regions with lower activation in JW than in controls are listed in Table 4 and shown in Figure 14.

Table 4. Cluster peaks of activated cortical regions for the contrast controls > JW in words and nonwords of WN

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
words						
Precentral Gyrus	R	1122	30	-12	44	4.41
Superior Frontal Gyrus	L	319	-6	36	48	3.9
Inferior Frontal Gyrus, pars triangularis	R	449	52	26	4	3.68
nonwords						
Supramarginal Gyrus, posterior division	R	3675	38	-44	18	4.99
Superior Parietal Lobe	L	918	-12	-56	60	4.35
Lateral Occipital Cortex, posterior division	L	457	-42	-78	30	4.17
Supplementary Motor Cortex	R	314	12	-2	58	4.04
Frontal Operculum Cortex	R	706	46	16	4	3.73

T-contrasts with $Z > 2.3$, $p_{corr} < 0.05$.

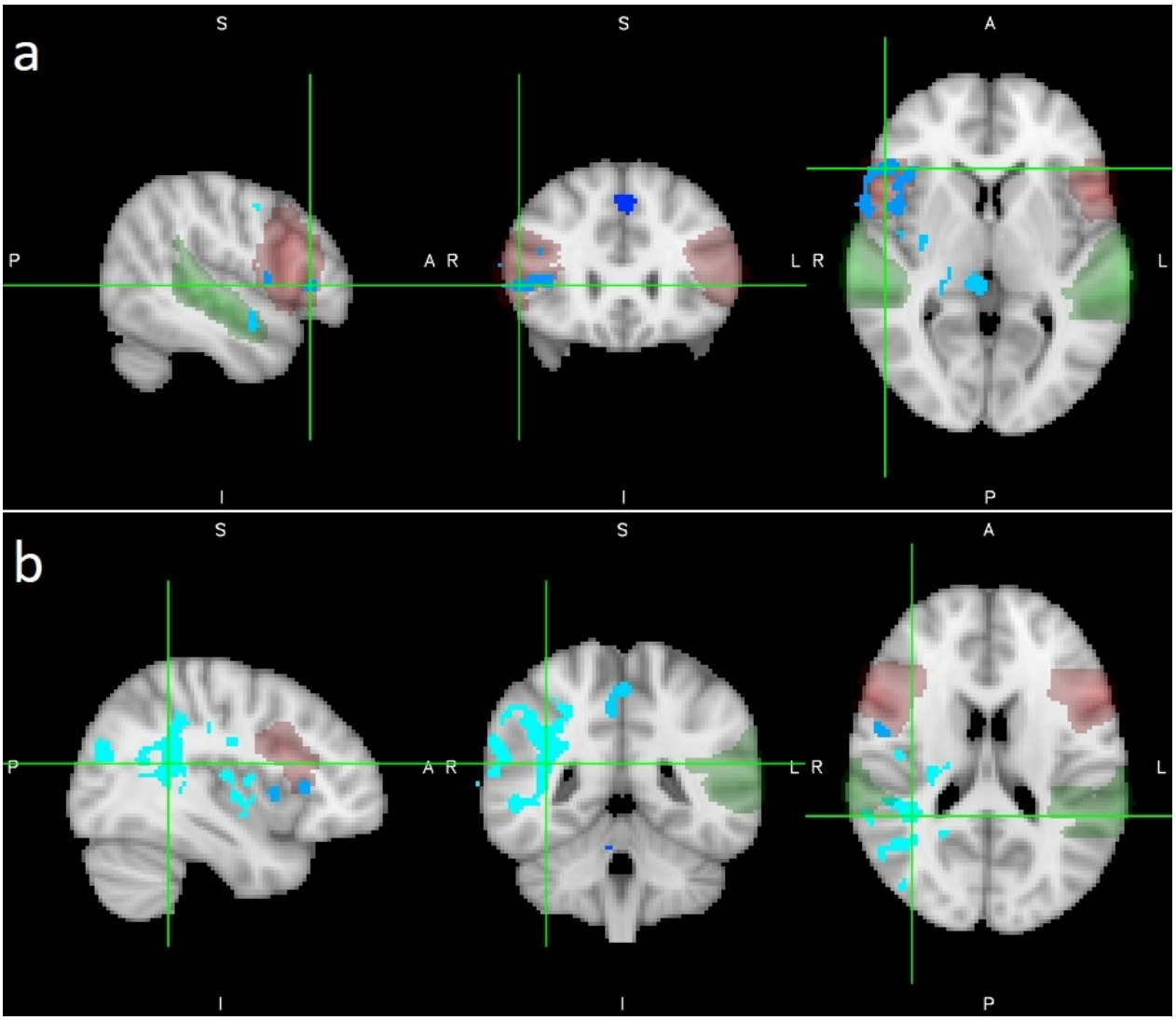

Figure 14. Brain activation clusters (Z > 2.3, p_{corr} < 0.05) for the contrast controls > JW in words (a) and nonwords (b) of WN, represented in blue. Crosshair is on the Right Inferior Frontal Gyrus, pars triangularis, in (a), and on the Supramarginal Gyrus, posterior division, in (b). Activated brain areas include some portion of the RIFG and RSTG, represented respectively in transparent red and transparent green.

7.3.2 ROI analyses

Effects of tasks, stimulus type (for LD and WN) and ROIs on brain activation were analysed with mixed effect models for healthy young adults and PWD. Relevant connections between ROIs were investigated with partial correlation analyses per task and stimulus type (for LD and WN). Due to the small sample size, ROI analyses were not performed for PWA.

7.3.2.1 Analysis of tasks

7.3.2.1.1 Healthy young adults

7.3.2.1.1.1 Effect of task on ROI mean brain activation

A 3 x 4 (task x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of all three experimental tasks across the pooled data of the healthy young adult population group. The analysis showed a significant interaction of ROI and task ($F(6,1389) = 18.51$, $p < 0.001$).

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) showed that activation LIFG for the LD ($t(39) = 8.03$, $p < 0.001$) and WN tasks ($t(39) = 12.61$, $p < 0.001$), activation in the LSTG for CP ($t(39) = 2.37$), $p = 0.03$) and WN tasks ($t(39) = 11.56$, $p < 0.001$), activation in the RIFG for the LD ($t(39) = 5.01$, $p < 0.001$) and WN tasks ($t(39) = 8.82$, $p < 0.001$) and activation in the RSTG for the CP ($t(39) = 4.23$, $p < 0.001$) and WN tasks ($t(39) = 14.08$, $p < 0.001$) were significantly different from zero (Figure 15 and Table 5).

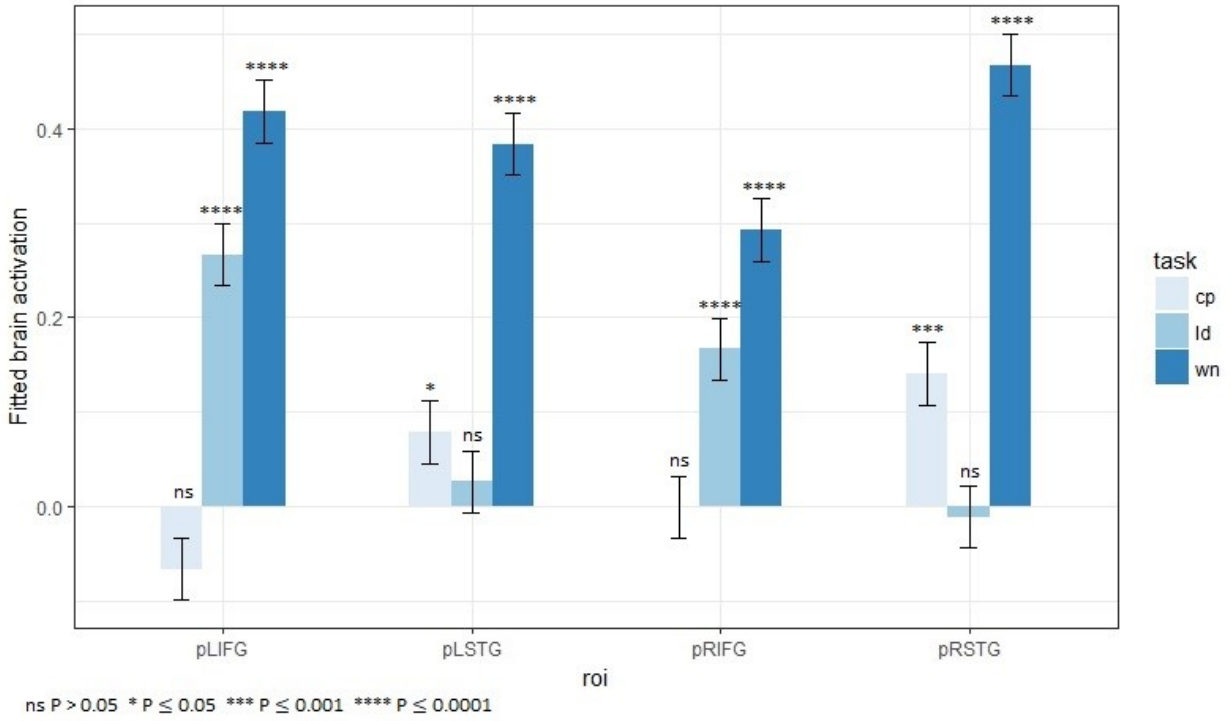

Figure 15. Fitted mean brain activation per ROI and task in healthy young adults. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 5. Contrast analyses for fitted mean brain activations per ROI and task in healthy young adults

Contrast	Estimate	SE	df	*t*	*p*
LIFG: CP	-0.07	0.03	39	-2.00	0.07
LIFG: LD	0.27	0.03	39	8.03	< 0.001
LIFG: WN	0.42	0.03	39	12.61	< 0.001
LSTG: CP	0.08	0.03	39	2.37	0.03
LSTG: LD	0.03	0.03	39	0.78	0.53
LSTG: WN	0.38	0.03	39	11.56	< 0.001
RIFG: CP	0.00	0.03	39	-0.02	0.98
RIFG: LD	0.17	0.03	39	5.01	< 0.001
RIFG: WN	0.29	0.03	39	8.82	< 0.001
RSTG: CP	0.14	0.03	39	4.23	< 0.001
RSTG: LD	-0.01	0.03	39	-0.34	0.81
RSTG: WN	0.47	0.03	39	14.08	< 0.001

7.3.2.1.1.2 Connectivity analysis per task

Partial correlation analyses were performed by task between the fitted mean brain activations of the target network ROIs. All tasks showed some significant correlations, which suggest the most prominent co-ROI-activities to solve the task. These were LIFG/LSTG, LIFG/RIFG, LSTG/RSTG and LIFG/RSTG for CP, LIFG/RIFG, LSTG/RSTG and LIFG/RSTG for LD and LIFG/RIFG, LIFG/RSTG and LSTG/RSTG for WN (Tables 6 to 8).

Table 6. Partial correlation analyses for fitted mean brain activations of CP

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	***0.23***	***0.39***	***0.21***
LSTG	0.23	1.00	0.14	***0.50***
RIFG	0.39	0.14	1.00	0.05
RSTG	0.21	0.50	0.05	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 7. Partial correlation analyses for fitted mean brain activations of LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.08	***0.35***	***0.19***
LSTG	0.08	1.00	0.13	***0.43***
RIFG	0.35	0.13	1.00	0.14
RSTG	0.19	0.43	0.14	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 8. Partial correlation analyses for fitted mean brain activations of WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.05	***0.53***	***0.28***
LSTG	0.05	1.00	0.07	***0.49***
RIFG	0.53	0.07	1.00	0.03
RSTG	0.28	0.49	0.03	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

7.3.2.1.2 PWD

7.3.2.1.2.1 Effect of task on ROI mean brain activation

A 3 x 4 (task x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of all three experimental tasks of the PWD sample. The analysis showed a significant interaction of ROI and task ($F(6,199) = 2.25$, $p = 0.04$).

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) showed that WN induced activation that was significantly different from zero in all ROIs of the target network (Figure 16 and Table 9): LIFG ($t(5) = 7.48$, $p < 0.01$), LSTG ($t(5) = 3.92$, $p = 0.03$), RIFG ($t(5) = 4.40$, $p = 0.03$) and RSTG ($t(5) = 5.55$, $p = 0.02$).

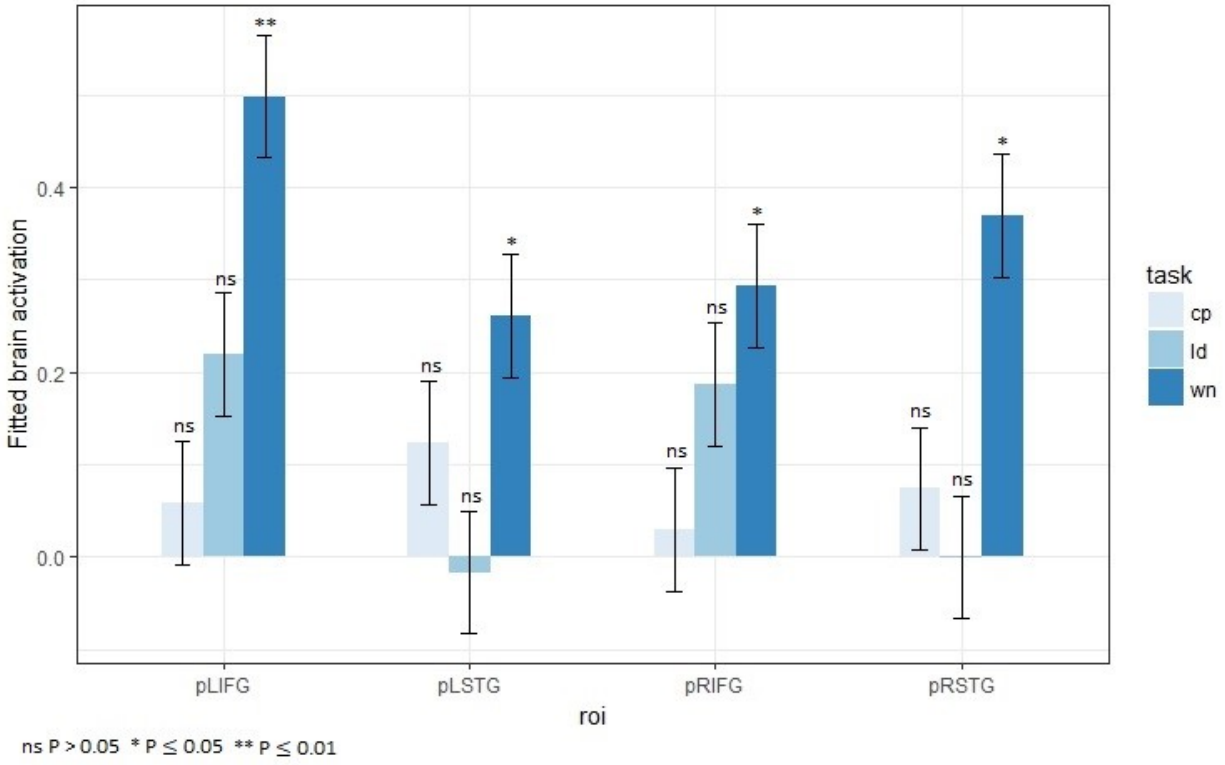

Figure 16. Fitted mean brain activation per ROI and task in PWD. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 9. Contrast analyses for fitted mean brain activations per ROI and task in PWD

Contrast	Estimate	SE	df	*t*	*p*
LIFG: CP	0.06	0.07	5	0.88	0.56
LIFG: LD	0.22	0.07	5	3.29	0.052
LIFG: WN	0.50	0.07	5	7.48	0.008
LSTG: CP	0.12	0.07	5	1.86	0.21
LSTG: LD	-0.02	0.07	5	-0.25	0.89
LSTG: WN	0.26	0.07	5	3.92	0.03
RIFG: CP	0.03	0.07	5	0.45	0.80
RIFG: LD	0.19	0.07	5	2.81	0.08
RIFG: WN	0.29	0.07	5	4.40	0.03
RSTG: CP	0.07	0.07	5	1.11	0.47
RSTG: LD	0.00	0.07	5	0.00	1.00
RSTG: WN	0.37	0.07	5	5.55	0.02

7.3.2.1.2.2 Connectivity analysis per task

Partial correlations between the fitted mean brain activations of the target network ROIs were performed per task for PWD. All tasks showed some significant correlations between ROIs, suggesting that these reflect prominent ROI co-activity to solve the task at hand. Significant correlations were LIFG/RIFG and LSTG/RSTG for CP, LIFG/RIFG for LD and LIFG/LSTG and LSTG/RSTG for WN (Tables 10 to 12).

Table 10. Partial correlation analyses for fitted mean brain activations of CP

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.28	***0.68***	-0.25
LSTG	0.28	1.00	-0.02	***0.75***
RIFG	0.68	-0.02	1.00	0.27
RSTG	-0.25	0.75	0.27	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 11. Partial correlation analyses for fitted mean brain activations of LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.01	***0.51***	-0.29
LSTG	-0.01	1.00	0.35	0.14
RIFG	0.51	0.35	1.00	0.21
RSTG	-0.29	0.14	0.21	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 12. Partial correlation analyses for fitted mean brain activations of WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	***0.69***	0.22	-0.15
LSTG	0.69	1.00	-0.20	***0.55***
RIFG	0.22	-0.20	1.00	0.06
RSTG	-0.15	0.55	0.06	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

7.3.2.2 Analysis of words and nonwords in LD

7.3.2.2.1 Healthy young adults

7.3.2.2.1.1 Effect of stimulus type on ROI mean brain activation

A 2 x 4 (stimulus type x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of words and nonwords in the LD task data of the healthy young adult sample. The analysis showed a main effect of ROI ($F(3,913) = 21.43$, $p < 0.001$).

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) showed that words and nonwords induced activation on the frontal nodes (LIFG and RIFG) that were significantly different from zero (Figure 17 and Table 13): words on LIFG ($t(39) = 7.79$, $p < 0.001$), nonwords on LIFG ($t(39) = 7.14$, $p < 0.001$), words on RIFG ($t(39) = 4.73$, $p < 0.001$) and nonwords on RIFG ($t(39) = 4.60$, $p < 0.001$).

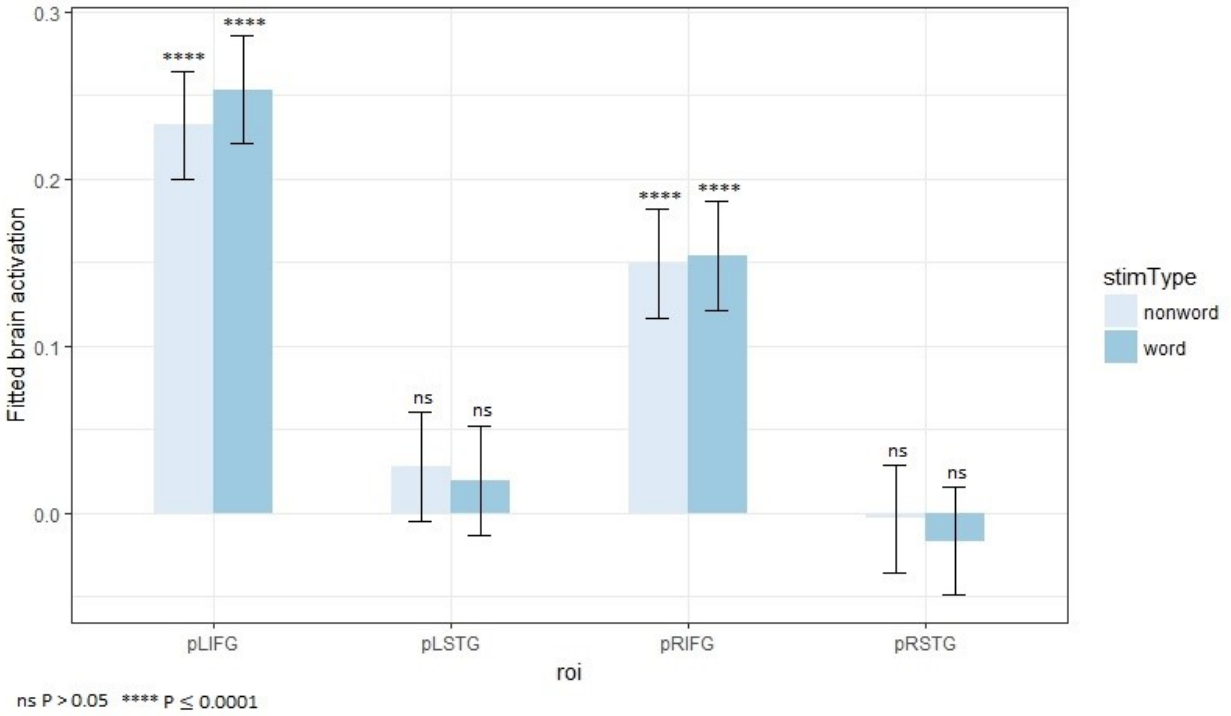

Figure 17. Fitted mean brain activation per ROI and stimulus type for LD in healthy young adults. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 13. Contrast analyses for fitted mean brain activations per ROI and stimulus type in LD for healthy young adults

Contrast	Estimate	SE	df	*t*	*p*
LIFG: nonword	0.23	0.03	39	7.14	< 0.001
LIFG: word	0.25	0.03	39	7.79	< 0.001
LSTG: nonword	0.03	0.03	39	0.85	0.64
LSTG: word	0.02	0.03	39	0.60	0.70
RIFG: nonword	0.15	0.03	39	4.60	< 0.001
RIFG: word	0.15	0.03	39	4.73	< 0.001
RSTG: nonword	0.00	0.03	39	-0.10	0.92
RSTG: word	-0.02	0.03	39	-0.51	0.70

7.3.2.2.1.2 Connectivity analysis per stimulus type

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs per stimulus type (i.e., word and nonword). Both stimulus types showed some

significant correlations, suggesting that the corresponding ROI co-activities are the most prominent to solve the task at hand. These were LIFG/RIFG and LSTG/RSTG for word and LIFG/RIFG, LSTG/RSTG and RIFG/LSTG for nonword (Tables 14 and 15).

Table 14. Partial correlation analyses for fitted mean brain activations in words of LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.10	***0.42***	0.15
LSTG	0.10	1.00	0.07	***0.45***
RIFG	0.42	0.07	1.00	0.14
RSTG	0.15	0.45	0.14	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 15. Partial correlation analyses for fitted mean brain activations in nonwords of LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.05	***0.33***	0.17
LSTG	0.05	1.00	***0.20***	***0.40***
RIFG	0.33	0.20	1.00	0.17
RSTG	0.17	0.40	0.17	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

7.3.2.2.2 PWD

7.3.2.2.2.1 Effect of stimulus type on ROI mean brain activation

A 2 x 4 (stimulus type x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of words and nonwords in the LD task data of the PWD sample. The analysis showed a significant main effect of ROI ($F(3,131) = 4.87$, $p < 0.01$).

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) showed that none of the ROI mean activations was significantly different from zero (Figure 18 and Table 16).

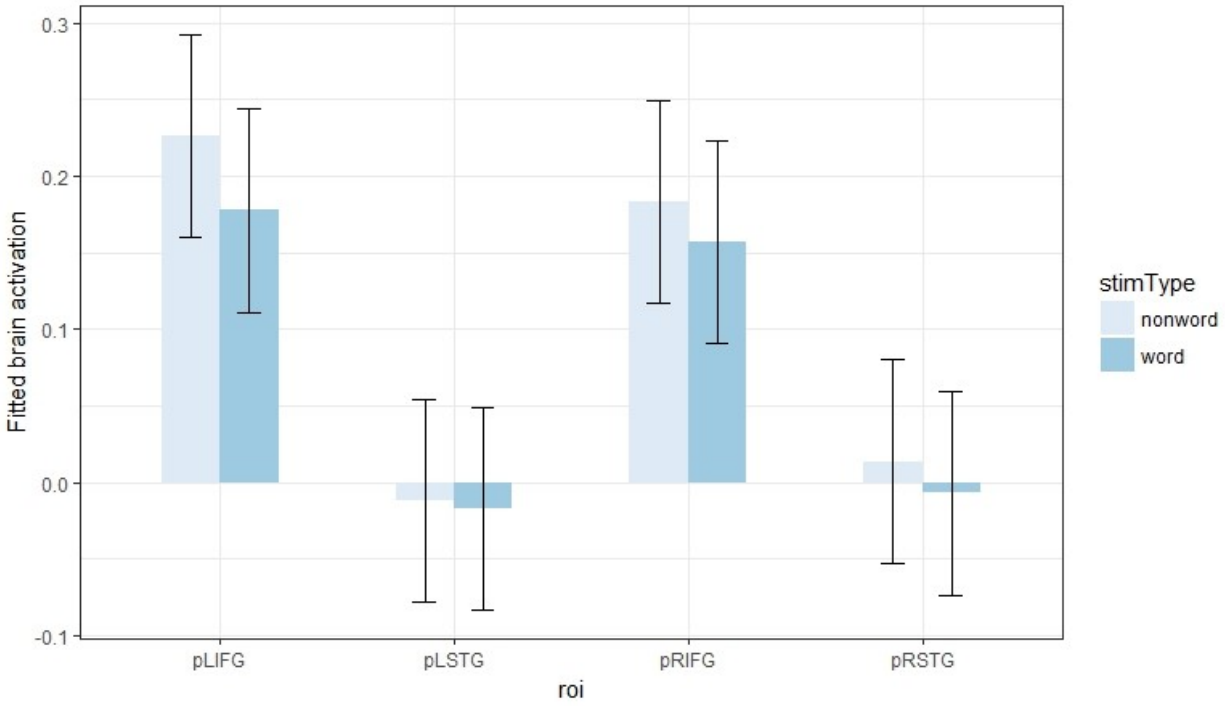

Figure 18. Fitted mean brain activation per ROI and stimulus type for LD in PWD. The x-axis displays the ROIs. The y-axis displays the mean parameter estimates of fitted brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 16. Contrast analyses for fitted mean brain activations per ROI and stimulus type in LD for PWD

Contrast	Estimate	SE	df	*t*	*p*
LIFG: nonword	0.23	0.07	5	3.42	0.12
LIFG: word	0.18	0.07	5	2.68	0.12
LSTG: nonword	-0.01	0.07	5	-0.19	0.92
LSTG: word	-0.02	0.07	5	-0.26	0.92
RIFG: nonword	0.18	0.07	5	2.76	0.12
RIFG: word	0.16	0.07	5	2.37	0.13
RSTG: nonword	0.01	0.07	5	0.21	0.92
RSTG: word	-0.01	0.07	5	-0.11	0.92

7.3.2.2.2.2 Connectivity analysis per stimulus type

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs per stimulus type (i.e., word or nonword). Both stimulus types showed one

significant correlation each, suggesting these to be the most prominent ROI co-activity to solve the task at hand: the RIFG/LSTG for word and the LIFG/RIFG for nonword (Tables 17 and 18).

Table 17. Partial correlation analyses for fitted mean brain activations in words of LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.08	0.46	-0.19
LSTG	-0.08	1.00	***0.51***	0.09
RIFG	0.46	0.51	1.00	0.33
RSTG	-0.19	0.09	0.33	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 18. Partial correlation analyses for fitted mean brain activations in nonwords of LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.02	***0.55***	-0.14
LSTG	0.02	1.00	0.18	0.16
RIFG	0.55	0.18	1.00	0.17
RSTG	-0.14	0.16	0.17	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

7.3.2.3 Analysis of words and nonwords in WN

7.3.2.3.1 Healthy young adults

7.3.2.3.1.1 Effect of stimulus type on ROI mean brain activation

A 2 x 4 (stimulus type x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of words and nonwords in the WN task data of the healthy young adult sample. The analysis showed a significant interaction of ROI and stimulus type ($F(3,913) = 3.70$, $p = 0.01$).

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) showed that both the stimulus type word and nonword induced activation that was significantly different from zero in all the target network ROIs. This can be seen on Figure 19 and on Table 19.

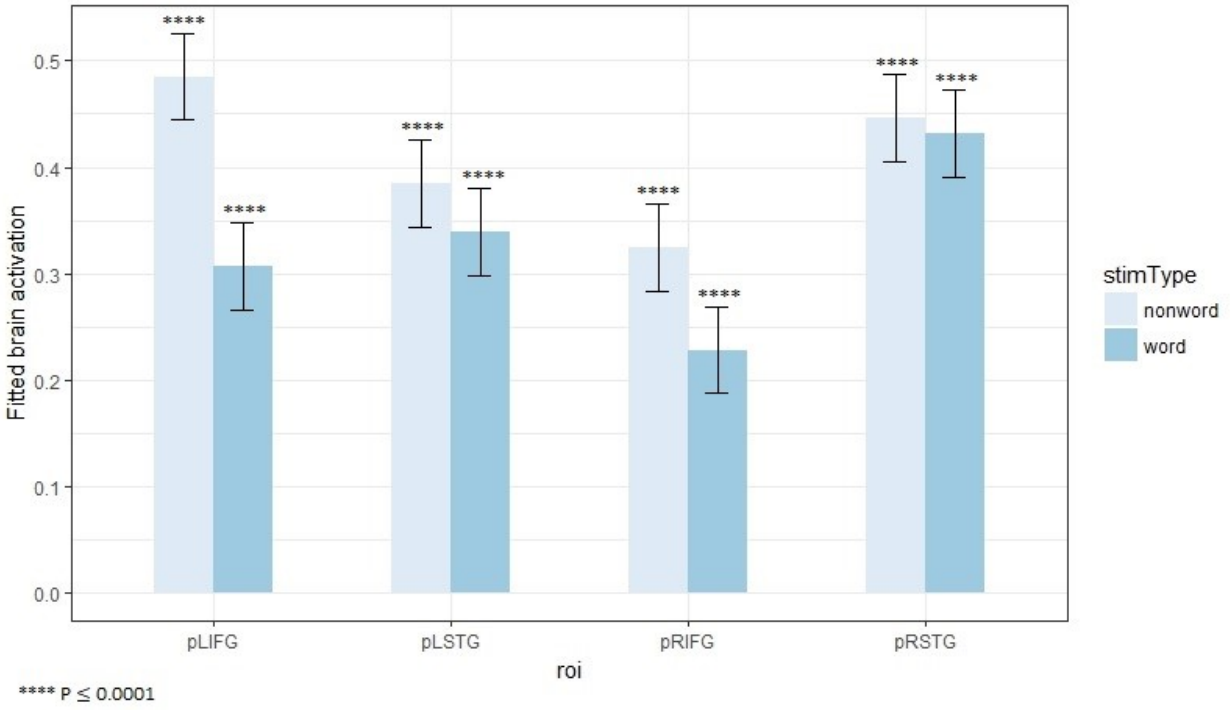

Figure 19. Fitted mean brain activation per ROI and stimulus type for WN in healthy young adults. The x-axis displays the ROIs. The y-axis displays the mean parameter estimates of fitted brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 19. Contrast analyses for fitted mean brain activations per ROI and stimulus type in WN for healthy young adults

Contrast	Estimate	SE	df	*t*	*p*
LIFG: nonword	0.48	0.04	39	11.87	< 0.001
LIFG: word	0.31	0.04	39	7.50	< 0.001
LSTG: nonword	0.38	0.04	39	9.41	< 0.001
LSTG: word	0.34	0.04	39	8.30	< 0.001
RIFG: nonword	0.32	0.04	39	7.95	< 0.001
RIFG: word	0.23	0.04	39	5.59	< 0.001
RSTG: nonword	0.45	0.04	39	10.92	< 0.001
RSTG: word	0.43	0.04	39	10.56	< 0.001

7.3.2.3.1.2 Connectivity analysis per stimulus type

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs per stimulus type (i.e., word and nonword). Both stimulus types induced

significant correlations, suggesting that these are relevant ROI co-activity to solve the task at hand. These were the LIFG/RIFG, LIFG/RSTG and LSTG/RSTG for both stimulus types (Tables 20 and 21).

Table 20. Partial correlation analyses for fitted mean brain activations in words of WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.04	***0.54***	***0.29***
LSTG	0.04	1.00	0.13	***0.47***
RIFG	0.54	0.13	1.00	0.05
RSTG	0.29	0.47	0.05	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 21. Partial correlation analyses for fitted mean brain activations in nonwords of WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.05	***0.52***	***0.26***
LSTG	0.05	1.00	0.07	***0.49***
RIFG	0.52	0.07	1.00	0.03
RSTG	0.26	0.49	0.03	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

7.3.2.3.2 PWD

7.3.2.3.2.1 Effect of stimulus type on ROI mean brain activation

A 2 x 4 (stimulus type x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of words and nonwords in the WN task data of the PWD sample. The analysis showed a significant main effect of ROI ($F(1,131) = 4.63$, $p < 0.01$).

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) showed that both stimulus types (i.e., word and nonword) induced activation in the target network ROIs that were significantly different from zero (Figure 20 and Table 22).

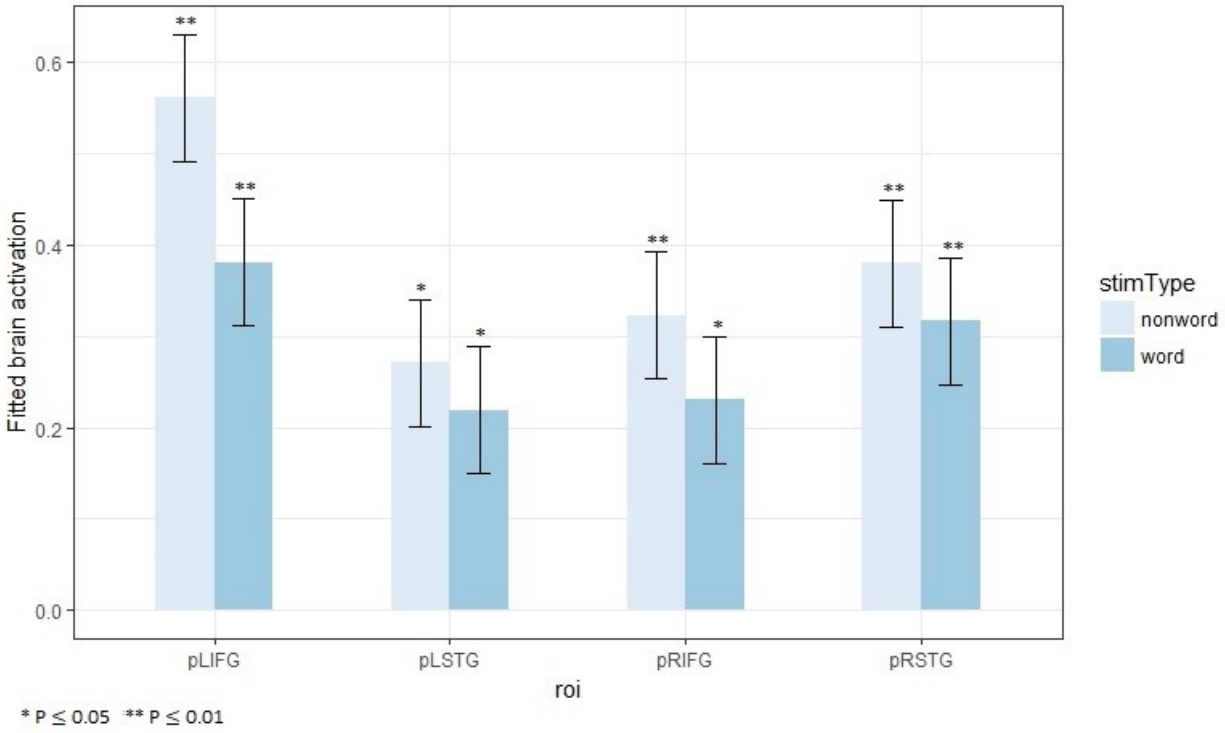

Figure 20. Fitted mean brain activation per ROI and stimulus type for WN in PWD. The x-axis displays the ROIs. The y-axis displays the mean parameter estimates of fitted brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 22. Contrast analyses for fitted mean brain activations per ROI and stimulus type in WN for PWD

Contrast	Estimate	SE	df	*t*	*p*
LIFG: nonword	0.56	0.07	5	8.05	< 0.01
LIFG: word	0.38	0.07	5	5.46	< 0.01
LSTG: nonword	0.27	0.07	5	3.89	0.02
LSTG: word	0.22	0.07	5	3.14	0.03
RIFG: nonword	0.32	0.07	5	4.64	< 0.01
RIFG: word	0.23	0.07	5	3.31	0.02
RSTG: nonword	0.38	0.07	5	5.45	< 0.01
RSTG: word	0.32	0.07	5	4.54	< 0.01

7.3.2.3.2.2 Connectivity analysis per stimulus type

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs per stimulus type (i.e., word and nonword) for PWD. Both stimulus types showed significant correlations, suggesting these to be prominent ROI co-activity to solve the task at hand. These were LIFG/LSTG and LSTG/RSTG for word and LIFG/LSTG for nonword (Tables 23 and 24).

Table 23. Partial correlation analyses for fitted mean brain activations in words of WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	***0.64***	0.33	-0.25
LSTG	0.64	1.00	-0.31	***0.57***
RIFG	0.33	-0.31	1.00	0.15
RSTG	-0.25	0.57	0.15	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 24. Partial correlation analyses for fitted mean brain activations in nonwords of WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	***0.71***	0.25	-0.01
LSTG	0.71	1.00	-0.21	0.44
RIFG	0.25	-0.21	1.00	0.01
RSTG	-0.01	0.44	0.01	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

7.4. DISCUSSION

This study aimed to investigate the task load modulation of brain activation with tasks involving phonological processing in healthy young adults, PWD and PWA. Tasks were chosen in a range from speech perception to speech production. This range of tasks was assumed to rely on the dorsal pathway of phonological processing (Liebenthal et al., 2013; Saur, 2008) with different weights for its endpoints, the LIFG and the LSTG. Speech perception tasks were assumed to rely

more on the LSTG end, whilst production tasks were assumed to rely more on the LIFG (Amunts et al., 1999; Indefrey, 2011; Lee et al., 2012; Liakakis et al., 2011; Liebenthal et al., 2013). Results suggest that brain activation was modulated by task load.

Expectations on the recruitment of the right homologues of the endpoints of the dorsal pathway was high for populations known to have deficits of phonological processing (i.e., in this study, PWD and PWA; Blumstein et al., 1977; Braber et al., 2005; Brunswick et al., 1999; Hoeft et al., 2006; Moineau et al., 2005). For healthy young adults these expectations were lower. However, results of this study showed that participation of right homologues in phonological processing was in fact high for healthy adults. This might have been caused by task difficulty (Gur et al., 2000). Alternatively, phonological processing, although typically found lateralised to the left hemisphere, may have a somewhat bilateral distribution in the brain (Hickok, 2009; Liebenthal et al., 2013; Okada & Hickok, 2006a, 2006b).

7.4.1 Healthy young adults

Healthy young adult participants showed task modulation of brain activation on the nodes of the dorsal pathway of phonological processing (i.e., the LIFG and LSTG) and on their right homologues across the range of tasks from speech perception to speech production. Brain activation during CP, a prototypical speech perception task, showed higher involvement of the temporal regions than of the frontal regions, as expected (Lee et al., 2012; Liebenthal et al., 2013). The LD task, on the other hand, induced the reverse pattern, with a more pronounced involvement of the frontal regions. This does not meet the assumption that the LD would present a pattern of activation closer to that of a speech perception task than that of a speech production task, given that overt articulation, thought to be a crucial element to distinguish these patterns (Fiez et al.,

1995), was absent. However, this result is consistent with research that has shown that the phonological processing involved in word recognition is dependent on phonetic features (Lukatela et al., 2004), and therefore, highly dependent on the frontal end of the dorsal pathway.

A WN task was used as a prototypical speech production task. This task induced the most pronounced activation of the LIFG among all the three experimental tasks, as expected for speech production tasks (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011). Activation of the LSTG, nonetheless, was similarly high. This result suggests that the lexical access in reading aloud, dependent on posterior temporal regions (Binder et al., 2016), is similarly relevant for the task. To investigate if the higher level of activation observed for WN could be at least partially explained by motion artifacts (Barch et al., 1999; Gorgolewski et al., 2013, although decreased activation could also be expected as head motion adds noise to the signal, Barch et al., 1999; Caballero-Gaudes & Reynolds, 2016), statistical comparisons were performed between the WN and LD (the tasks matched by stimuli) per-volume head parameters calculated as part of the MCFLIRT motion correction pre-processing. A higher amplitude of head motion could be expected for WN because this task involved participants speaking in the scanner, whilst LD involved responses with a button box. However, no significant difference was found for head motion between WN and LD, showing that evidence is insufficient to support that results for WN are merely artifactual. In order to minimise the interference of head motion on the results, motion correction was carried out during pre-processing of the brain images with the MCFLIRT tool (Jenkinson et al., 2002) and the ICA-AROMA tool (Pruim, Mennes, Buitelaar et al., 2015; Pruim, Mennes, van Rooij et al., 2015) and motion parameters were included as nuisance covariates in the statistical models to regress out the influence of motion on performance (Johnstone et al., 2006) (c.f. chapter 4).

The stimulus types of words and nonwords were also expected to modulate brain activation. The processing of words was assumed to be more dependent on temporal regions, whilst the processing of nonwords was assumed to be more dependent on frontal regions (Binder et al., 2003; Fiebach et al., 2002; Forster & Chambers, 1973; Levy et al., 2009; Marshall & Newcombe, 1973; Nosarti et al., 2010; Patterson & Shewell, 1987). However, the expected difference between the processing of words and nonwords was rather overridden by the task profile of brain activation. For both stimulus types, frontal regions were the most prominent in LD, whilst both frontal and temporal regions showed similar high level of involvement in WN. With regard to the WN task, however, a trend where the frontal regions, particularly the LIFG, seems more involved in the processing of nonwords than in the processing of words could be observed.

The significant connections between regions of the target network (LIFG, LSTG, RIFG and RSTG) across all the tasks and stimulus types used in this study are suggestive of the network strategies used by the brain to handle the tasks at hand. The LIFG/RIFG and the LSTG/RSTG connections were often observed. These indicate that the endpoints of the dorsal pathway (LIFG and LSTG) work together with their right homologues to solve tasks that involve phonological processing, at least when a high level of difficulty is present (Gur et al., 2000). The LIFG/LSTG connection was also sometimes observed. This particular connection corresponds to the canonical dorsal pathway of phonological processing (Liebenthal et al., 2013; Saur, 2008), and therefore, it came as no surprise. However, the fact that this connection is not the most frequently observed, could be surprising. Nonetheless, this probably reflects that other network strategies were preferable to handle the challenges posed by the experimental tasks. In general, the connections that arose significant matched the task modulated pattern of brain activation observed. For example, LSTG/RSTG was the most significant connection for the CP task, a task in which the

temporal regions showed the most prominent activation. However, significant connections that do not match the task modulated pattern of brain activation were also observed. For example, the LIFG/RIFG connection appeared as highly significant for the CP task. It is possible that this connection reflects extra cognitive effort, as shown in studies that investigated brain strategies for conditions of task difficulty or in aging (Churchill et al., 2016; Davis et al., 2008; Meinzer et al., 2009). In the particular case of CP, the LIFG has indeed been pointed out as crucial for the processing of complex stimuli (Blumstein et al., 2005, Braber et al., 2005; Moineau et al., 2005).

7.4.2 PWD and PWA

PWD and PWA also showed task modulation in their pattern of brain activation in tasks that involved phonological processing. Overall, PWD presented a similar pattern to that observed in healthy young adults. However, results were less robust, possibly reflecting the suboptimal work of the dorsal pathway due to their deficit in phonological processing (Georgiewa, 1999; Ramus, 2004). The highest level of activation in PWD was found for the WN task. Although the highest level of activation in this task broadly matches the pattern observed in healthy young adults, it has been noted that the LIFG activation was considerably higher than the LSTG activation for PWD. This difference may be due to the typical pattern of brain activation that subserves phonological processing in PWD. Typically, hypoactivation of the LSTG and hyperactivation of the LIFG are found (Brunswick et al., 1999; Georgiewa et al., 1999; Ruff et al., 2003). The LIFG can therefore potentially perform more satisfactorily than the LSTG in tasks where their roles are similarly relevant.

Significant differences in cortical brain activation between PWA and controls were only observed for the LD and the WN tasks, where PWA presented with lower level of brain activation

than controls. This is consistent with the expected pattern of processing difficulties for PWA with a frontal profile of aphasia. The processing of tasks that relied more on the LIFG was expected to be more disrupted than the processing of tasks that relied more on temporal areas. Both JW and MB showed lower activation than controls in right frontal areas, JW during the WN task and MB during the LD task. This suggests that the right hemisphere in these PWA does not give proper contribution to phonological processing as it does for healthy controls. On the other hand, this finding also suggests that the left perilesional region in these PWA might be functional to some extent. MB also showed lower activation in bilateral temporal fusiform regions during the LD task. The particular lower activation of the left temporal fusiform gyrus might be associated with some level of deficit in visual word recognition (Devlin et al., 2006). It should be noted, however, that the study with PWA, designed as case-control, has potentially low reliability as an important limitation (as n = 1 for PWA for each singleton analysis). Therefore, interpretation of results should be taken cautiously. If we consider the chance of any one participant from the samples used for the singleton analyses in this study to have a statistical significant difference when compared to the group in a permutation test, the minimum permutation p-value for any one participant would be 1/43 = 0.023. Hence, it would be possible to find a significant difference between any one participant and the group, although the minimum permutation p-value is rather discrete. The significant results in the study could be possibly due either to individual differences (Van Horn et al., 2008) or to a genuine hypoactivation caused by aphasia (Sandberg et al., 2017; Yang et al., 2016; Zhu et al., 2014).

CHAPTER 8:

NEURAL CORRELATES OF TASK LOAD MODULATION OF THE EFFECTS OF tDCS OVER THE LIFG FOR PHONOLOGICAL PROCESSING IN HEALTHY YOUNG ADULTS

8.1 INTRODUCTION

In chapter 5, I investigated the task load modulation of anodal tDCS and cathodal tDCS over the LIFG on behaviour for phonological processing in healthy young adults, whist in this chapter I investigated the corresponding neural correlates. To accomplish this aim, I conducted a study where tDCS stimulation of the LIFG and fMRI were combined during the administration of the same language tasks used in the behavioural experiments described in chapter 5. As in that chapter, the CP, LD and WN tasks were used to represent a range from speech perception to speech production, and were assumed to increasingly engage the LIFG (c.f. Figure 1 in chapter 3 for an overview of predictions on task load modulation of the effects of tDCS over the LIFG).

I recall that language perception and language production rely on network of connected brain areas (Goodale & Milner, 1992; Hickok & Poeppel, 2004; Kümmerer et al., 2013; Saur et al., 2008; Ungerleider & Mishkin, 1982). Therefore, the investigation of neural correlates that subserve the effects of tDCS over the LIFG on performance went beyond the local effects of the direct current, but had particular interest in covering potential mechanisms of network node communication, especially mechanisms of compensation. The target network analysed in this experiment comprised the LIFG, the LSTG, the RIFG and the RSTG (see chapter 3).

8.1.1 CP

The role of the LIFG in speech perception is assumed to relate phonemes to the motor codes for articulation (Meister et al., 2007; Watkins & Paus, 2004). This role is considered minor compared to the role of the LSTG, which is essential for the processing of linguistic auditory information (Chang et al., 2010; Leonard & Chang, 2014). The task load of CP for the LIFG was therefore considered low, or the LIFG a node of low relevance for the task. Compared to baseline

or sham activation, anodal tDCS of the LIFG was expected to reduce its activation, as a result of increased efficiency of the target of stimulation to solve the task. However, since the task-induced degree of neuronal engagement on a node of low relevance for the task is low, the effect of the direct current on the LIFG could be modest and appear to be a null effect. Anodal tDCS was expected to have an effect rather locally on the target. No changes in the baseline pattern of inter-node communication to solve this task were predicted.

Compared to baseline or sham stimulation, cathodal tDCS of the LIFG during the CP task was expected to increase its activation, as a sign of reduced efficiency to solve the task. However, the multi-node framework predicts that a node of low relevance for the task has room for compensation by other network nodes of higher relevance for the task. Compensation of cathodal tDCS-induced downregulation of the LIFG by other network nodes was therefore expected, which was supported by behavioural results reported in chapter 5. Compensation should appear as increased activation of these nodes of higher relevance for the task when compared to their baseline or sham activation, or as strengthening of their connections, as to ensure satisfactory accomplishment of the task. Compensation was mainly expected from the LSTG.

8.1.2 LD

As alluded to in chapter 5, the relevance of the LIFG for the LD task was considered intermediate in a range of its relevance for tasks from speech perception to speech production. In addition, the lack of overt articulation would rather shift this task towards the speech perception end of the range. The task load of LD for the LIFG was therefore considered intermediate to low, or the LIFG a node of intermediate to low relevance for the task. Compared to baseline or sham activation, anodal tDCS of the LIFG during LD was expected to increase its efficiency to solve the

task, resulting in reduced activation. The pattern of connectivity within the network was expected to remain similar to that of baseline stimulation. Furthermore, since the LIFG is assumed to be a node of intermediate relevance for LD, effects were likely to be larger than for the CP task, but smaller than for the WN task.

Relative to the baseline or sham stimulation, cathodal tDCS of the LIFG during LD was expected to decrease its efficiency to solve the task, resulting in increased activation. However, some level of compensation by network nodes more relevant for the task was expected. The LSTG was mainly expected to compensate for the LIFG to cover the extra demand or burden induced by the downregulation of the LIFG. Nevertheless, compensation was likely to be less satisfactory than that for the CP task because the room for compensation in LD was comparatively smaller.

8.1.3 WN

The role of the LIFG for the WN task was considered to be highly relevant, since this region is canonically associated with speech production (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011). The task load of WN for the LIFG was therefore considered high. Compared to baseline or sham stimulation, anodal tDCS was expected to increase the LIFG efficiency to solve the task, what should appear as a significant decrease in its activation. Anodal tDCS was expected to have a local effect on the target. No significant change from baseline should thus be observed in network connectivity.

Relative to baseline or sham stimulation, cathodal tDCS was expected to disrupt the LIFG role in the processing of WN, inducing local increase in brain activation. Because the target was a node of high relevance for the task, compensation by less relevant nodes was expected to be insufficient to avoid deterioration of the LIFG efficiency. However, the improved behavioural

performance induced by cathodal stimulation of the LIFG reported in chapter 5 for the WN task suggests that satisfactory compensation of downregulation of the LIFG can occur in speech production. In this case, predictions for the effect of cathodal stimulation of the LIFG in network connectivity would be the same as those for the CP task, i.e., connections between nodes should be strengthened to facilitate compensation.

8.1.4 Words and nonwords

The relevance of the LIFG for the processing of nonwords was assumed to be higher than for the processing of words. In general, nonwords have been shown to be more demanding to the LIFG (Heim et al., 2005; Nosarti et al., 2010; Xiao et al., 2005) because they rely more on a phonological or sublexical pathway of processing, whilst words rely more on a lexical pathway of processing (Binder et al., 2003; Fiebach et al., 2002; Forster & Chambers, 1973; Levy et al., 2009; Marshall & Newcombe, 1973; Patterson & Shewell, 1987). The task load of words for the LIFG was therefore considered to be low and the task load of nonwords was considered to be high. Predictions for words and nonwords would follow those for the CP and the WN tasks, for which the LIFG was also assumed to be, respectively, a node of low and a node of high relevance for the task. However, as has been suggested in chapter 5, the inhibitory framework can also be suitable to understand the processing of words and nonwords and should be complementarily considered.

The two main approaches of the inhibitory framework consider that inhibitory functions either depend on inhibitory synapses or on the balance between inhibitory and excitatory synapses. The inhibitory role of the LIFG in word processing is believed to relate to the suppression of non-targets in tasks of word recognition to allow the target to be successfully selected (Mirman & Graziano, 2013; Snyder et al., 2007). It therefore matches the second main approach of the

inhibitory framework, with a mechanism that depends on inhibitory synapses to suppress non-target candidates, but also on excitatory synapses to select the target.

In the current study, predictions for tDCS during processing of words and nonwords were based on task load, following the multi-node framework. The inhibitory framework was only considered for the interpretation of results, if appropriate. Under the multi-node framework perspective, anodal tDCS was expected to increase the LIFG efficiency to process both words and nonwords, but more strongly for nonwords, for which the LIFG was a node of higher relevance. Activation of the LIFG should be decreased in relation to that of baseline or sham for both stimulus types, with a larger decrease for nonwords than for words. No significant change from baseline was expected in network connectivity.

Compared to the baseline or sham activation, cathodal tDCS was expected to increase the LIFG activation for both words and nonwords as a sign of local disruption of the target to accomplish the task. An attempt for compensation by other network nodes was likely to be more successful for words, for which the LIFG was a node of low relevance, than for nonwords, which had less room for compensation. Increased activation of compensatory nodes or strengthening of connections between nodes should be observed.

8.2 METHODS

Methods are as described in chapter 4 Methods. For the current study, 20 young healthy adults (mean age: 20.5 years, SD: 2.35, 9 females) who met the inclusion criteria, described in chapter 4, were included in the sample. All three experiments (CP, LD and WN) were performed by all the participants in the sample (n = 20), in counterbalanced order, as a within-subject design study with task, run and tDCS stimulation (anodal, cathodal and sham) as within-subject factors.

This sample of participants was used in the study described in the current chapter and also in Chapter 7. In Chapter 7, the baseline data of the current sample helped to form the sample of healthy young adults.

8.3 RESULTS

Whole brain analyses were conducted with task, stimulus type (for the LD and WN tasks) and tDCS as factors. Significant effects of tDCS over the LIFG on whole brain activation were only observed for WN, which was the task with the highest task load for the LIFG. Results are presented in Appendix 2. Results of ROI analyses are presented in the next subsection.

8.3.1 ROI analyses

Effects of task, stimulus type (for LD and WN), tDCS condition and ROIs on brain activation were analysed with mixed effect models. Relevant connections between ROIs were investigated with partial correlation analyses per task, stimulus type (for LD and WN) and tDCS condition. Both types of analyses are presented by task.

8.3.1.1 CP

8.3.1.1.1 Task and tDCS effects on ROI mean brain activation

A 2 x 4 (tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of both anodal and cathodal tDCS conditions. No significant interaction of tDCS and ROI was observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were performed, but none of them appeared significantly different from zero (Figure 1 and Table 1).

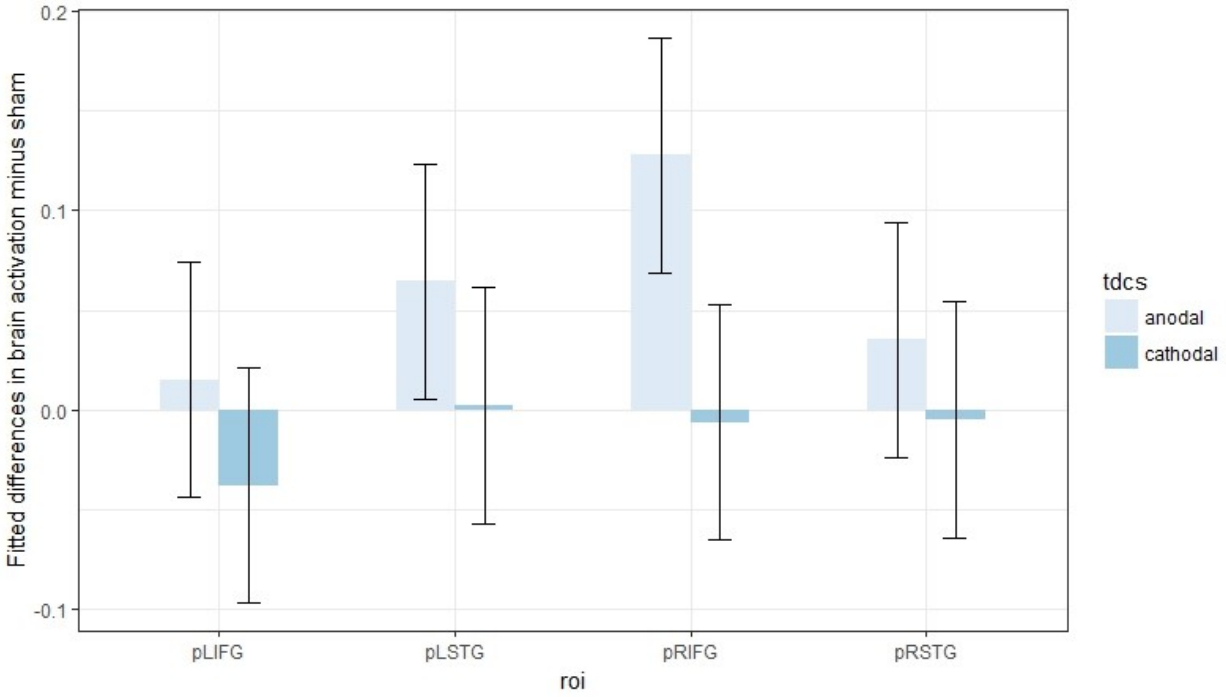

Figure 1. Fitted mean brain activation per ROI and tDCS for CP. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 1. Contrast analyses for fitted mean brain activations per ROI and tDCS

Contrast	Estimate	SE	df	*t*	*p*
LIFG: anodal	0.02	0.06	19	0.25	0.97
LIFG: cathodal	-0.04	0.06	19	-0.64	0.97
LSTG: anodal	0.06	0.06	19	1.09	0.97
LSTG: cathodal	0.00	0.06	19	0.03	0.97
RIFG: anodal	0.13	0.06	19	2.16	0.35
RIFG: cathodal	-0.01	0.06	19	-0.11	0.97
RSTG: anodal	0.03	0.06	19	0.59	0.97
RSTG: cathodal	-0.01	0.06	19	-0.09	0.97

8.3.1.1.2 Connectivity analysis per tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by tDCS condition. Cathodal tDCS induced more significant correlations than

anodal tDCS. These were LIFG/RIFG, LSTG/RSTG and RIFG/RSTG for cathodal tDCS and LIFG/RIFG for anodal tDCS (Tables 2 and 3).

Table 2. Partial correlation analyses for fitted mean brain activations under anodal tDCS in CP

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.35	***0.57***	0.03
LSTG	0.35	1.00	-0.11	0.28
RIFG	0.57	-0.11	1.00	0.36
RSTG	0.03	0.28	0.36	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 3. Partial correlation analyses for fitted mean brain activations under cathodal tDCS in CP

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.30	***0.70***	-0.22
LSTG	0.30	1.00	-0.28	***0.72***
RIFG	0.70	-0.28	1.00	***0.48***
RSTG	-0.22	0.72	0.48	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

8.3.1.2 LD

8.3.1.2.1 Task and tDCS effects on ROI mean brain activation

A 2 x 4 (tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of both anodal and cathodal tDCS conditions. A significant main effect of ROI was observed ($F(3,133) = 4.28$, $p < 0.01$).

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were performed, but none of them appeared significantly different from zero (Figure 2 and Table 4).

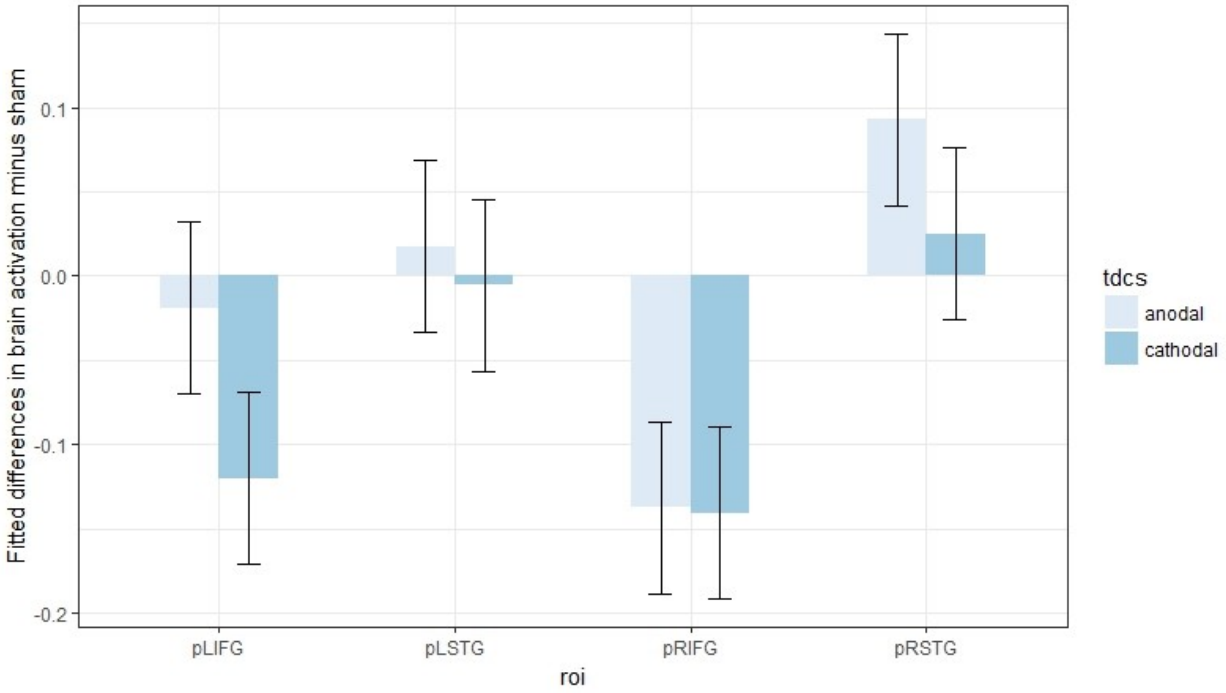

Figure 2. Fitted mean brain activation per ROI and tDCS for LD. The x-axis displays the ROIs. The y-axis displays fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 4. Contrast analyses for fitted brain activation per ROI and tDCS

Contrast	Estimate	SE	df	*t*	*p*
LIFG: anodal	-0.02	0.05	19	-0.37	0.84
LIFG: cathodal	-0.12	0.05	19	-2.36	0.08
LSTG: anodal	0.02	0.05	19	0.34	0.84
LSTG: cathodal	-0.01	0.05	19	-0.11	0.92
RIFG: anodal	-0.14	0.05	19	-2.69	0.06
RIFG: cathodal	-0.14	0.05	19	-2.76	0.06
RSTG: anodal	0.09	0.05	19	1.82	0.17
RSTG: cathodal	0.02	0.05	19	0.49	0.84

8.3.1.2.2 Connectivity analysis per tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by tDCS condition. Cathodal stimulation induced more significant

correlations than anodal tDCS. These were LIFG/LSTG, LIFG/RIFG, RIFG/LSTG, LSTG/RSTG and RIFG/RSTG for cathodal tDCS and LSTG/RSTG for anodal tDCS (Tables 5 and 6).

Table 5. Partial correlation analyses for fitted mean brain activations under anodal tDCS in LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.14	0.28	0.27
LSTG	-0.14	1.00	0.28	***0.68***
RIFG	0.28	0.28	1.00	0.00
RSTG	0.27	0.68	0.00	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 6. Partial correlation analyses for fitted mean brain activations under cathodal tDCS in LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	***0.48***	***0.83***	-0.45
LSTG	0.48	1.00	***-0.67***	***0.67***
RIFG	0.83	-0.67	1.00	***0.63***
RSTG	-0.45	0.67	0.63	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

8.3.1.3 WN

8.3.1.3.1 Task and tDCS effects on ROI mean brain activation

A 2 x 4 (tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of both anodal and cathodal tDCS conditions. No significant interaction of tDCS and ROI was observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were performed, but none of them appeared significantly different from zero (Figure 3 and Table 7).

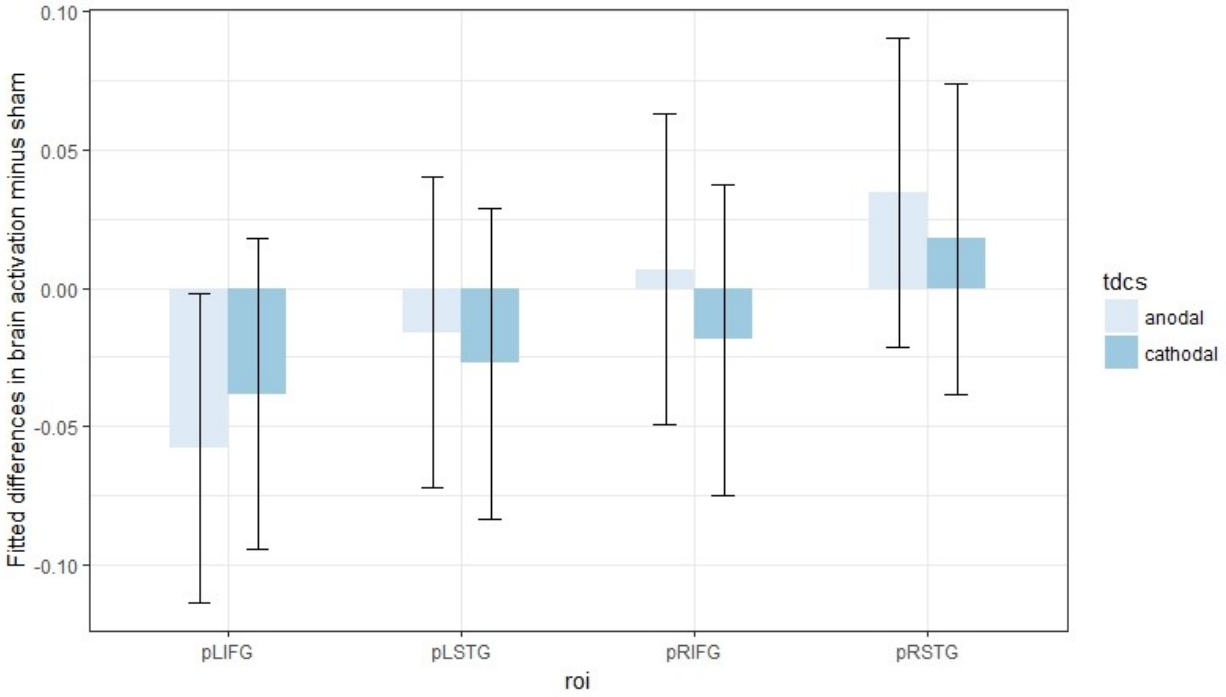

Figure 3. Fitted mean brain activation per ROI and task for WN. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 7. Contrast analyses for fitted mean brain activations per ROI and tDCS

Contrast	Estimate	SE	df	*t*	*p*
LIFG: anodal	-0.06	0.06	19	-1.03	0.89
LIFG: cathodal	-0.04	0.06	19	-0.68	0.89
LSTG: anodal	-0.02	0.06	19	-0.29	0.89
LSTG: cathodal	-0.03	0.06	19	-0.49	0.89
RIFG: anodal	0.01	0.06	19	0.12	0.91
RIFG: cathodal	-0.02	0.06	19	-0.33	0.89
RSTG: anodal	0.03	0.06	19	0.62	0.89
RSTG: cathodal	0.02	0.06	19	0.32	0.89

8.3.1.3.2 Connectivity analysis per tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by tDCS condition. Both anodal and cathodal tDCS induced significant

correlations between the same pairs of ROIs: the LIFG/RIFG and the LSTG/RSTG (Tables 8 and 9).

Table 8. Partial correlation analyses for fitted mean brain activations under anodal tDCS in WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.18	***0.76***	-0.07
LSTG	0.18	1.00	0.01	***0.60***
RIFG	0.76	0.01	1.00	0.22
RSTG	-0.07	0.60	0.22	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 9. Partial correlation analyses for fitted mean brain activations under cathodal tDCS in WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.18	***0.69***	-0.19
LSTG	0.18	1.00	0.00	***0.52***
RIFG	0.69	0.00	1.00	0.40
RSTG	-0.19	0.52	0.40	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

8.3.1.4 Analysis of words and nonwords in LD

8.3.1.4.1 Stimulus type and tDCS effects on ROI mean brain activation

A 2 x 3 x 4 (stimulus type x tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of words and nonwords in the LD task data of the healthy young adult sample whose target of stimulation was the LIFG. Main effects of tDCS ($F(1,288) = 3.88$, $p = 0.049$) and ROI ($F(3,288) = 3.91$, $p < 0.01$) were observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were conducted, and some significant changes in activation were induced by both anodal tDCS and cathodal tDCS for the stimulus type nonword: cathodal tDCS on LIFG ($t(19) = -3.05$, $p = 0.046$)

and on RIFG ($t(19) = -3.17$, $p = 0.046$), anodal tDCS on RIFG ($t(19) = -2.93$, $p = 0.046$) (Figure 4 and Table 10).

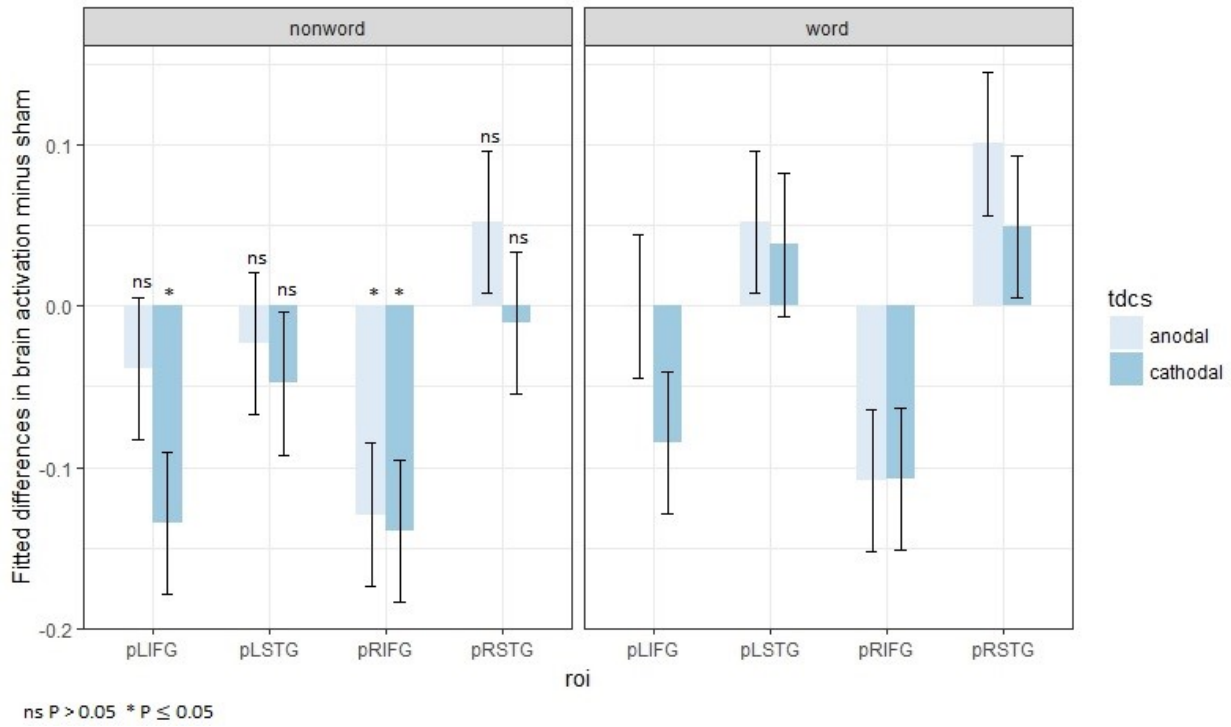

Figure 4. Fitted mean brain activation per ROI and stimulus type in LD. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 10. Contrast analyses for fitted brain activations per ROI and stimulus type

Contrast	Estimate	SE	df	*t*	*p*
LIFG: nonword/anodal	-0.04	0.04	19	-0.88	0.49
LIFG: word/anodal	0.00	0.04	19	0.00	1.00
LIFG: nonword/cathodal	-0.13	0.04	19	-3.05	0.046
LIFG: word/cathodal	-0.08	0.04	19	-1.92	0.16
LSTG: nonword/anodal	-0.02	0.04	19	-0.52	0.70
LSTG: word/anodal	0.05	0.04	19	1.18	0.42
LSTG: nonword/cathodal	-0.05	0.04	19	-1.09	0.42
LSTG: word/cathodal	0.04	0.04	19	0.86	0.49
RIFG: nonword/anodal	-0.13	0.04	19	-2.93	0.046
RIFG: word/anodal	-0.11	0.04	19	-2.45	0.08
RIFG: nonword/cathodal	-0.14	0.04	19	-3.17	0.046
RIFG: word/cathodal	-0.11	0.04	19	-2.43	0.08
RSTG: nonword/anodal	0.05	0.04	19	1.18	0.42
RSTG: word/anodal	0.10	0.04	19	2.28	0.09
RSTG: nonword/cathodal	-0.01	0.04	19	-0.23	0.87
RSTG: word/cathodal	0.05	0.04	19	1.12	0.42

8.3.1.4.2 Connectivity analysis per stimulus type and tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by stimulus type and tDCS condition. Cathodal tDCS induced more significant correlations than anodal tDCS, as well as the stimulus type word induced more significant correlations than the stimulus type nonword. These were LIFG/RIFG, LIFG/RSTG, RIFG/LSTG, RIFG/RSTG and LSTG/RSTG for cathodal tDCS with words, LIFG/RIFG, LSTG/RSTG and RIFG/LSTG for cathodal tDCS with nonwords and LSTG/RSTG for anodal with words. Anodal tDCS during nonwords induced no significant correlations between the target network ROIs (Tables 11 through 14).

Table 11. Partial correlation analyses for fitted mean brain activations in words of LD under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.26	0.27	0.34
LSTG	-0.26	1.00	-0.15	***0.85***
RIFG	0.27	-0.15	1.00	0.26
RSTG	0.34	0.85	0.26	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 12. Partial correlation analyses for fitted mean brain activations in nonwords of LD under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.10	0.31	0.17
LSTG	0.10	1.00	0.37	0.40
RIFG	0.31	0.37	1.00	0.10
RSTG	0.17	0.40	0.10	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

Table 13. Partial correlation analyses for fitted mean brain activations in words of LD under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.43	***0.87***	***-0.58***
LSTG	0.43	1.00	***-0.61***	***0.65***
RIFG	0.87	-0.61	1.00	***0.72***
RSTG	-0.58	0.65	0.72	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 14. Partial correlation analyses for fitted mean brain activations in nonwords of LD under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.43	***0.71***	-0.09
LSTG	0.43	1.00	***-0.64***	***0.58***
RIFG	0.71	-0.64	1.00	0.35
RSTG	-0.09	0.58	0.35	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

8.3.1.5 Analysis of words and nonwords in WN

8.3.1.5.1 Stimulus type and tDCS effects on ROI mean brain activation

A 2 x 3 x 4 (stimulus type x tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of words and nonwords in the WN task data of the healthy young adult sample. A significant interaction of stimulus type and tDCS was observed ($F(1,258) = 6.74$, $p < 0.01$).

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were conducted, but no significant result was observed (Figure 5 and Table 15).

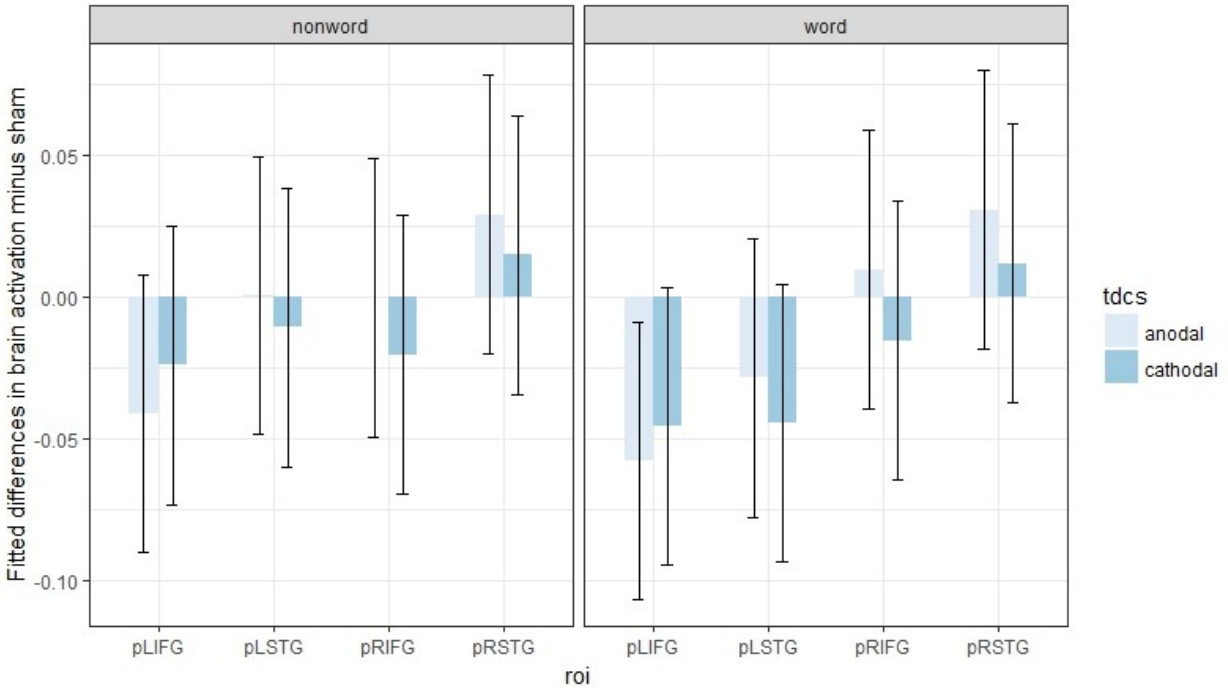

Figure 5. Fitted mean brain activation per ROI and stimulus type in WN. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 15. Contrast analyses for fitted brain activations per ROI and stimulus type

Contrast	Estimate	SE	df	*t*	*p*
LIFG: nonword/anodal	-0.04	0.05	19	-0.84	0.97
LIFG: word/anodal	-0.06	0.05	19	-1.18	0.97
LIFG: nonword/cathodal	-0.02	0.05	19	-0.49	0.97
LIFG: word/cathodal	-0.05	0.05	19	-0.93	0.97
LSTG: nonword/anodal	0.00	0.05	19	0.01	1.00
LSTG: word/anodal	-0.03	0.05	19	-0.58	0.97
LSTG: nonword/cathodal	-0.01	0.05	19	-0.22	0.97
LSTG: word/cathodal	-0.04	0.05	19	-0.91	0.97
RIFG: nonword/anodal	0.00	0.05	19	0.00	1.00
RIFG: word/anodal	0.01	0.05	19	0.19	0.97
RIFG: nonword/cathodal	-0.02	0.05	19	-0.42	0.97
RIFG: word/cathodal	-0.02	0.05	19	-0.32	0.97
RSTG: nonword/anodal	0.03	0.05	19	0.59	0.97
RSTG: word/anodal	0.03	0.05	19	0.63	0.97
RSTG: nonword/cathodal	0.01	0.05	19	0.30	0.97
RSTG: word/cathodal	0.01	0.05	19	0.24	0.97

8.3.1.5.2 Connectivity analysis per stimulus type and tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by stimulus type and tDCS. Under cathodal tDCS, the stimulus type word induced more significant correlations than the stimulus type nonwords: LIFG/RIFG, LSTG/RSTG and RIFG/RSTG for words and LIFG/RIFG for nonwords. Under anodal tDCS, both stimulus types induced the same significant correlations: LIFG/RIFG and LSTG/RSTG (Tables 16 through 19).

Table 16. Partial correlation analyses for fitted mean brain activations in words of WN under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.15	***0.74***	-0.19
LSTG	0.15	1.00	0.23	***0.57***
RIFG	0.74	0.23	1.00	0.22
RSTG	-0.19	0.57	0.22	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 17. Partial correlation analyses for fitted mean brain activations in nonwords of WN under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.01	***0.68***	0.29
LSTG	0.01	1.00	0.04	***0.57***
RIFG	0.68	0.04	1.00	0.00
RSTG	0.29	0.57	0.00	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 18. Partial correlation analyses for fitted mean brain activations in words of WN under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.44	***0.71***	-0.37
LSTG	0.44	1.00	-0.08	***0.59***
RIFG	0.71	-0.08	1.00	***0.48***
RSTG	-0.37	0.59	0.48	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 19. Partial correlation analyses for fitted mean brain activations in nonwords of WN under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.05	***0.61***	-0.03
LSTG	-0.05	1.00	0.18	0.40
RIFG	0.61	0.18	1.00	0.28
RSTG	-0.03	0.40	0.28	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

8.4. DISCUSSION

This study aimed to investigate whether the effects of tDCS on the LIFG would be modulated by task load in healthy young adults. To accomplish this aim, tasks involving phonological processing in a range from speech perception to speech production were used. Speech perception tasks were assumed to pose low load to the LIFG (Lee et al., 2012; Liebenthal et al., 2013), whilst speech production tasks were assumed to pose higher load to the LIFG (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011). As tDCS effects depend on

the level of neuronal engagement of the target of stimulation with the task (Bikson et al., 2013; Nozari, Woodard, & Thompson-Schill, 2014; Pope et al., 2015), outcomes of anodal and cathodal tDCS over the LIFG were expected to differ across the speech perception to speech production range. In a condition of high task load, anodal tDCS should engender robust facilitatory effects, while cathodal tDCS should produce inhibitory effects. In a condition of low task load, anodal should induce low facilitatory effects, whereas cathodal tDCS should produce low inhibitory effects. Furthermore, cathodal tDCS could induce compensation in a condition of low task load (Nozari, Woodard, & Thompson-Schill, 2014). This would be due to the work of other brain areas whose relevance for the task was higher, compensating for the downregulation of the target (Jacobson et al., 2012). Results of this study suggest that task load modulates the tDCS effects, guiding the network strategies used by the brain to deal with the tDCS perturbations.

Task load modulation of tDCS effects appeared more evident from the cathodal tDCS ability to induce compensation throughout the range of tasks and stimulus types used in these experiments. The amount of compensation generated was evaluated in terms of significant prominent connections between the ROIs of the target network (i.e., LIFG, LSTG, RIFG and RSTG) that arose as a result of tDCS stimulation. As cathodal tDCS ability to induce compensation was assumed to be negatively related to task load (Nozari, Woodard, & Thompson-Schill, 2014), cathodal stimulation of the LIFG during a speech perception task was expected to trigger more compensation than when a speech production task was used. This was also expected for the stimulus type word, that should trigger more compensation than nonwords. This pattern was observed in the results of this study. For example, cathodal stimulation of the LIFG induced more compensation for the CP task than for the WN task, as well as more compensation for words than for nonwords.

Anodal tDCS, on the other hand, demonstrated an effect of optimising the network strategies used by the ROIs that subserve the phonological processing across tasks and stimulus types as appropriate, as can be inferred from the pattern of significant prominent connections between the ROIs observed. For example, at baseline (chapter 7) the processing of the LD task involved both a temporal (LSTG/RSTG) and a frontal strategy (LIFG/RIFG). However, under anodal stimulation, only the temporal strategy remained (LSTG/RSTG). It may be that the frontal strategy was not satisfactory to handle the task difficulty and reducing its influence would have a facilitatory effect. This interpretation is consistent with Meinzer et al.'s (2013) finding, where improved performance of the elderly in cognitive tasks was reached by decreasing their frontal hyperactivation with anodal tDCS. Conversely, outcomes of anodal tDCS of the LIFG for the CP task suggest that the frontal strategy (LIFG/RIFG) is crucial to handle the task demands (Blumstein et al., 2005; Braber et al., 2005; Moineau et al., 2005), as the LIFG/RIFG connection was the only one among those connections identified as significant in the baseline experiment (chapter 7) that also appeared significant under anodal tDCS. These results are consistent with findings in the literature that show that anodal stimulation can act as a regulator and induce facilitation via a reduction of brain activation (e.g., Meinzer et al., 2013), an increase of brain activation (as inferred from Costanzo et al., 2016a, 2016b behavioural outcomes for anodal tDCS of the LSTG) or an increase of the connectivity strength between brain regions (Baxter et al., 2017; Meinzer et al., 2012) as needed.

CHAPTER 9:

NEURAL CORRELATES OF TASK LOAD MODULATION OF THE EFFECTS OF tDCS OVER THE LSTG FOR PHONOLOGICAL PROCESSING IN HEALTHY YOUNG ADULTS

9.1 INTRODUCTION

In chapter 6, I investigated the task load modulation of anodal tDCS and cathodal tDCS of the LSTG on behaviour for phonological processing in healthy young adults. In this chapter I investigated the corresponding neural correlates. To accomplish this aim, I conducted a study where tDCS stimulation of the LSTG and fMRI were combined during the administration of the same language tasks used in the behavioural experiments that are described in chapter 6. Predictions were made according to the multi-node framework and tasks used to be representative of a range from speech perception to speech production: CP, LD and WN. Since across this range, the relevance of the LSTG for each task is assumed to be the opposite of that of the LIFG, outcomes of task load modulation of tDCS effects with the LSTG as target were expected to reverse those where the LIFG was the target (c.f. Figure 1 in chapter 3 for an overview of these predictions).

As chapters 5, 6 and 8 suggest, tDCS can be expected to have an effect both locally and on other parts of the network that underlie a particular task or function (Hartwig et al., 2015; Jacobson et al., 2012; Pirulli et al., 2014). Given these and previous evidence that language perception and language production involve networks of connected areas (Goodale & Milner, 1992; Hickok & Poeppel, 2004; Kümmerer et al., 2013; Saur et al., 2008; Ungerleider & Mishkin, 1982), predictions were made for both local and network effects of the direct current. As discussed in chapter 3, the target network for this thesis consisted of the LIFG, the LSTG, the RIFG and the RSTG nodes.

9.1.1 CP

The task load of CP to the LSTG was assumed to be high because the LSTG is considered crucial for the processing of linguistic auditory stimuli (Chang et al., 2010; Leonard & Chang, 2014). This task was therefore expected to engage the LSTG the most (Lee et al., 2012; Liebenthal

et al., 2013) compared to the other tasks in the speech perception to speech production range used in this study. Anodal tDCS of the LSTG was expected to reduce its activation to improve its efficiency to solve the task. Because the LSTG was a node of high relevance for the task, the effect of anodal tDCS on the LSTG was expected to be large and rather local on the target. No significant change in the baseline pattern of inter-node connectivity was expected.

Cathodal tDCS of the LSTG was expected to increase its activation to decrease its efficiency to solve the task. Because the target of tDCS was a node of high relevance for the task, compensation of the downregulation by other network nodes was expected to be unsatisfactory. However, findings reported in chapter 6, in which improved behavioural performance in CP was induced by cathodal tDCS, suggest that some degree of compensation of the LSTG by other network nodes may take place. For that case, predictions for the effects of cathodal tDCS were that compensation of the LSTG by other network nodes would be satisfactory.

9.1.2 LD

As described previously in chapter 6, the task load of LD for the LSTG was assumed to be intermediate compared to that of the CP and of the WN tasks. However, it was considered to be shifted to the speech perception end of the speech perception to speech production range due to the lack of overt articulation, which is the most relevant differential feature of speech production (Fiez et al., 1995). Anodal tDCS of the LSTG was expected to decrease its level of activation, resulting in its increased efficiency to solve the task. The task-induced level of neuronal engagement was expected to be large, although smaller than that caused by the CP task. No changes in the baseline pattern of network connectivity were expected.

Cathodal tDCS of the LSTG was expected to increase its level of activation, resulting in its decreased efficiency to solve the task. Compensation of cathodal tDCS downregulation of the LSTG by other network nodes was expected to be rather inefficient, since the LSTG was a node of intermediate relevance for the task, and therefore, with small room for compensation.

9.1.3 WN

As described previously in chapter 6, the task load of WN for the LSTG was assumed to be low, since speech production is more strongly associated with the LIFG (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011). The LSTG was therefore expected to be the least engaged with the task compared to the other tasks used in this study. Anodal tDCS of the LSTG was expected to increase its level of activation, resulting in its increased efficiency to solve the task. However, since effects of the direct current are a function of task load and the LSTG was a node of low relevance for the task, effects could be small and appear to be a null result. No significant changes from the baseline pattern of network connectivity were expected.

Cathodal tDCS of the LSTG was expected to increase its level of activation, resulting in its decreased efficiency to solve the task. However, compensation of cathodal tDCS-induced dowregulation of the LSTG by other network nodes, specially the LIFG, was expected to be successful, as suggested by results in the study reported in chapter 6, since the LSTG was a node of low relevance for the task. Connections between nodes should be strengthened to allow satisfactory compensation to take place.

9.1.4 Words and nonwords

As described previously in chapter 6, the task load of words was considered to be higher for the LSTG than the task load of nonwords (Okada & Hickok, 2006a), as inferred by reversing the pattern expected for the LIFG (Heim et al., 2005; Nosarti et al., 2010; Xiao et al., 2005). That is, it is generally agreed that processing of nonwords is predominantly subserved by a phonological or sublexical-dependent pathway, whilst the processing of words is predominantly subserved by a lexical-dependent pathway (Binder et al., 2003; Fiebach et al., 2002; Forster & Chambers, 1973; Levy et al., 2009; Marshall & Newcombe, 1973; Patterson & Shewell, 1987). Reliance on the phonological-dependent pathway could also reflect a frequency effect, where nonwords would be considered to be the most infrequent stimuli (Nosarti et al., 2010). Task-induced engagement of the LSTG was therefore assumed to be larger for words than for nonwords.

Anodal tDCS of the LSTG was expected to decrease its level of activation, resulting in increased efficiency to solve the task, for both words and nonwords. However, the effect of anodal tDCS was expected to be larger for words than for nonwords, as a function of task-induced level of engagement of the LSTG. Outcomes could vary from an apparent null effect of stimulation to a significant effect of the direct current. No significant changes from baseline were expected in network connectivity.

Cathodal tDCS of the LSTG was expected to increase its level of activation, resulting in its decreased efficiency to process both words and nonwords. Compensation of cathodal tDCS-induced downregulation of the LSTG by other network nodes was expected to be more satisfactory for nonwords, for which the LSTG was a node of low relevance. and therefore the room for compensation was large, than for nonwords, for which the LSTG was a node of higher relevance. Strengthening of network connections was expected to underly satisfactory compensation.

9.2 METHODS

Methods are as described in chapter 4 Methods. For the current study, 20 young healthy adults (mean age: 22.45 years, SD: 3.05, 8 females) met the inclusion criteria that was described in chapter 4 and were included in the sample. All three experiments (CP, LD and WN) were performed by all the participants in the sample (n = 20), in counterbalanced order, as a within-subject design study with task, run and tDCS stimulation (anodal, cathodal and sham) as within-subject factors. This sample of participants was used in the study described in the current chapter and also in Chapter 7. In Chapter 7, the baseline data of the current sample helped to form the sample of healthy young adults.

9.3 RESULTS

Whole brain analyses were conducted with task, stimulus type (for the LD and WN tasks) and tDCS as factors. No significant results were observed. Results of ROI analyses are presented in the next subsection.

9.3.1 ROI analyses

Effects of task, stimulus type (for LD and WN), tDCS condition and ROIs on brain activation were analysed with mixed effect models. Relevant connections between ROIs were investigated with partial correlation analyses per task, stimulus type (for LD and WN) and tDCS condition. Both types of analyses are presented by task.

9.3.1.1 CP

9.3.1.1.1 Task and tDCS effects on ROI mean brain activation

A 2 x 4 (tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of both anodal and cathodal tDCS conditions. No significant interaction of tDCS and ROI was observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were performed, but none of them appeared significantly different from zero (Figure 1 and Table 1).

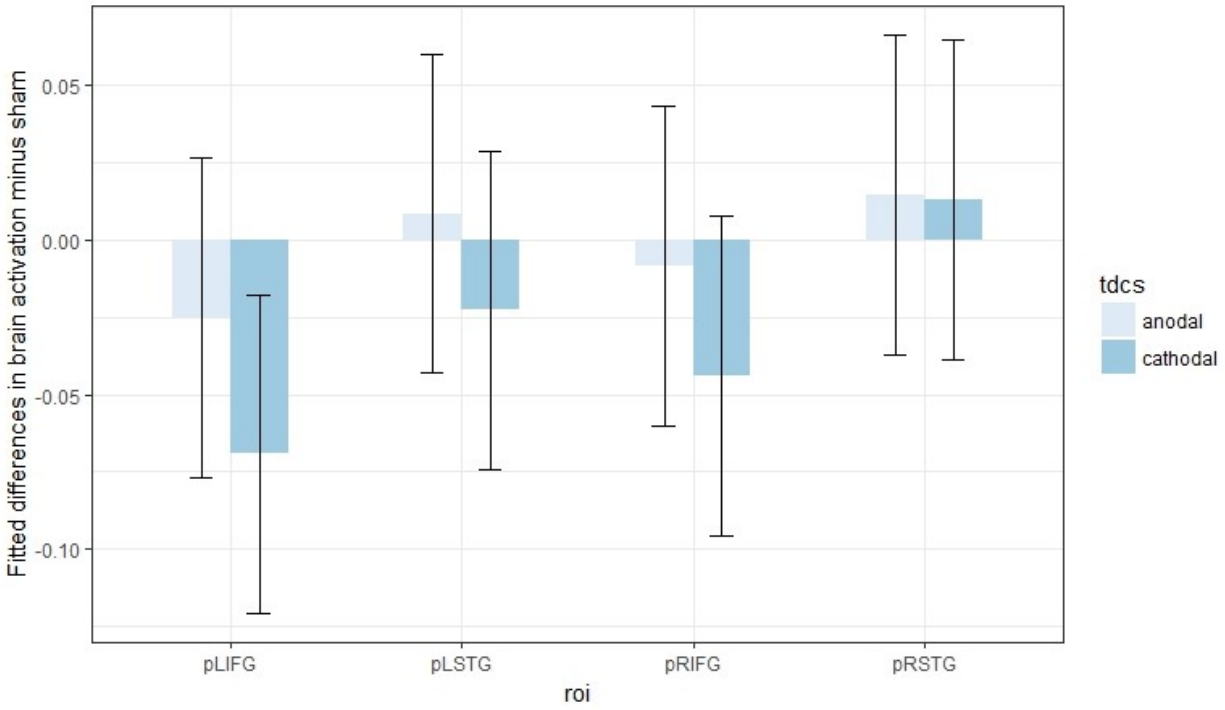

Figure 1. Fitted mean brain activation per ROI and tDCS for CP. The x-axis displays the ROIs. The y-axis displays the mean parameter estimates of fitted brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 1. Contrast analyses for fitted brain activations per ROI and tDCS

Contrast	Estimate	SE	df	*t*	*p*
LIFG: anodal	-0.03	0.05	19	-0.49	0.87
LIFG: cathodal	-0.07	0.05	19	-1.34	0.87
LSTG: anodal	0.01	0.05	19	0.17	0.87
LSTG: cathodal	-0.02	0.05	19	-0.44	0.87
RIFG: anodal	-0.01	0.05	19	-0.16	0.87
RIFG: cathodal	-0.04	0.05	19	-0.85	0.87
RSTG: anodal	0.01	0.05	19	0.29	0.87
RSTG: cathodal	0.01	0.05	19	0.25	0.87

9.3.1.1.2 Connectivity analysis per tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by tDCS condition. Only anodal tDCS induced significant correlations, and these were LIFG/LSTG and LSTG/RSTG (Tables 2 and 3).

Table 2. Partial correlation analyses for fitted mean brain activations under anodal tDCS in CP

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	***0.67***	0.25	-0.21
LSTG	0.67	1.00	0.16	***0.65***
RIFG	0.25	0.16	1.00	0.01
RSTG	-0.21	0.65	0.01	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 3. Partial correlation analyses for fitted mean brain activations under cathodal tDCS in CP

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.18	0.36	0.33
LSTG	0.18	1.00	0.24	0.38
RIFG	0.36	0.24	1.00	-0.07
RSTG	0.33	0.38	-0.07	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

9.3.1.2 LD

9.3.1.2.1 Task and tDCS effects on ROI mean brain activation

A 2 x 4 (tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of both anodal and cathodal tDCS conditions. No significant interaction of tDCS and ROI was observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were performed, but none of them appeared significantly different from zero (Figure 2 and Table 4).

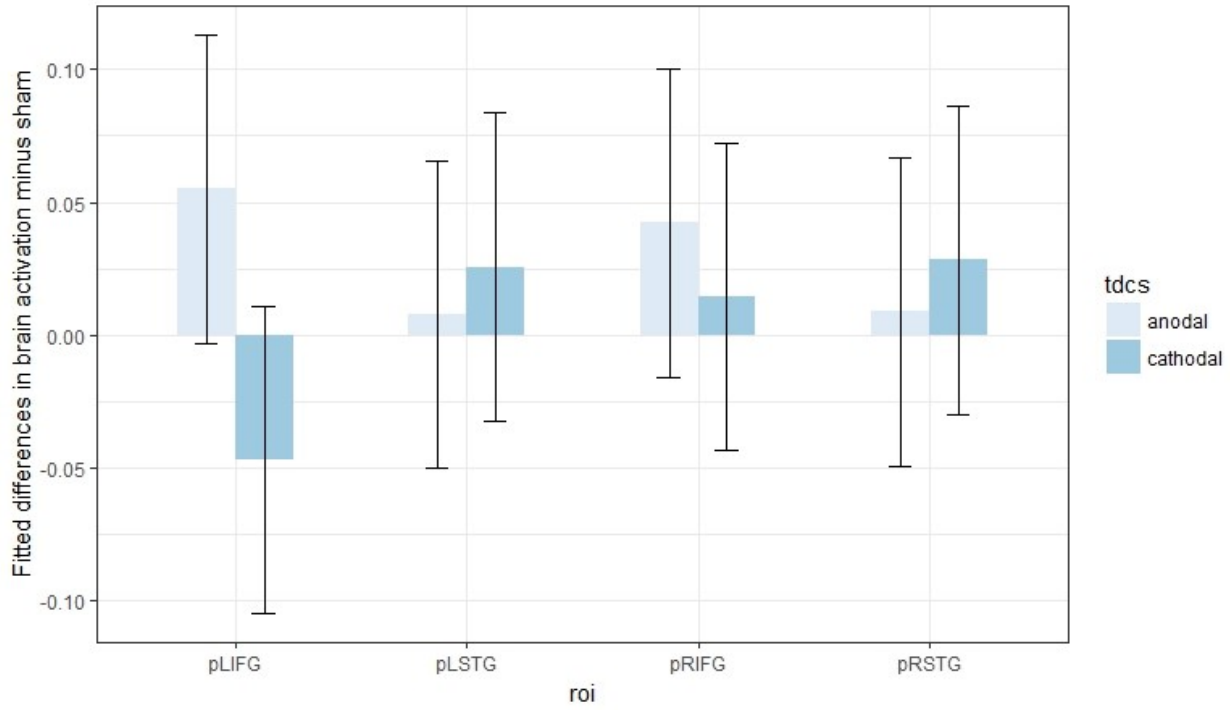

Figure 2. Fitted mean brain activation per ROI and tDCS for LD. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation.

Table 4. Contrast analyses for fitted brain activations per ROI and tDCS

Contrast	Estimate	SE	df	*t*	*p*
LIFG: anodal	0.06	0.06	19	0.95	0.90
LIFG: cathodal	-0.05	0.06	19	-0.81	0.90
LSTG: anodal	0.01	0.06	19	0.13	0.90
LSTG: cathodal	0.03	0.06	19	0.44	0.90
RIFG: anodal	0.04	0.06	19	0.73	0.90
RIFG: cathodal	0.01	0.06	19	0.25	0.90
RSTG: anodal	0.01	0.06	19	0.15	0.90
RSTG: cathodal	0.03	0.06	19	0.48	0.90

9.3.1.2.2 Connectivity analysis per tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network by tDCS condition. Both anodal tDCS and cathodal tDCS induced significant correlations. These were LIFG/RSTG for anodal and LSTG/RSTG for cathodal (Tables 5 and 6).

Table 5. Partial correlation analyses for fitted mean brain activations under anodal tDCS in LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.19	-0.12	***0.49***
LSTG	0.19	1.00	0.18	0.39
RIFG	-0.12	0.18	1.00	0.47
RSTG	0.49	0.39	0.47	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 6. Partial correlation analyses for fitted mean brain activations under cathodal tDCS in LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.18	0.42	0.21
LSTG	-0.18	1.00	-0.09	***0.64***
RIFG	0.42	-0.09	1.00	0.27
RSTG	0.21	0.64	0.27	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

9.3.1.3 WN

9.3.1.3.1 Task and tDCS effects on ROI mean brain activation

A 2 x 4 (tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of both anodal and cathodal tDCS conditions. No significant interaction between tDCS and ROI was observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were performed, but none of them appeared significantly different from zero (Figure 3 and Table 7).

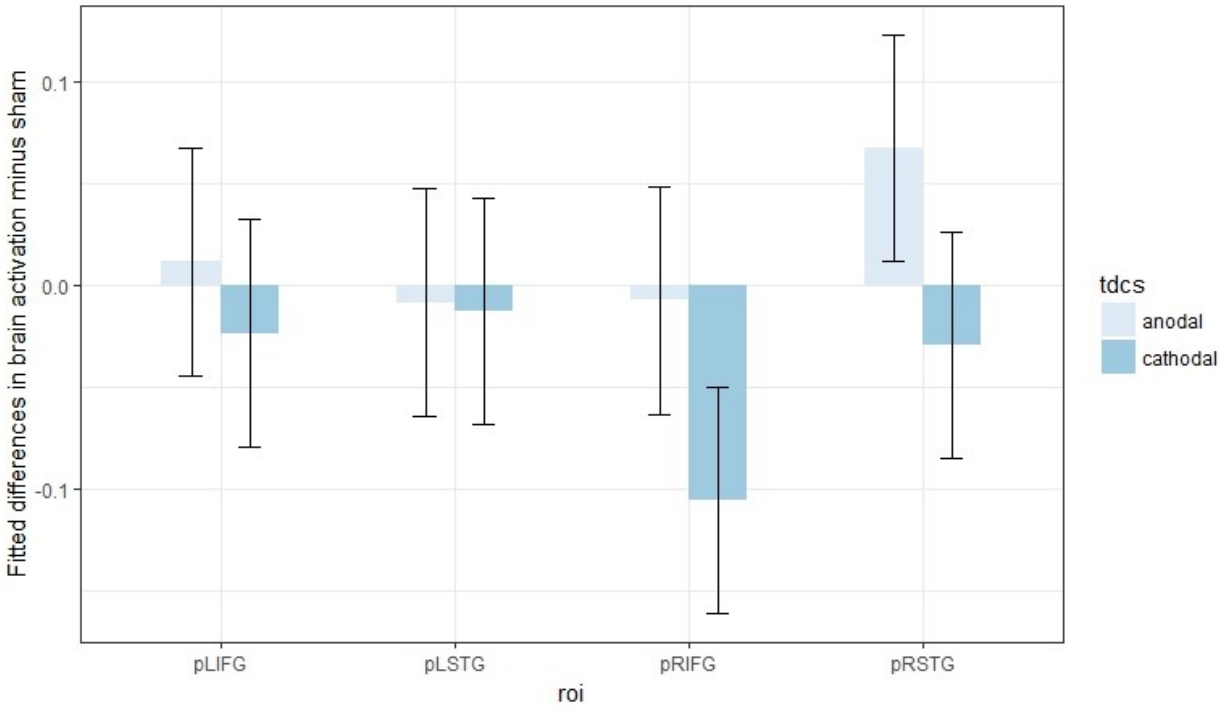

Figure 3. Fitted mean brain activation per ROI and task for WN. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 7. Contrast analyses for fitted brain activations per ROI and tDCS

Contrast	estimate	SE	df	t	P
LIFG: anodal	0.01	0.06	19	0.21	0.90
LIFG: cathodal	-0.02	0.06	19	-0.42	0.90
LSTG: anodal	-0.01	0.06	19	-0.15	0.90
LSTG: cathodal	-0.01	0.06	19	-0.23	0.90
RIFG: anodal	-0.01	0.06	19	-0.13	0.90
RIFG: cathodal	-0.11	0.06	19	-1.89	0.59
RSTG: anodal	0.07	0.06	19	1.21	0.90
RSTG: cathodal	-0.03	0.06	19	-0.53	0.90

9.3.1.3.2 Connectivity analysis per tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by tDCS condition. Only cathodal tDCS induced significant correlations, and these were the LIFG/RSTG and the LSTG/RSTG (Tables 8 and 9).

Table 8. Partial correlation analyses for fitted mean brain activations under anodal tDCS in WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.40	0.29	0.34
LSTG	0.40	1.00	0.05	0.40
RIFG	0.29	0.05	1.00	0.13
RSTG	0.34	0.40	0.13	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

Table 9. Partial correlation analyses for fitted mean brain activations under cathodal tDCS in WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.27	-0.02	***0.63***
LSTG	-0.27	1.00	-0.08	***0.77***
RIFG	-0.02	-0.08	1.00	0.19
RSTG	0.63	0.77	0.19	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

9.3.1.4 Analysis of words and nonwords in LD

9.3.1.4.1 Stimulus type and tDCS effects on ROI mean brain activation

A 2 x 3 x 4 (stimulus type x tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of words and nonwords in the LD task data of the healthy young adult sample whose target of stimulation was the LSTG. No significant interactions were observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were conducted, but no significant result was observed (Figure 4 and Table 10).

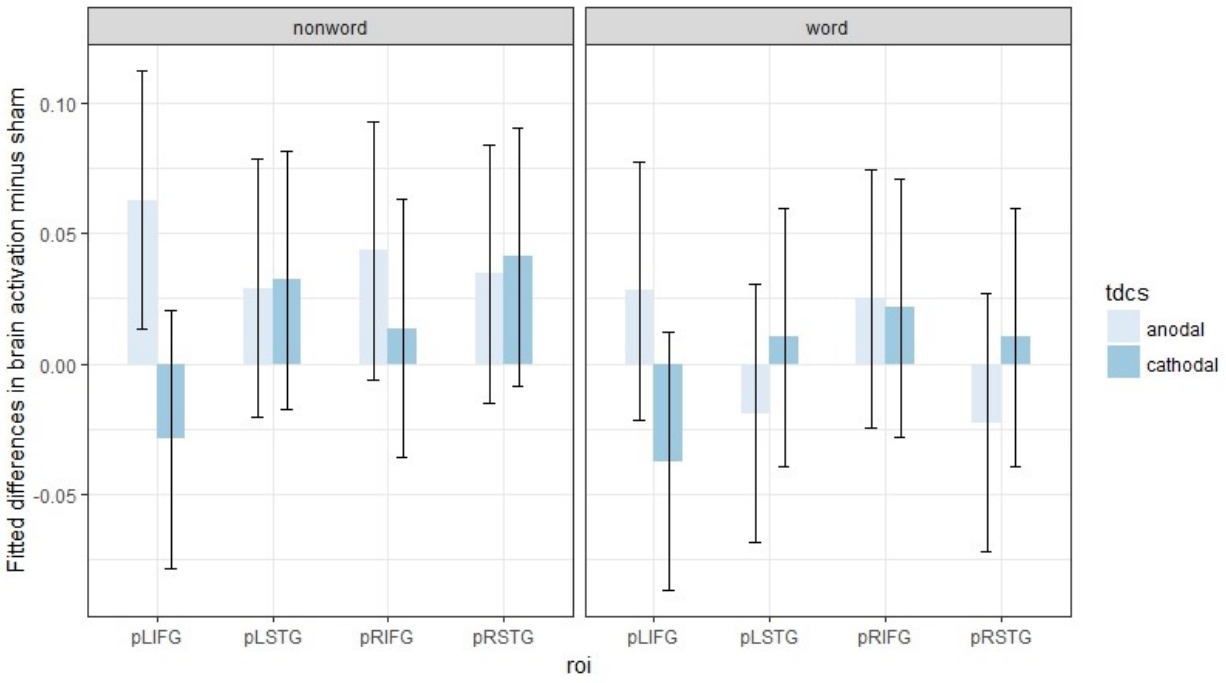

Figure 4. Fitted mean brain activation per ROI and stimulus type in LD. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation.

Table 10. Contrast analyses for fitted brain activations per ROI and stimulus type

Contrast	Estimate	SE	df	*t*	*p*
LIFG: nonword/anodal	0.06	0.05	19	1.27	0.84
LIFG: word/anodal	0.03	0.05	19	0.57	0.84
LIFG: nonword/cathodal	-0.03	0.05	19	-0.58	0.84
LIFG: word/cathodal	-0.04	0.05	19	-0.76	0.84
LSTG: nonword/anodal	0.03	0.05	19	0.58	0.84
LSTG: word/anodal	-0.02	0.05	19	-0.39	0.84
LSTG: nonword/cathodal	0.03	0.05	19	0.65	0.84
LSTG: word/cathodal	0.01	0.05	19	0.21	0.84
RIFG: nonword/anodal	0.04	0.05	19	0.88	0.84
RIFG: word/anodal	0.03	0.05	19	0.51	0.84
RIFG: nonword/cathodal	0.01	0.05	19	0.27	0.84
RIFG: word/cathodal	0.02	0.05	19	0.43	0.84
RSTG: nonword/anodal	0.03	0.05	19	0.70	0.84
RSTG: word/anodal	-0.02	0.05	19	-0.46	0.84
RSTG: nonword/cathodal	0.04	0.05	19	0.83	0.84
RSTG: word/cathodal	0.01	0.05	19	0.21	0.84

9.3.1.4.2 Connectivity analysis per stimulus type and tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by stimulus type and tDCS condition. The stimulus type nonword induced more significant correlations than the stimulus type word under both anodal tDCS and cathodal tDCS. Significant correlations with the stimulus type nonword were LIFG/RSTG and RIFG/RSTG under anodal tDCS and LIFG/RIFG and LSTG/RSTG under cathodal tDCS. The stimulus type word presented with the same significant correlation for both anodal tDCS and cathodal tDCS: the LSTG/RSTG (Tables 11 through 14).

Table 11. Partial correlation analyses for fitted mean brain activations in words of LD under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.02	-0.07	0.40
LSTG	0.02	1.00	0.01	***0.65***
RIFG	-0.07	0.01	1.00	0.43
RSTG	0.40	0.65	0.43	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 12. Partial correlation analyses for fitted mean brain activations in nonwords of LD under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.31	-0.21	***0.53***
LSTG	0.31	1.00	0.27	0.19
RIFG	-0.21	0.27	1.00	***0.56***
RSTG	0.53	0.19	0.56	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 13. Partial correlation analyses for fitted mean brain activations in words of LD under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.07	0.34	0.10
LSTG	-0.07	1.00	0.00	***0.74***
RIFG	0.34	0.00	1.00	0.10
RSTG	0.10	0.74	0.10	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 14. Partial correlation analyses for fitted mean brain activations in nonwords of LD under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.18	***0.47***	0.24
LSTG	-0.18	1.00	-0.12	***0.51***
RIFG	0.47	-0.12	1.00	0.36
RSTG	0.24	0.51	0.36	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

9.3.1.5 Analysis of words and nonwords in WN

9.3.1.5.1 Stimulus type and tDCS effects on ROI mean brain activation

A 2 x 3 x 4 (stimulus type x tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of words and nonwords in the WN task data of the healthy young adult sample. No significant interaction was observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were conducted, but no significant result was observed (Figure 5 and Table 15).

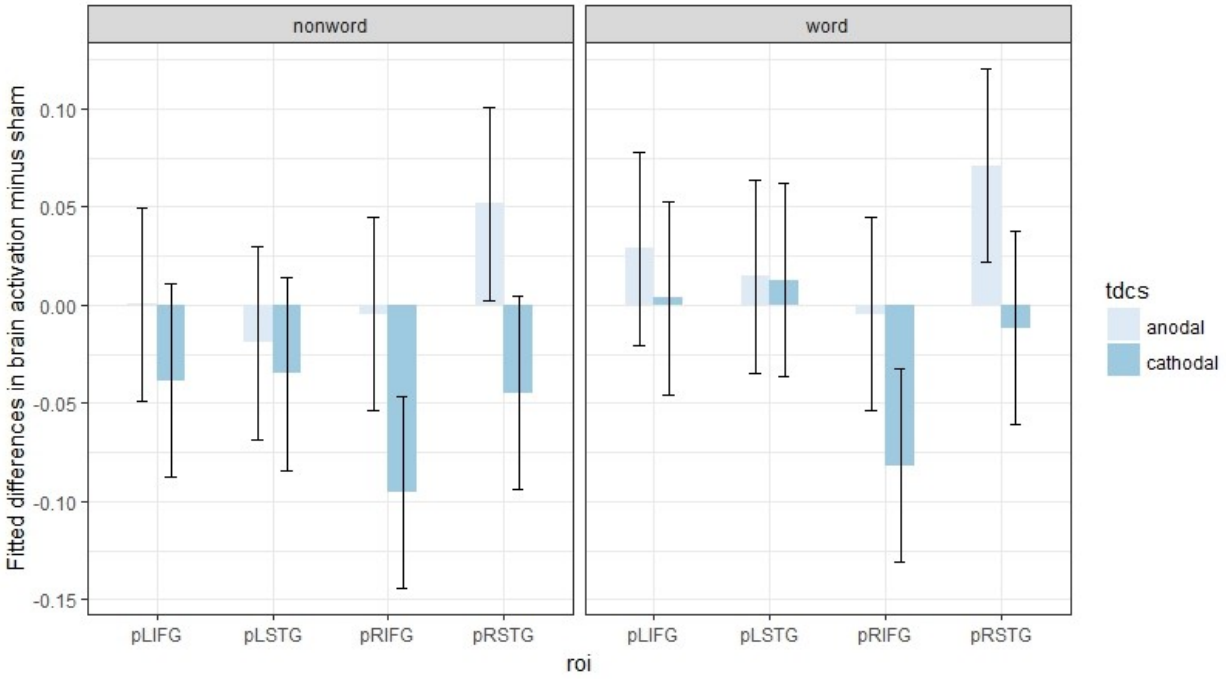

Figure 5. Fitted mean brain activation per ROI and stimulus type in WN. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 15. Contrast analyses for fitted brain activations per ROI and stimulus type

Contrast	estimate	SE	df	t	P
LIFG: nonword/anodal	0.00	0.05	19	0.01	0.99
LIFG: word/anodal	0.03	0.05	19	0.59	0.99
LIFG: nonword/cathodal	-0.04	0.05	19	-0.78	0.99
LIFG: word/cathodal	0.00	0.05	19	0.07	0.99
LSTG: nonword/anodal	-0.02	0.05	19	-0.39	0.99
LSTG: word/anodal	0.01	0.05	19	0.30	0.99
LSTG: nonword/cathodal	-0.03	0.05	19	-0.71	0.99
LSTG: word/cathodal	0.01	0.05	19	0.26	0.99
RIFG: nonword/anodal	0.00	0.05	19	-0.09	0.99
RIFG: word/anodal	0.00	0.05	19	-0.10	0.99
RIFG: nonword/cathodal	-0.10	0.05	19	-1.94	0.88
RIFG: word/cathodal	-0.08	0.05	19	-1.66	0.88
RSTG: nonword/anodal	0.05	0.05	19	1.05	0.99
RSTG: word/anodal	0.07	0.05	19	1.45	0.88
RSTG: nonword/cathodal	-0.04	0.05	19	-0.91	0.99
RSTG: word/cathodal	-0.01	0.05	19	-0.24	0.99

9.3.1.5.2 Connectivity analysis per stimulus type and tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by stimulus type and tDCS. More significant correlations were observed for nonwords than for words under cathodal stimulation, whilst the reverse pattern was observed for anodal stimulation. Under cathodal tDCS, significant correlations were LIFG/RSTG and LSTG/RSTG for nonwords and LSTG/RSTG for words. Under anodal stimulation, only words induced a significant correlation: the LSTG/RSTG (Tables 16 through 19).

Table 16. Partial correlation analyses for fitted mean brain activations in words of WN under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.25	0.25	0.29
LSTG	0.25	1.00	0.01	***0.60***
RIFG	0.25	0.01	1.00	0.17
RSTG	0.29	0.60	0.17	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 17. Partial correlation analyses for fitted mean brain activations in nonwords of WN under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.43	0.31	0.41
LSTG	0.43	1.00	0.14	0.21
RIFG	0.31	0.14	1.00	0.10
RSTG	0.41	0.21	0.10	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

Table 18. Partial correlation analyses for fitted mean brain activations in words of WN under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.06	0.37	0.33
LSTG	-0.06	1.00	0.13	***0.80***
RIFG	0.37	0.13	1.00	-0.16
RSTG	0.33	0.80	-0.16	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 19. Partial correlation analyses for fitted mean brain activations in nonwords of WN under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.08	0.17	***0.65***
LSTG	-0.08	1.00	-0.05	***0.61***
RIFG	0.17	-0.05	1.00	0.21
RSTG	0.65	0.61	0.21	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

9.4. DISCUSSION

The aim of this study was to investigate the task load modulation of the effects of tDCS over the LSTG on the brain activation of healthy young adults with tasks that involve phonological processing. These tasks were chosen in a range from speech perception to speech production, and were assumed to pose decreasingly less task load to the LSTG (Amunts et al., 1999; Indefrey, 2011; Lee et al., 2012; Liakakis et al., 2011; Liebenthal et al., 2013). According to the multi-node framework, tDCS was expected to have more robust effects when the task load was higher for the target of stimulation (Bikson et al., 2013; Nozari, Woodard, & Thompson-Schill, 2014; Pope et al., 2015). The facilitatory effect of anodal tDCS and the inhibitory effect of cathodal tDCS should be therefore more evident for speech perception tasks than for speech production tasks. Speech production tasks during downregulation of the LSTG were more likely to induce facilitation via compensation, since the room for compensation when a node of lower relevance for the task is targeted is larger. Results of this study indicate that the network mechanisms used by the brain to handle tDCS perturbations are consistent with these predictions based on task load.

In general, task load modulation was observed in both cathodal tDCS and anodal tDCS of the LSTG during performance in tasks of speech perception and speech production. Since effects of tDCS are directly related to task load (Bikson et al., 2013; Nozari, Woodard, & Thompson-Schill, 2014; Pope et al., 2015), anodal tDCS on the LSTG was expected to decrease facilitation whilst cathodal tDCS on the LSTG was expected to decrease inhibition across the range of speech perception to speech production tasks. This pattern of response should similarly apply from words to nonwords. Conversely, facilitation via compensation induced by cathodal tDCS should increase across the range of tasks or stimulus types. Effects matching these predictions were noticed in terms

of significant prominent connections between the ROIs of the target network (LIFG, LSTG, RIFG and RSTG) caused by both anodal tDCS and cathodal tDCS.

Anodal tDCS had a higher facilitatory effect on the CP than on the WN task, and similarly a higher effect on the word stimuli than on the nonword stimuli of the WN task. The target (LSTG), for which CP and the word stimuli would have a high task load (Chang et al., 2010; Leonard & Chang, 2014; Okada & Hickok, 2006a), had its engagement in efficient network strategies (LIFG/LSTG, LSTG/RSTG in this example) facilitated by anodal tDCS. Consistent with these findings, no connection was boosted by anodal tDCS of the LSTG when the WN task and the nonword stimuli were used, as their task load for the LSTG was low. However, this result should be taken cautiously, since it is not possible to disambiguate between lack of statistical power to detect a small effect or absence of an effect from non-significant results.

Cathodal tDCS differentially induced compensation across the range of speech perception to speech production tasks and word and nonword stimulus types. For example, for the CP task, which has high task load for the LSTG, the impact of inhibition was large, and no compensation seems to have been induced (this is a tentative theoretically motivated interpretation that should be taken cautiously, since no definitive conclusions can be drawn from non-significant results). Similarly, compensation was small for the stimulus type word in the WN task. It seems that only an attempt of self-compensation was possible, as the only significant connection observed was the LSTG/RSTG. On the other hand, compensation seems to have been more effective for the WN task and the nonword stimuli for both the LD and the WN tasks. Their task load was lower and the number of significant connections caused by stimulation was higher. These findings support the compensatory neural mechanism based on task load inferred and discussed in chapter 3 (section

3.1.3.4) from Nozari, Woodard and Thompson-Schill's (2014) set of behavioural findings for cathodal tDCS.

CHAPTER 10:

NEURAL CORRELATES OF TASK LOAD MODULATION OF THE EFFECTS OF tDCS OVER THE LIFG FOR PHONOLOGICAL PROCESSING IN DYSLEXIA

10.1 INTRODUCTION

In this chapter, I investigated the neural correlates of task load modulation of the effects of tDCS for phonological processing in PWD under the multi-node framework. The target of stimulation was the LIFG. However, since PWD have been shown to have an altered pattern of brain activity that subserves phonological processing compared to healthy young adults (Brunswick et al., 1999; Carter et al., 2009; Georgiewa et al., 1999; Klingberg et al., 2000; Pagnotta et al., 2015; Rimrodt et al., 2010; Ruff et al., 2003; Waldie et al., 2013), predictions should be adjusted accordingly. The aim of this study was therefore to investigate task load modulation of the effects of tDCS over the LIFG considering the particular altered pattern of brain activity for phonological processing presented by PWD (c.f. Figure 1 in chapter 3 for an overview of predictions on task load modulation of the effects of tDCS over the LIFG for the healthy brain).

Developmental dyslexia is a hereditary language disorder characterised by a difficulty in learning to read that is not attributable to cognitive or sensory deficits or lack of educational opportunities (Ramus, 2004). It has been suggested that a deficit in phonological processing is always involved in all cases (Ramus, 2004), which is supported by neuroimaging studies that show altered patterns of brain activity and white matter integrity in areas involved with phonological processing (typically the LIFG and LSTG cortical areas and the arcuate and superior longitudinal fasciculi, Burton, 2001; Saur et al., 2008). The usual pattern of cortical alteration typically involves hypoactivation of the LSTG and hyperactivation of the LIFG (Brunswick et al., 1999; Georgiewa et al., 1999; Ruff et al., 2003). Communication between the frontal and temporal hubs has been shown to be weakened in both resting state and task-based analyses of functional connectivity (Schurz et al., 2015), as well as the relevant underlying white matter has been shown to have some degree of damage (Carter et al., 2009; Klingberg et al., 2000; Rimrodt et al., 2010). Furthermore,

PWD have been demonstrated to have (maladaptive) compensatory mechanisms that commonly include the overactivation of the LIFG, RIFG and RSTG (Pagnotta et al., 2015; Waldie et al., 2013). Costanzo et al.'s (2016a, 2016b) applied anodal tDCS to the LSTG and cathodal tDCS to the RSTG, and they found that brain stimulation was beneficial in improving the reading abilities in PWD. These results suggest that the LSTG has a potential to recover and that the RSTG might have a maladaptive role in dyslexia. Moreover, they support the view that tDCS shows promise for the treatment of dyslexia (Vicario & Nitsche, 2013).

In the study that is reported in this chapter, compensatory LIFG and right cortical hyperactivation was expected to be evident for PWD. Predictions are presented in the subsections below by task. References to other more relevant nodes for compensation of the LIFG include the LSTG, the RIFG and the RSTG, i.e., the target network for this thesis. Although the LSTG seemed a preferred candidate among these network nodes because it is typically involved in phonological processing, the functional and structural connectivity between the LIFG and the LSTG in PWD could be impaired to some degree (Carter et al., 2009; Klingberg et al., 2000; Rimrodt et al., 2010; Schurz et al., 2015), and the alternative route of right compensation could prevail. Furthermore, as shown in chapter 7, findings suggest that task difficulty could also induce strategies of compensation beyond the canonical left pathway of phonological processing.

10.1.1 CP

Behavioural (chapter 5) and fMRI (chapter 8) results seem to support the assumption that CP has low task load for the LIFG (Lee et al., 2012; Liebenthal et al., 2013) at least for healthy young adults. This assumption should also apply for PWD. However, PWD are known to have a hyperactivated LIFG (Brunswick et al., 1999; Georgiewa et al., 1999; Hoeft et al., 2006; Ruff et

al., 2003), that is likely to reflect maladaptive functioning (Brunswick et al., 1999; Meinzer et al., 2013). It was expected that anodal tDCS would increase the efficiency of the LIFG by reducing its level of activation (Meinzer et al., 2013). However, the effect could be considerably small, given the low task load involved. No significant changes from baseline were expected in network connectivity.

Cathodal tDCS was expected to increase the baseline level of neuronal activation of the LIFG for both healthy young adults and PWD, resulting in decreased efficiency of the LIFG to solve the task. Downregulation of a node of low relevance for the task was expected to induce compensation by more relevant network nodes to respond to the acute extra demand, as the results in chapter 8 suggest. In PWD, however, the LSTG is known to be hypoactivated (Brunswick et al., 1999; Georgiewa et al., 1999; Hoeft et al., 2006; Ruff et al., 2003). Results could therefore vary from successful compensation, but weaker than that for healthy young adults, to an unsuccessful compensation. Strengthening of network connections should be observed for successful compensation.

10.1.2 LD

LD was assumed to have intermediate task load for the LIFG. Anodal tDCS of the LIFG was therefore expected to induce facilitation, that should be higher than that expected for CP. No significant changes from baseline were expected in network connectivity.

Similar to the predictions made for CP, cathodal stimulation of the LIFG was expected to increase its level of neuronal activation and decrease its efficiency in solving the task for PWD as it was for healthy young adults. Compensation of cathodal tDCS-induced downregulation of the LIFG by other network nodes was similarly expected through overactivation of network nodes or

strengthening of their connections. However, compensation in LD was likely to be more modest than in CP, because the LIFG was assumed to have less room for compensation in the LD task. As mentioned previously for the CP task, compensation could be negatively affected by the LSTG hypoactivation present in PWD (Brunswick et al., 1999; Georgiewa et al., 1999; Hoeft et al., 2006; Ruff et al., 2003).

10.1.3 WN

The LIFG was assumed to be a node of high relevance for the WN since this was a task placed on the production end of the speech perception to speech production range (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011). Similar to healthy young adults, anodal tDCS of the LIFG was expected to decrease the baseline level of activation for PWD with consequent increased LIFG efficiency in solving the task. In PWD, anodal tDCS should decrease maladaptive hyperactivation, an effect expected to be beneficial (Meinzer et al., 2013). No significant changes from baseline were expected in network connectivity.

Similar to controls, cathodal tDCS was expected to increase the baseline level of activation of the target in PWD with a consequent reduction in LIFG efficiency in solving the task. Compensation of cathodal tDCS-induced downregulation was expected to be unsatisfactory for both populations because the target was a node of high relevance for the task, and therefore, with less room for compensation.

10.1.4 Words and nonwords

The LIFG was assumed to be a node of higher relevance for nonwords than for words (Heim et al., 2005; Nosarti et al., 2010; Xiao et al., 2005). Anodal tDCS of the LIFG was expected to have

for PWD the typical effect of reducing the target level of activation with a consequent increased efficiency to solve the task. However, anodal tDCS effects were expected to be stronger for nonwords than for words, and results could vary from an apparent null effect of stimulation to a significant result. No significant changes from baseline were expected in network connectivity.

Cathodal tDCS of the LIFG was expected to increase the LIFG level of activation and consequently decrease its efficiency in task solving also as a function of task load. Compensation of cathodal tDCS-induced downregulation by other network nodes was expected to be more successful for words than for nonwords because the LIFG was a node of comparatively less relevance for words. Compensatory activation of non-target nodes should be therefore higher for words than for nonwords, as well as increased the level of network connectivity. However, compensation in PWD was overall expected to be weaker than for healthy young adults because of the hypoactivation of the LSTG (Brunswick et al., 1999; Georgiewa et al., 1999; Hoeft et al., 2006; Ruff et al., 2003).

10.2 METHODS

Methods are as described in chapter 4 Methods. For the current study, six PWD (mean age: 20 years, SD: 1.94, 3 females) who met the inclusion criteria described in chapter 4 were included in the sample. All three experiments (CP, LD and WN) were performed by the PWD (and controls), in counterbalanced order across participants, with task, run (baseline or online) and tDCS stimulation (anodal, cathodal and sham) as a within-subject factor. Analyses were performed both within the PWD group, with a within-subject design (ROI analyses and within group whole brain analyses), and between PWD and controls (whole brain analyses), with group as a between-subject factor, in a mixed design. The sample of PWD used in the current study is the same as that used in

the study described in Chapter 7. Healthy young adult participants in the fMRI study where the LIFG was target of stimulation were used as controls in whole brain analyses (n = 20, mean age: 20.5 years, SD: 2.35, 9 females).

10.3 RESULTS

Whole brain analyses were conducted with task, stimulus type (for the LD and WN tasks) and tDCS as factors. Results of the effects of tDCS of the LIFG on whole brain activation in PWD are presented in Appendix 3. Results of ROI analyses are presented in the next subsection.

10.3.1 ROI analyses

Effects of task, stimulus type (for LD and WN), tDCS condition and ROIs on brain activation were analysed with mixed effect models for PWD. Relevant connections between ROIs were investigated with partial correlation analyses per task, stimulus type (for LD and WN) and tDCS condition. Both types of analyses are presented by task.

10.3.1.1 CP

10.3.1.1.1 Task and tDCS effects on ROI mean brain activation

A 2 x 4 (tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of both anodal and cathodal tDCS conditions. No significant interaction between tDCS and ROI was observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were performed, but none of them appeared significantly different from zero (Figure 1 and Table 1).

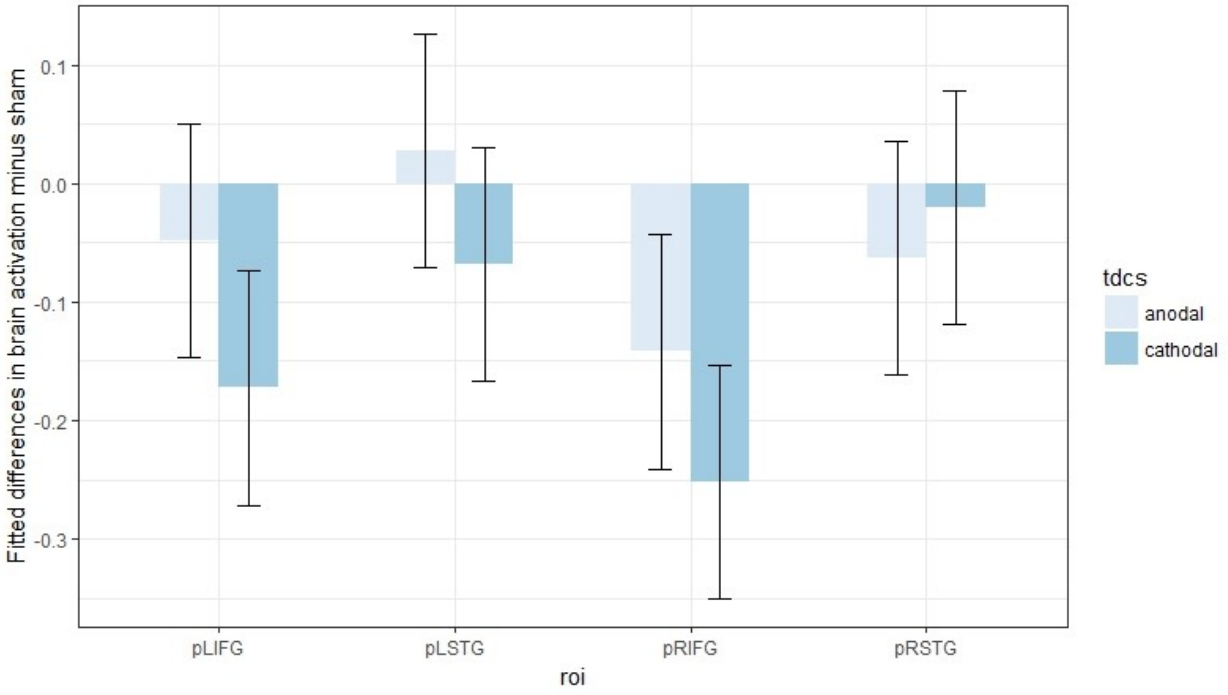

Figure 1. Fitted mean brain activation per ROI and tDCS for CP. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 1. Contrast analyses for fitted brain activations per ROI and tDCS

Contrast	Estimate	SE	df	*t*	*p*
LIFG: anodal	-0.05	0.10	5	-0.50	0.85
LIFG: cathodal	-0.17	0.10	5	-1.75	0.56
LSTG: anodal	0.03	0.10	5	0.28	0.85
LSTG: cathodal	-0.07	0.10	5	-0.69	0.85
RIFG: anodal	-0.14	0.10	5	-1.44	0.56
RIFG: cathodal	-0.25	0.10	5	-2.56	0.41
RSTG: anodal	-0.06	0.10	5	-0.64	0.85
RSTG: cathodal	-0.02	0.10	5	-0.21	0.85

10.3.1.1. 2 Connectivity analysis per tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by tDCS condition. Only anodal tDCS induced significant correlations, and these were: LSTG/RSTG and RIFG/RSTG (Tables 2 and 3).

Table 2. Partial correlation analyses for fitted mean brain activations under anodal tDCS in CP

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.85	0.95	-0.85
LSTG	0.85	1.00	-0.92	***0.98***
RIFG	0.95	-0.92	1.00	***0.95***
RSTG	-0.85	0.98	0.95	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 3. Partial correlation analyses for fitted mean brain activations under cathodal tDCS in CP

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.55	0.78	-0.51
LSTG	0.55	1.00	-0.86	0.95
RIFG	0.78	-0.86	1.00	0.89
RSTG	-0.51	0.95	0.89	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

10.3.1.2 LD

10.3.1.2.1 Task and tDCS effects on ROI mean brain activation

A 2 x 4 (tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of both anodal and cathodal tDCS conditions. No significant interaction of tDCS and ROI was observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were performed, but none of them appeared significantly different from zero (Figure 2 and Table 4).

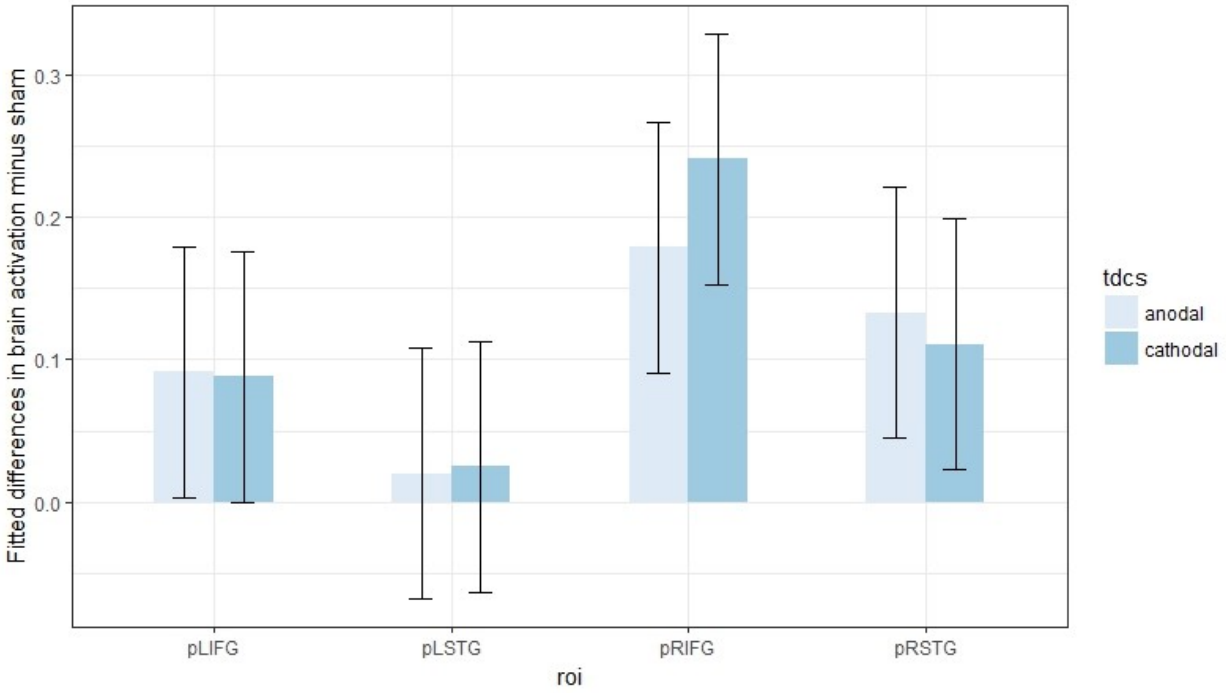

Figure 2. Fitted brain activation per ROI and tDCS for LD. The x-axis displays the ROIs. The y-axis displays fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 4. Contrast analyses for fitted brain activations per ROI and tDCS

Contrast	Estimate	SE	df	*t*	*p*
LIFG: anodal	0.09	0.09	5	1.04	0.48
LIFG: cathodal	0.09	0.09	5	1.00	0.48
LSTG: anodal	0.02	0.09	5	0.23	0.83
LSTG: cathodal	0.02	0.09	5	0.28	0.83
RIFG: anodal	0.18	0.09	5	2.03	0.39
RIFG: cathodal	0.24	0.09	5	2.74	0.33
RSTG: anodal	0.13	0.09	5	1.51	0.48
RSTG: cathodal	0.11	0.09	5	1.26	0.48

10.3.1.2.2 Connectivity analysis per tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by tDCS condition. Neither anodal tDCS nor cathodal tDCS induced significant correlations at $p \leq 0.05$ (Tables 5 and 6).

Table 5. Partial correlation analyses for fitted mean brain activations under anodal tDCS in LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.08	0.61	0.84
LSTG	-0.08	1.00	0.50	0.48
RIFG	0.61	0.50	1.00	-0.74
RSTG	0.84	0.48	-0.74	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

Table 6. Partial correlation analyses for fitted mean brain activations under cathodal tDCS in LD

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.01	0.30	0.20
LSTG	0.01	1.00	-0.18	0.67
RIFG	0.30	-0.18	1.00	0.60
RSTG	0.20	0.67	0.60	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

10.3.1.3 WN

10.3.1.3.1 Task and tDCS effects on ROI mean brain activation

A 2 x 4 (tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of both anodal and cathodal tDCS conditions. No significant interactions were observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were performed, but none of them appeared significantly different from zero (Figure 3 and Table 7).

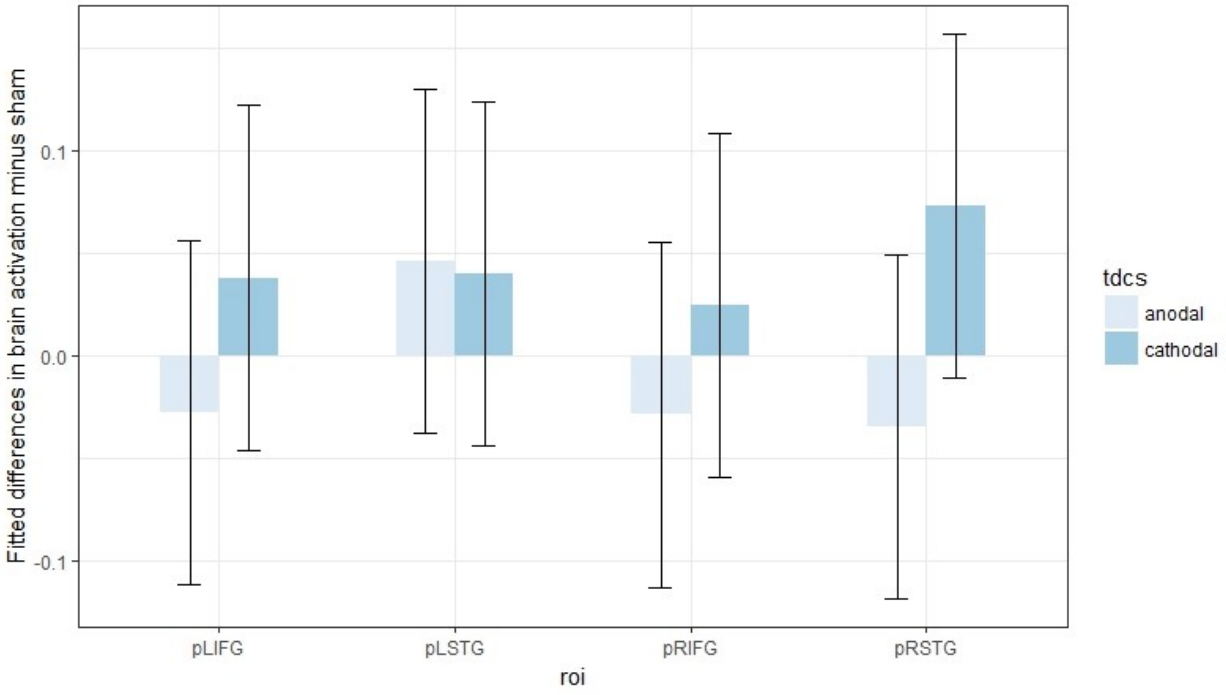

Figure 3. Fitted mean brain activation per ROI and task for WN. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 7. Contrast analyses for fitted brain activations per ROI and tDCS

Contrast	Estimate	SE	df	*t*	*p*
LIFG: anodal	-0.03	0.08	5	-0.33	0.78
LIFG: cathodal	0.04	0.08	5	0.45	0.78
LSTG: anodal	0.05	0.08	5	0.55	0.78
LSTG: cathodal	0.04	0.08	5	0.48	0.78
RIFG: anodal	-0.03	0.08	5	-0.35	0.78
RIFG: cathodal	0.02	0.08	5	0.29	0.78
RSTG: anodal	-0.04	0.08	5	-0.42	0.78
RSTG: cathodal	0.07	0.08	5	0.87	0.78

10.3.1.3.2 Connectivity analysis per tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by tDCS condition. Anodal tDCS induced the frontal LIFG/RIFG significant

correlation. Cathodal tDCS induced the left lateralised LIFG/LSTG significant correlation (Tables 8 and 9).

Table 8. Partial correlation analyses for fitted mean brain activations under anodal tDCS in WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.10	***0.96***	-0.94
LSTG	-0.10	1.00	0.33	-0.06
RIFG	0.96	0.33	1.00	0.94
RSTG	-0.94	-0.06	0.94	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 9. Partial correlation analyses for fitted mean brain activations under cathodal tDCS in WN

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	***0.98***	0.67	-0.18
LSTG	0.98	1.00	-0.68	0.30
RIFG	0.67	-0.68	1.00	0.30
RSTG	-0.18	0.30	0.30	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

10.3.1.4 Analysis of words and nonwords in LD

10.3.1.4.1 Stimulus type and tDCS effects on ROI mean brain activation

A 2 x 3 x 4 (stimulus type x tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of words and nonwords in the LD task data of PWD. No significant interactions were observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were conducted, but no significant result was observed (Figure 4 and Table 10).

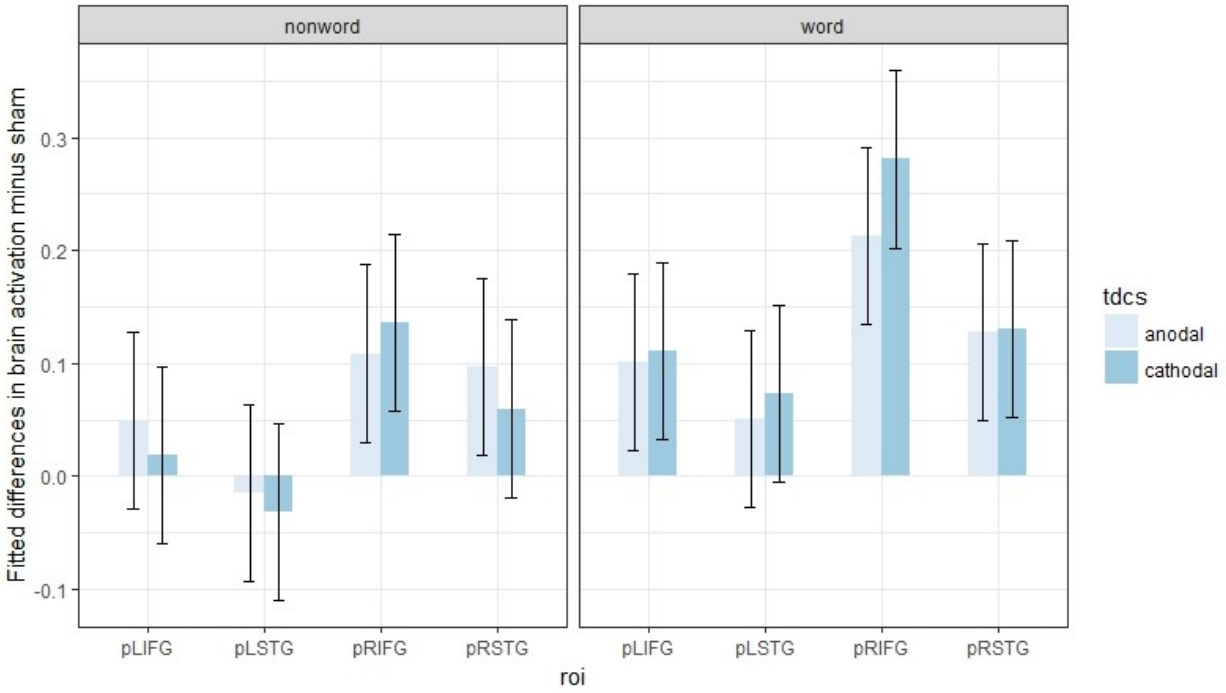

Figure 4. Fitted mean brain activation per ROI and stimulus type in LD. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 10. Contrast analyses for fitted brain activations per ROI and stimulus type

Contrast	Estimate	SE	df	*t*	*p*
LIFG: nonword/anodal	0.05	0.08	5	0.63	0.69
LIFG: word/anodal	0.10	0.08	5	1.29	0.48
LIFG: nonword/cathodal	0.02	0.08	5	0.24	0.86
LIFG: word/cathodal	0.11	0.08	5	1.42	0.48
LSTG: nonword/anodal	-0.01	0.08	5	-0.19	0.86
LSTG: word/anodal	0.05	0.08	5	0.65	0.69
LSTG: nonword/cathodal	-0.03	0.08	5	-0.41	0.80
LSTG: word/cathodal	0.07	0.08	5	0.94	0.63
RIFG: nonword/anodal	0.11	0.08	5	1.39	0.48
RIFG: word/anodal	0.21	0.08	5	2.72	0.33
RIFG: nonword/cathodal	0.14	0.08	5	1.74	0.48
RIFG: word/cathodal	0.28	0.08	5	3.58	0.25
RSTG: nonword/anodal	0.10	0.08	5	1.24	0.48
RSTG: word/anodal	0.13	0.08	5	1.63	0.48
RSTG: nonword/cathodal	0.06	0.08	5	0.76	0.69
RSTG: word/cathodal	0.13	0.08	5	1.67	0.48

10.3.1.4.2 Connectivity analysis per stimulus type and tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by stimulus type (i.e., word and nonword) and tDCS. Only anodal tDCS with the stimulus type word induced a significant correlation, the RIFG/LSTG (Tables 11 through 14).

Table 11. Partial correlation analyses for fitted mean brain activations in words of LD under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.74	-0.63	0.23
LSTG	0.74	1.00	***0.96***	0.47
RIFG	-0.63	0.96	1.00	-0.53
RSTG	0.23	0.47	-0.53	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 12. Partial correlation analyses for fitted mean brain activations in nonwords of LD under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.12	0.81	0.84
LSTG	-0.12	1.00	0.21	0.40
RIFG	0.81	0.21	1.00	-0.70
RSTG	0.84	0.40	-0.70	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

Table 13. Partial correlation analyses for fitted mean brain activations in words of LD under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.23	0.15	0.00
LSTG	0.23	1.00	-0.18	0.58
RIFG	0.15	-0.18	1.00	0.85
RSTG	0.00	0.58	0.85	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

Table 14. Partial correlation analyses for fitted mean brain activations in nonwords of LD under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.21	-0.16	0.56
LSTG	-0.21	1.00	-0.36	0.62
RIFG	-0.16	-0.36	1.00	0.79
RSTG	0.56	0.62	0.79	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

10.3.1.5 Analysis of words and nonwords in WN

10.3.1.5.1 Stimulus type and tDCS effects on ROI mean brain activation

A 2 x 3 x 4 (stimulus type x tDCS x ROI) linear mixed effect model was fitted to the mean parameter estimates of ROI activation data of words and nonwords in the WN task data of the healthy young adult sample. No significant interaction was observed.

Post hoc contrast analyses (Benjamini-Hochberg corrected for multiple comparisons) were conducted, but no significant result was observed (Figure 5 and Table 15).

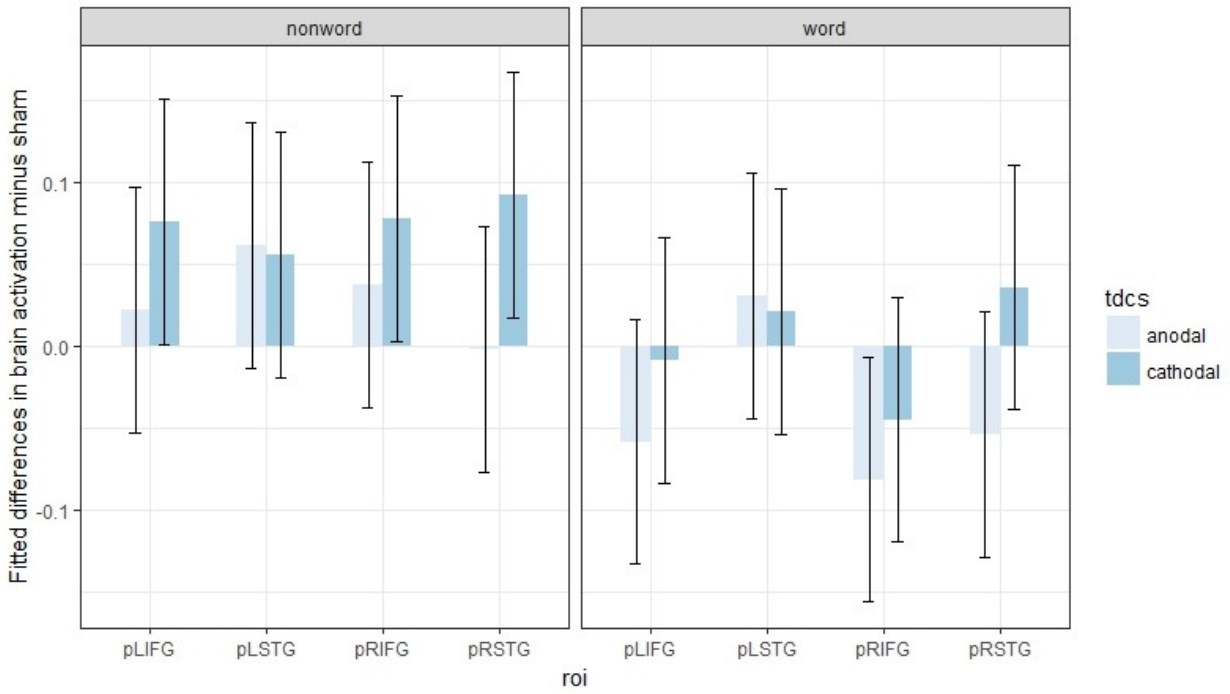

Figure 5. Fitted mean brain activation per ROI and stimulus type in WN. The x-axis displays the ROIs. The y-axis displays the fitted mean brain activation. Error bars represent the contrast estimate ± the pooled standard error.

Table 15. Contrast analyses for fitted brain activations per ROI and stimulus type

Contrast	Estimate	SE	df	*t*	*p*
LIFG: nonword/anodal	0.02	0.07	5	0.30	0.90
LIFG: word/anodal	-0.06	0.07	5	-0.78	0.90
LIFG: nonword/cathodal	0.08	0.07	5	1.01	0.90
LIFG: word/cathodal	-0.01	0.07	5	-0.11	0.98
LSTG: nonword/anodal	0.06	0.07	5	0.82	0.90
LSTG: word/anodal	0.03	0.07	5	0.42	0.90
LSTG: nonword/cathodal	0.06	0.07	5	0.75	0.90
LSTG: word/cathodal	0.02	0.07	5	0.29	0.90
RIFG: nonword/anodal	0.04	0.07	5	0.50	0.90
RIFG: word/anodal	-0.08	0.07	5	-1.09	0.90
RIFG: nonword/cathodal	0.08	0.07	5	1.04	0.90
RIFG: word/cathodal	-0.04	0.07	5	-0.60	0.90
RSTG: nonword/anodal	0.00	0.07	5	-0.02	0.98
RSTG: word/anodal	-0.05	0.07	5	-0.72	0.90
RSTG: nonword/cathodal	0.09	0.07	5	1.23	0.90
RSTG: word/cathodal	0.04	0.07	5	0.48	0.90

10.3.1.5.2 Connectivity analysis per stimulus type and tDCS condition

Partial correlation analyses were performed between the fitted mean brain activations of the target network ROIs by stimulus type (i.e., word and nonword) and tDCS condition. Only anodal tDCS with stimulus type word induced significant correlations, which were the LIFG/RSTG, LIFG/LSTG, LIFG/RIFG, LSTG/RSTG and RIFG/RSTG (Tables 16 through 19).

Table 16. Partial correlation analyses for fitted mean brain activations in words of WN under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	***0.96***	***0.97***	***-0.97***
LSTG	0.96	1.00	-0.90	***0.96***
RIFG	0.97	-0.90	1.00	***0.97***
RSTG	-0.97	0.96	0.97	1.00

Pearson's *r* for each pair of ROIs with significant correlations at $p \leq 0.05$ marked in bold.

Table 17. Partial correlation analyses for fitted mean brain activations in nonwords of WN under anodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	-0.16	0.83	-0.66
LSTG	-0.16	1.00	0.53	0.05
RIFG	0.83	0.53	1.00	0.70
RSTG	-0.66	0.05	0.70	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

Table 18. Partial correlation analyses for fitted mean brain activations in words of WN under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.86	0.39	-0.15
LSTG	0.86	1.00	-0.66	0.43
RIFG	0.39	-0.66	1.00	0.37
RSTG	-0.15	0.43	0.37	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

Table 19. Partial correlation analyses for fitted mean brain activations in nonwords of WN under cathodal tDCS

	LIFG	LSTG	RIFG	RSTG
LIFG	1.00	0.81	-0.17	0.35
LSTG	0.81	1.00	0.27	0.15
RIFG	-0.17	0.27	1.00	0.17
RSTG	0.35	0.15	0.17	1.00

Pearson's *r* for each pair of ROIs. No significant correlation at $p \leq 0.05$ was observed.

10.4. DISCUSSION

The aim of this study was to investigate how the dyslexic brain would handle tDCS perturbations during the performance in tasks which involve phonological processing, a language function that is affected in PWD (Brunswick et al., 1999; Ramus et al., 2004). More specifically, I investigated whether task load of tasks involving phonological processing would have a differential effect on the outcomes of tDCS stimulation of the LIFG in PWD. To accomplish this aim, tasks covering a range from speech perception to speech production were used. This range was assumed

to pose increasingly higher task load to the LIFG (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Lee et al., 2012; Liakakis et al., 2011; Liebenthal et al., 2013).

Typical predictions for the effects of tDCS as a function of task load were as follows for the tDCS of the LIFG. Anodal tDCS was expected to increasingly induce facilitation across the speech perception to speech production range of tasks, whilst cathodal stimulation was expected to increasingly induce inhibition. Cathodal tDCS was also expected to induce facilitation via compensation, which was more likely to occur in conditions of lower task load. However, due to the phonological processing deficit in PWD, some of these typical predictions could not apply or weaker responses (for example in terms of brain activation or number of significant connections between network nodes) could be generated for PWD compared to healthy young adults. For example, compensation of the downregulation of the LIFG for a task of speech perception was expected to be at least weaker. This is because the LSTG, a brain area highly relevant for phonological processing in speech perception tasks (Lee et al., 2012; Liebenthal et al., 2013), is known to be hypoactivated in PWD (Brunswick et al., 1999; Georgiewa et al., 1999; Hoeft et al., 2006; Ruff et al., 2003), and therefore less likely to offer compensation. Results of this study suggest that the baseline brain activation associated with the phonological deficit in PWD restricts the network strategies that can be used by the brain and modulates responses that otherwise should follow predictions based on task load for the healthy brain.

Outcomes were evaluated in terms of significant prominent connections between the target network nodes induced by the direct current. In general, results of both anodal tDCS and cathodal tDCS were contrary to predictions based on task load for the healthy brain. Anodal tDCS of the LIFG should increase facilitation, whilst cathodal tDCS should increase inhibition, across the tasks in the range from speech perception to speech production and from words to nonwords.

Compensation induced by cathodal tDCS was expected to be decreasingly lower. Contrary to task load based predictions, anodal tDCS caused larger facilitation for CP than for WN, whilst cathodal tDCS-induced compensation was larger for WN than for CP. Similarly, in both the LD and the WN tasks, anodal tDCS facilitation was larger for words than for nonwords, whereas cathodal tDCS had an apparently equivalent inhibitory effect for both stimulus types, when compensation was expected for words. It should be noted, however, that in all these comparisons, the part said to have smaller facilitatory effect had non-significant results, that were interpreted as so for theoretical reasons. Nevertheless, since no definitive conclusions can be drawn from non-significant results, this interpretation should be taken cautiously.

Taken together, these brain stimulation results and the known pattern of inefficient brain activation (LIFG hyperactivation compensating for the LSTG hypoactivation) for phonological processing in PWD suggest a (maladaptive) shift of function from the LSTG to the LIFG (Brunswick et al., 1999). Consequently, the roles previously attributed to the LIFG cannot be performed at a suitable level. This interpretation would explain findings where the LIFG showed to be more responsive to anodal tDCS during the CP task and with the stimulus type words (for both LD and WN) instead of during the WN task and with the stimulus type nonwords, as justified by the new LIFG duties. Because the LIFG is overloaded and its multi-task role seems maladaptive, the inconsistent pattern of responses to old and new duties seems also justified. For example, cathodal tDCS strongly downregulated the LIFG (no significant prominent connections; as discussed above, a theoretically motivated tentative interpretation of a null finding) for nonwords in both LD and WN. Since no sign of compensation was observed, this indicates that nonwords had a high task load for the LIFG, as assumed for the healthy brain.

CHAPTER 11:

NEURAL CORRELATES OF TASK LOAD MODULATION OF THE EFFECTS OF tDCS OVER THE LIFG FOR PHONOLOGICAL PROCESSING IN APHASIA

11.1 INTRODUCTION

In this chapter, I investigated the neural correlates of task load modulation of the effects of tDCS over the LIFG for phonological processing in PWA, following the multi-node framework. However, due to the altered pattern of brain activation underlying PWA language disorders (Sandberg et al., 2017; Yang et al., 2016; Zhu et al., 2014), predictions based on the healthy brain (c.f. Figure 1 in chapter 3 for an overview) should be adjusted accordingly. Their possible mechanisms of recovery from aphasia (Torres et al., 2013) should also be considered.

Aphasia is a neurological language disorder that impairs speech production and comprehension to various degrees and whose most common cause is stroke (Koenig-Bruhin et al., 2013). Regarding the profile of damage, the stroke causes neuronal tissue loss in gray matter of areas of the (most commonly) left perisylvian region, which typically include the IFG and the STG (Kiran, 2012). Relevant underlying white matter is often also found affected, and typically includes the arcuate fasciculus (Basilakos et al., 2014; Li et al., 2017; Schlaug et al., 2009). Considering that some level of phonological processing deficit seems always to be present in aphasia (van Hees et al., 2013), white matter in the so-called dorsal pathway, involved with phonological processing (Saur et al., 2008), is particularly expected to always have diminished integrity. The dorsal pathway consists of the arcuate and the superior longitudinal fasciculi, which connect the superior temporal gyrus to frontal premotor cortices (Saur et al., 2008).

Consequently, functional integrity is also affected. A pattern of diminished activation of regions involved in language, as well as reduced connectivity between them, is observed. Reduced amplitude of low frequency fluctuation in resting state has been found on the left hemisphere (Yang et al., 2016), followed by an increased amplitude of low frequency fluctuation on the right hemisphere likely due to compensatory mechanisms (Yang et al., 2016). Cortical hypoconnectivity

in resting state networks, particularly left hemispheric networks involved with language, has also been reported (Sandberg et al., 2017; Zhu et al., 2014). However, lesions seem to influence the functioning of undamaged areas as well, as noted from an overall pattern of hypoconnectivity both within the left hemisphere and across brain hemispheres (Sandberg et al., 2017). On the other hand, some stronger connections have also been observed within the lesioned left hemisphere, what has been attributed to a potential compensatory mechanism (Sandberg et al., 2017). It should be noted, however, that potential for recovery exists despite the overall picture of hypoactivity and hypoconnectivity. For example, in a case study, Dominguez et al. (2014) succeeded in inducing improved language performance with anodal tDCS of the left perilesional area that was able to assume the language function. The pattern of (potential) recovery (Torres et al., 2013) should be closely observed for therapeutic interventions to be successful. The tDCS has here a potential as both diagnostic and therapeutic tool (Hamilton et al., 2011).

As discussed in chapter 2, the patterns of recovery from aphasia caused by stroke are variable. However, three basic models of recovery are typically observed (Torres et al., 2013). In one of the possible models, perilesional areas are able to assume the language function from the brain area damaged rather satisfactorily. In another path to recovery, the right homologue of the lesioned area assumes the language function instead. Two different models may arise in this case. In one of the models, the activity of the right homologue is maladaptive, and either shows inefficient performance or inhibits the perilesional areas on the left hemisphere. Alternatively, the right homologue might well perform satisfactorily to compensate for the function previously subserved by the left hemisphere.

A range of possible outcomes of tDCS stimulation of the LIFG has been presented in the next subsections under the assumption of responses from a perilesional area able to perform the

language function previously attributed to the frontal lesioned area (Torres et al., 2013). Otherwise, no response to tDCS was expected. For the predictions presented below, reference to other more relevant network nodes for LIFG compensation could include the LSTG, the RIFG or the RSTG, depending on the model of (potential) aphasia recovery (Torres et al., 2013).

11.1.1 CP

As alluded to and supported by empirical evidence in chapters 5 and 8, CP was assumed to have low task load for the LIFG. In controls, anodal tDCS of the LIFG was expected to decrease the baseline activation as a function of task load to ensure increased efficiency in solving the task. However, in cases where the baseline level of neuronal activation is abnormally low, such as in aphasia (Sandberg et al., 2017; Yang et al., 2016; Zhu et al., 2014), anodal tDCS is expected to normalise the baseline, i.e. to increase neuronal activation towards a satisfactory level to solve the task efficiently, which seems to have been the case for dyslexia in Costanzo et al.'s (2016a, 2016b) behavioural findings. This is expected to happen as a function of task load. For PWA, anodal tDCS of the LIFG was therefore expected to increase activation of the perilesional area compared to sham. Anodal tDCS was expected to have rather a local effect. However, due to the low task load of CP, and also contingent on the level of responsivity of the perilesional area, effects could be considerably weak.

Cathodal tDCS of the LIFG in PWA, such as predicted for controls, was expected to increase baseline activation as a result of decreased efficiency in solving the task, although potentially with a smaller effect due to the smaller responsivity to the direct current caused by the overall neuronal hypoactivity. However, compensation of cathodal tDCS-induced downregulation of the LIFG by more important nodes of the network, which is assumed to occur in healthy controls,

would depend on the degree of spared communication between the LIFG and other regions of the target network involved in phonological processing for PWA.

11.1.2 LD

LD was assumed to be a task of intermediate relevance for the LIFG compared to CP and WN. In controls, anodal tDCS of the LIFG was expected to reduce its activation compared to sham to increase the target efficiency in solving the task. However, as discussed in the section on CP, anodal tDCS in PWA was expected to regulate the abnormal baseline hypoactivation of the LIFG, inducing increase in activation. This should occur as a function of task load.

Cathodal stimulation of the LIFG was expected to increase baseline neuronal activation for both controls and PWA, resulting in decreased efficiency to solve the task. However, due to the overall neuronal hypoactivity in PWA, effects were expected to be smaller or less noticeable than for controls. Compensation of cathodal tDCS-induced downregulation of the LIFG in PWA could be smaller than that of controls, since the integrity of connections between the nodes of the target network was likely to be affected. Since the relevance of the LIFG for LD is assumed to be larger than its relevance for CP, compensation was expected to be overall comparatively smaller.

11.1.3 WN

As alluded to in chapters 5 and 8, the WN was assumed to be a task of high relevance for the LIFG. Results of anodal tDCS were therefore expected to be stronger than those observed for the CP, a task assumed to induce low level of neuronal engagement in the LIFG. Anodal tDCS of the LIFG in WN was expected to decrease baseline activation for controls, but to increase the

baseline activation of PWA to correct the abnormal hypoactivation, as to increase the LIFG efficiency in solving the task. Effects were expected to be rather local.

Cathodal tDCS was expected to decrease the LIFG efficiency in solving the task with an increase in baseline level of neuronal activation. Compensation of cathodal tDCS-induced downregulation of the LIFG was expected to be unsuccessful for PWA, as for controls, since the target was a node of high relevance for the task. However, compensation could be more unsuccessful for PWA than for controls because the LIFG could be less responsive to tDCS due to the overall neuronal hypoactivity. Furthermore, the diminished level of integrity of inter-node connections could also decrease the possibility of compensation in PWA. Nonetheless, findings reported in chapters 5 and 8 for cathodal tDCS on the LIFG for WN in healthy young adults suggest that some level of compensation by other network nodes may occur. If this is the case, compensatory overactivation should be observed in other network nodes, but to a smaller extent than for CP, since the relevance of the LIFG for WN is still assumed to be higher than that for CP.

11.1.4 Words and nonwords

Nonwords were assumed to have a comparatively higher relevance for the LIFG than words (Heim et al., 2005; Nosarti et al., 2010; Xiao et al., 2005). Predictions for the effects of anodal tDCS and cathodal tDCS of the LIFG where the task load is concerned were similar to those for the CP for words and to those for the WN for nonwords.

Anodal tDCS of the LIFG was expected to decrease the LIFG baseline activation in controls and to increase the LIFG abnormal hypoactivation in PWA to improve the efficiency of the target as a function of task load. Effects were therefore expected to be stronger for nonwords than for

words, and results could vary from an apparent null effect of stimulation to a significant difference in neuronal activation as compared to sham.

Cathodal tDCS of the LIFG was expected to increase the LIFG baseline activation, decreasing the efficiency of the target in processing both word and nonwords. Compensation of cathodal tDCS-induced downregulation of the LIFG by other network nodes was expected to be more successful for words than for nonwords, because nodes of lower relevance for the task have more room for compensation. The resulting level of activation of these other nodes should be higher than in sham condition. However, compensation was expected to be weaker in PWA because the LIFG could be less responsive to tDCS due to the overall neuronal hypoactivation. The lower quality of the spare inter-node communication should also decrease the efficiency of compensation in PWA.

11.2 METHODS

Methods are as described in chapter 4 Methods. For the current study, two right-handed PWA who met the inclusion criteria described in chapter 4 were included in the sample: JW (age: 51 years, female) and MB (age: 56 years, male). All three experiments (CP, LD and WN) were performed by the PWA (and controls), in counterbalanced order across participants, with task and tDCS stimulation (anodal, cathodal and sham) as a within-subject factor. Singleton whole brain analyses were separately conducted for JW and MB, with group as a between-subject factor, in a mixed design. The sample of PWA used in the current study is the same as that used in the study described in Chapter 7. Control data consisted of combined healthy young adult data for whom the target of tDCS was the LIFG (from chapter 8; n = 20, mean age: 20.5 years, SD: 2.35, 9 females) and additional healthy older adult data (n = 2; age 65, female, and age 63, male).

11.3 RESULTS

Whole brain analyses were conducted with task, stimulus type (for the LD and WN tasks) and tDCS as factors. Results of the effects of tDCS of the LIFG on whole brain activation of each PWA are presented in the current chapter by task and stimulus type. Due to the small sample size, ROI analyses were not conducted.

11.3.1 Whole brain analyses

11.3.1.1 CP

Significant results of tDCS during CP were only found for JW. No significant difference was observed for the contrast controls > JW under anodal tDCS in language areas involved in phonological processing (Figure 1). However, cathodal tDCS induced higher brain activation in JW than in controls in brain areas that included some portion of the LSTG (Figure 2). Cluster peaks for both contrasts are listed in Table 1.

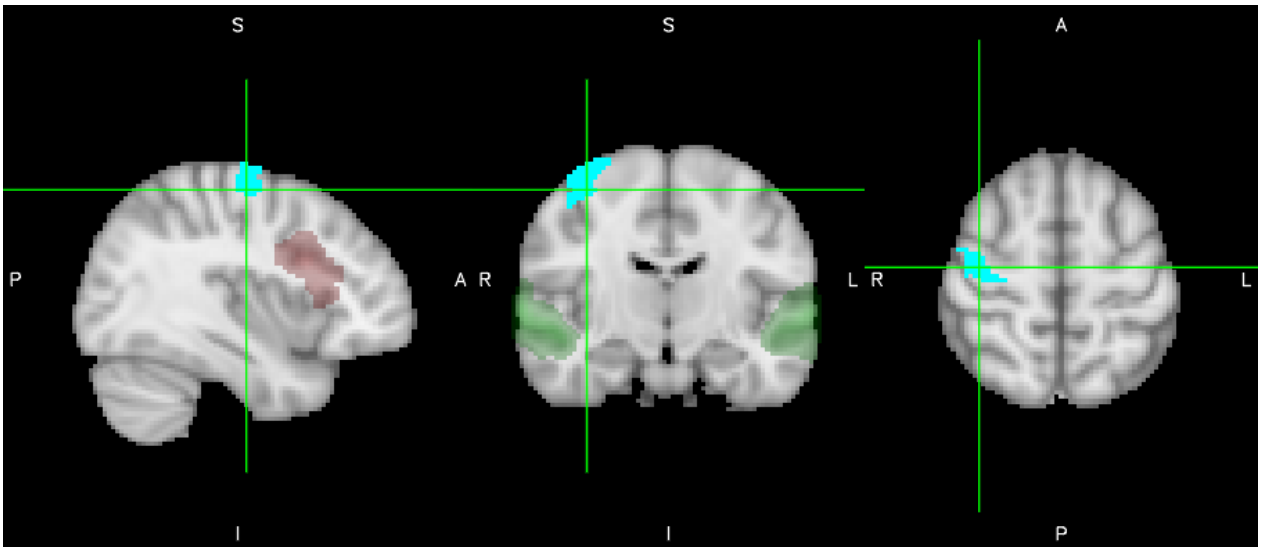

Figure 1. Brain activation clusters (Z > 2.3, p_{corr} < 0.05) for the contrast controls > JW in CP under anodal tDCS, represented in blue. Crosshair is on the highest cluster peak, the Precentral Gyrus. Activated brain areas do not include the LIFG or the RIFG, represented in transparent red, or the LSTG or RSTG, represented in transparent green.

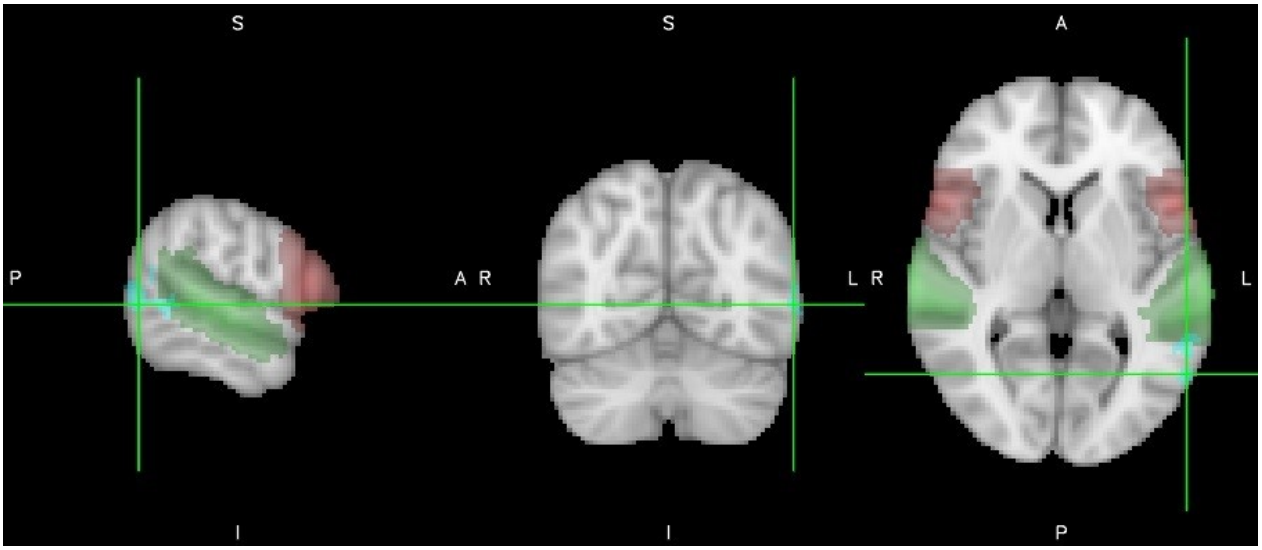

Figure 2. Brain activation clusters (Z > 2.3, p_{corr} < 0.05) for the contrast JW > controls in CP under cathodal tDCS, represented in blue. Crosshair is on the highest cluster peak, the Lateral Occipital Cortex, inferior division. Activated brain areas include some portion of the LSTG, represented in transparent green, but not of the LIFG or RIFG, represented in transparent red.

Table 1. Cluster peaks of activated cortical regions for JW in CP under anodal tDCS and cathodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
anodal tDCS						
controls > JW						
Precentral Gyrus	R	304	38	-14	58	3.4
cathodal tDCS						
JW > controls						
Lateral Occipital Cortex, inferior division	L	324	-58	-64	4	3.21

T-contrasts with $Z > 2.3$, $p_{corr} < 0.05$.

11.3.1.2 LD

No significant result was found in whole brain analysis of LD for JW or MB.

11.3.1.3 WN

Only JW showed significant differences in cortical activation from controls in WN under both anodal tDCS and cathodal tDCS, which induced higher level of activation for JW in regions of the right hemisphere (Table 2 and Figures 3 and 4).

Table 2. Cluster peaks of activated cortical regions for the contrast JW > controls in WN under anodal tDCS and cathodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
anodal tDCS						
Supramarginal Gyrus, posterior division	R	269	66	-32	32	3.48
cathodal tDCS						
Inferior Frontal Gyrus, pars triangularis	R	675	52	26	4	4.52
Supramarginal Gyrus, anterior division	R	795	64	-32	42	4.44
Superior Frontal Gyrus	L/R	260	0	32	46	4.01

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

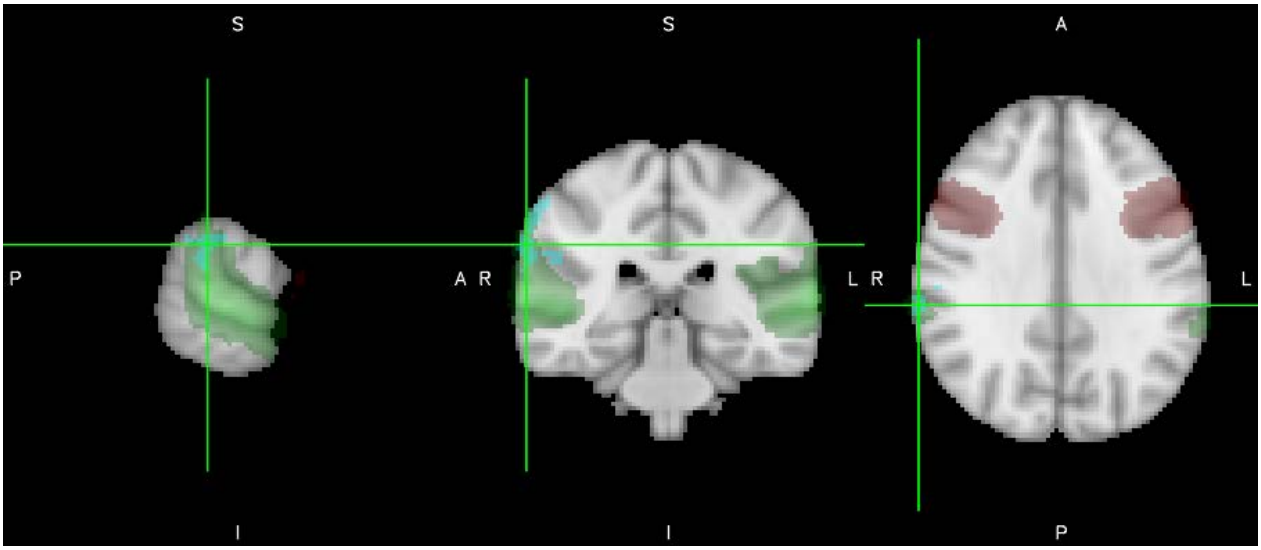

Figure 3. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast JW > controls in WN under anodal tDCS, represented in blue. Crosshair is on the highest cluster peak, the Right Supramarginal Gyrus, posterior division. Activated brain areas include some portion of the RSTG, represented in transparent green, but do not include the LSTG (also represented in transparent green) or LIFG or RIFG, represented in transparent red.

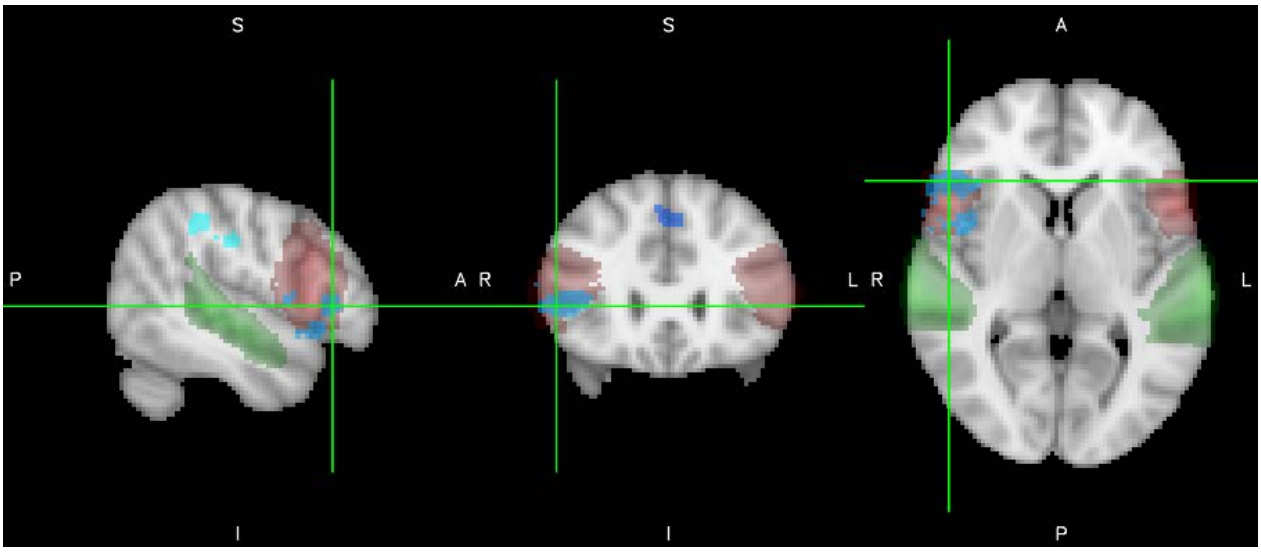

Figure 4. Brain activation clusters (Z > 2.3, p_{corr} < 0.05) for the contrast JW > controls in WN under cathodal tDCS, represented in blue. Crosshair is on the highest cluster peak, the Right Inferior Frontal Gyrus, pars triangularis. Activated brain areas include some portion of the RIFG, represented in transparent red, but do not include the LIFG (also represented in transparent red) or LSTG or RSTG, represented in transparent green.

11.3.1.4 Analysis of words and nonwords in LD

Significant results of tDCS for words and nonwords of LD were only found for JW under anodal tDCS with the contrast controls > JW. The occipital pole was the only region with significant activation for both words and nonwords (Figure 5 and Table 3).

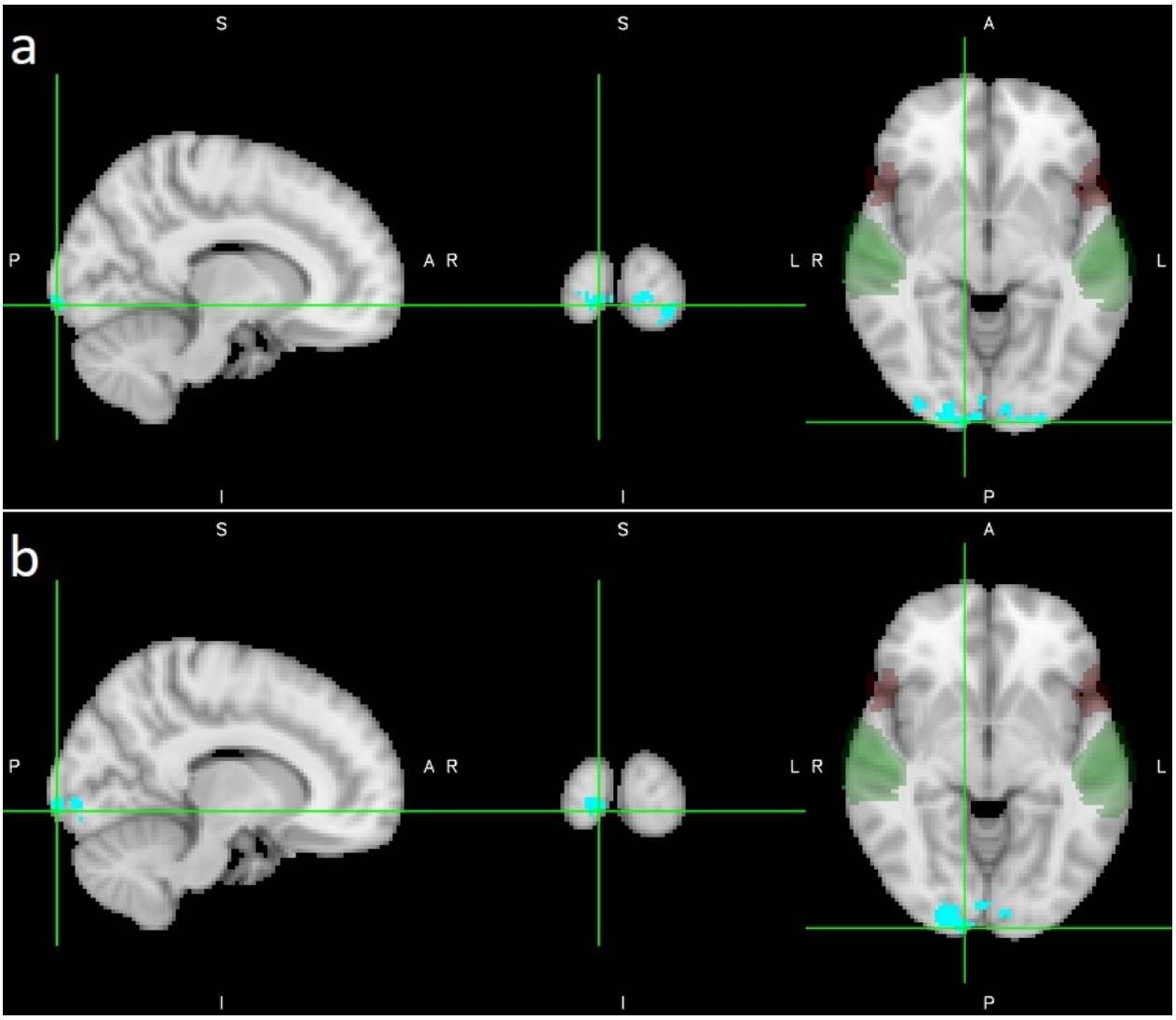

Figure 5. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast controls > JW in (a) words and (b) nonwords of LD under anodal tDCS, represented in blue. Crosshair is on the Right Occipital Pole for both contrasts. LIFG and RIFG are represented in transparent red, LSTG and RSTG are represented in transparent green.

Table 3. Cluster peaks of activated cortical regions for the contrast controls > JW in words and nonwords of LD under anodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
words						
Occipital Pole	R	386	12	-100	-6	3.36
nonwords						
Occipital Pole	R	379	14	-100	-6	3.43

T-contrasts with $Z > 2.3$, $p_{corr} < 0.05$.

11.3.1.5 Analysis of words and nonwords in WN

JW showed temporo-parietal and frontal regions on the right hemisphere for which activation was higher than for controls under tDCS stimulation, particularly under cathodal tDCS (Table 4 and Figures 6, 7 and 8).

Table 4. Cluster peaks of activated cortical regions for JW in words and nonwords of WN under anodal tDCS and cathodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
anodal tDCS						
words						
JW > controls						
Middle Frontal Gyrus	R	344	32	36	38	3.95
Paracingulate Gyrus	R	443	2	28	46	3.91
Precentral Gyrus	R	480	26	-4	44	3.42
cathodal tDCS						
words						
JW > controls						
Supramarginal Gyrus, anterior division	R	282	68	-30	32	3.65
controls > JW						
Frontal Pole	L	849	-6	72	12	4.08
Precuneous Cortex	L/R	840	0	-70	38	4.04
Angular Gyrus	R	538	54	-52	52	3.82
Angular Gyrus	L	352	-42	-58	36	3.6
nonwords						
JW > controls						
Supramarginal Gyrus, anterior division	R	1178	62	-32	42	4.71
Inferior Frontal Gyrus, pars triangularis	R	900	44	24	8	4.21
Middle Temporal Gyrus, temporoccipital part	R	327	62	-50	6	4.18
Superior Frontal Gyrus	R	484	28	26	60	3.96
controls > JW						
Frontal Pole	L	492	-6	72	12	4.17
Precuneous Cortex	L	801	-2	-52	46	4.15

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

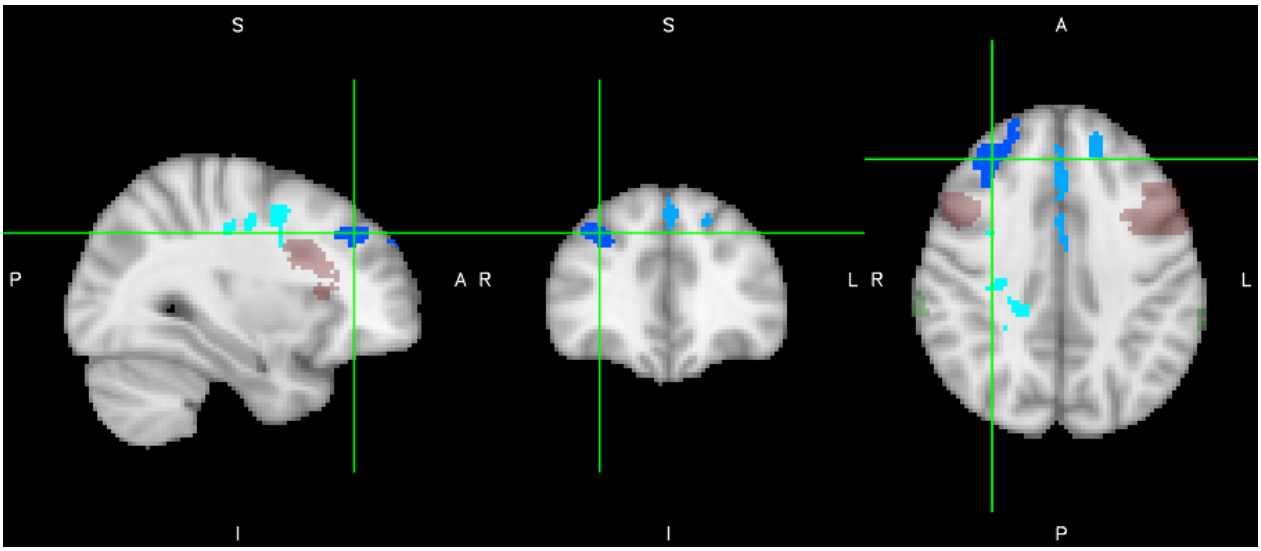

Figure 6. Brain activation clusters (Z > 2.3, p_{corr} < 0.05) for the contrast JW > controls in word of WN under anodal tDCS, represented in blue. Crosshair is on the highest cluster peak, the Right Middle Frontal Gyrus. LIFG and RIFG are represented in transparent red, LSTG and RSTG are represented in transparent green.

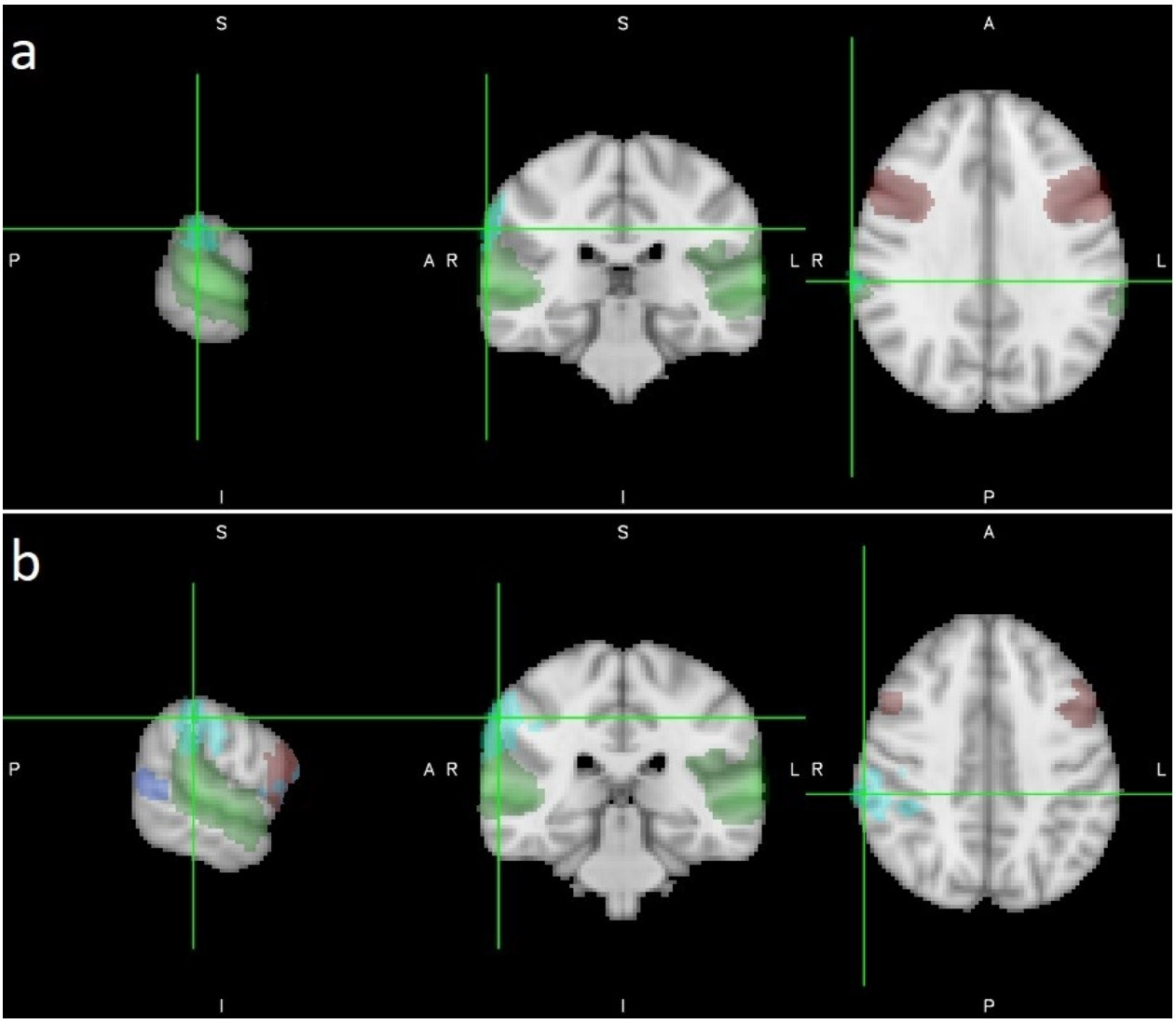

Figure 7. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast JW > controls in (a) words and in (b) nonwords of WN under cathodal tDCS, represented in blue. Crosshair is on the highest cluster peak of each stimulus type (depicted in a or b), i.e., the Right Supramarginal Gyrus, anterior division. Activated brain areas include some portion of the RIFG, represented in transparent red, and of the RSTG, represented in transparent green. LIFG is also represented in transparent red. LSTG is also represented in transparent green.

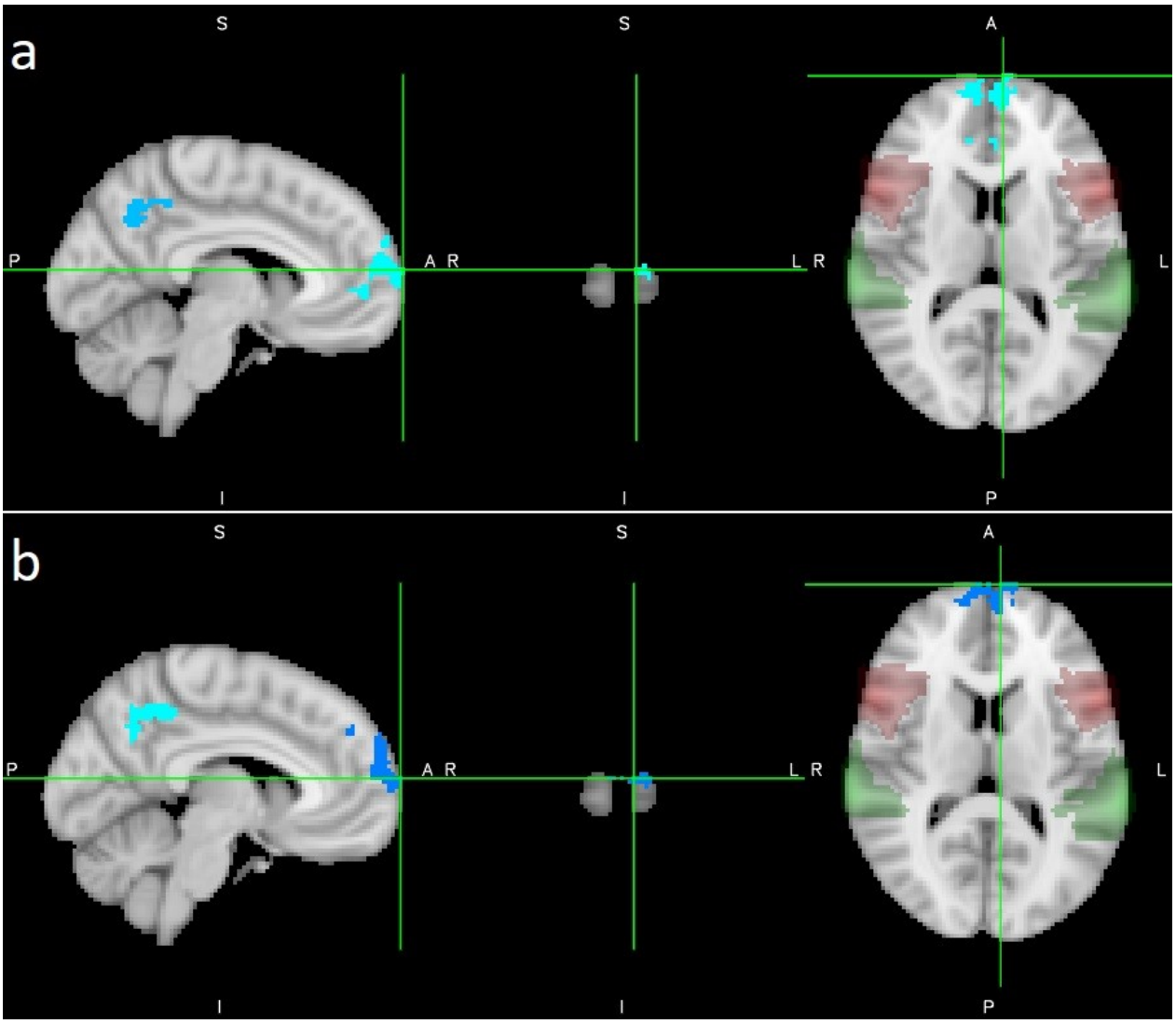

Figure 8. Brain activation clusters (Z > 2.3, $p_{corr} < 0.05$) for the contrast controls > JW in (a) words and in (b) nonwords of WN under cathodal tDCS, represented in blue. Crosshair is on the highest cluster peak of each stimulus type (depicted in a or b), i.e., the Left Frontal Pole. LIFG and RIFG are represented in transparent red, LSTG and RSTG are represented in transparent green.

Significant results of tDCS on the LIFG during words and nonwords of WN were only found for MB under cathodal tDCS. No language brain areas associated with phonological processing had higher activation for MB than for controls. However, controls showed higher activation than MB in the left supramarginal gyrus (Table 5 and Figures 9 and 10).

Table 5. Cluster peaks of activated cortical regions for MB in words and nonwords of WN under cathodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
words						
controls > MB						
Precuneous Cortex	R	337	6	-70	50	3.54
Planum Polare	L	402	-44	0	-12	3.3
nonwords						
MB > controls						
Paracingulate Gyrus	L	270	-6	52	6	3.44
controls > MB						
Supramarginal Gyrus, posterior division	L	277	-34	-50	24	3.33

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

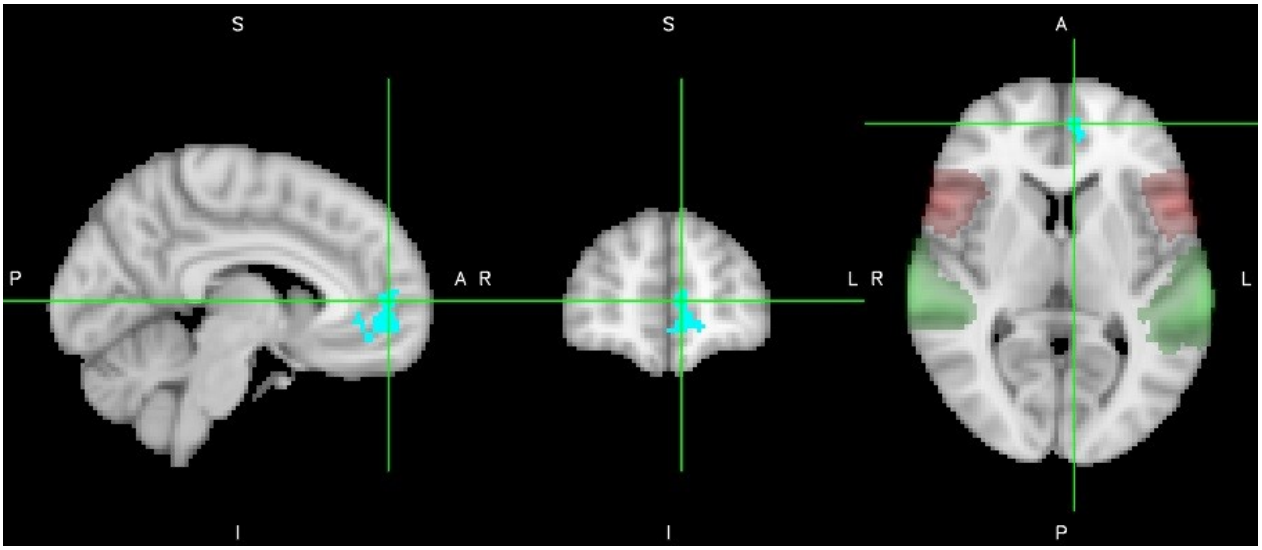

Figure 9. Brain activation cluster (Z > 2.3, $p_{corr} < 0.05$) for the contrast MB > controls in nonwords of WN under cathodal tDCS, represented in blue. Crosshair is on the Left Paracingulate Gyrus. LIFG and RIFG are represented in transparent red, LSTG and RSTG are represented in transparent green.

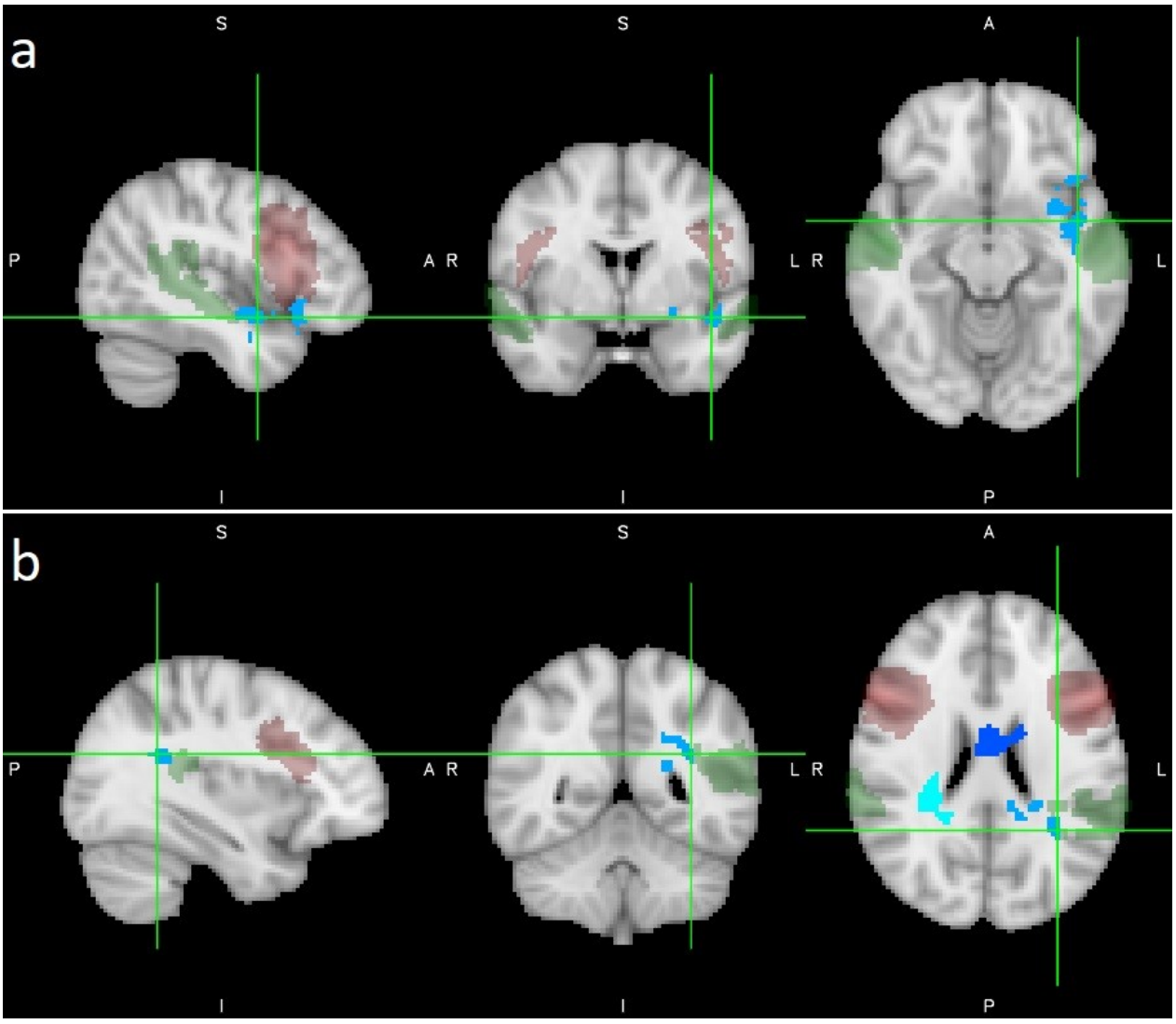

Figure 10. Brain activation clusters (Z > 2.3, p_{corr} < 0.05) for the contrast controls > MB in (a) words and in (b) nonwords of WN under cathodal tDCS, represented in blue. Crosshair is on the Left Planum Polare for (a) and on the Left Supramarginal Gyrus, posterior division for (b). LIFG and RIFG are represented in transparent red, LSTG and RSTG are represented in transparent green.

11.4 DISCUSSION

This study aimed to investigate whether the brain activation of PWA in response to tDCS of the LIFG during tasks involving phonological processing would at least broadly follow predictions of the multi-node framework based on task load. According to the multi-node framework, the higher the task load for the target of stimulation, the more the target should respond

to the stimulation. In this particular study, tasks which involved phonological processing were used. They represented a range from speech perception to speech production and were assumed to be increasingly more demanding for the LIFG (Amunts et al., 1999; Indefrey, 2011; Lee et al., 2012; Liakakis et al., 2011; Liebenthal et al., 2013). In healthy adults, anodal tDCS would be expected to induce an increasing facilitation across the range of tasks, whilst cathodal stimulation would be expected to induce an increasing inhibition. Compensation of the target downregulation, with a resulting facilitatory effect, was also expected for cathodal stimulation. This compensation should be more pronounced for targets where the task load was low, due to their larger room for compensation. However, the PWA who took part in this study had frontal aphasia, and their LIFG was damaged by the stroke event. Responses to tDCS of the LIFG would therefore be first contingent to these PWA's pattern of recovery, which was a determinant for how the LIFG currently responds to language tasks (Torres et al., 2013). Possible scenarios for the LIFG were a well-functioning perilesional area, a perilesional area able to work for the language function, but poorly recruited, or a perilesional area unable to assume the language function. Results of this study suggest that for both JW and MB the perilesional area is responsive to some extent. The particular models of recovery from aphasia inferred from findings of each PWA are discussed.

Results showed that the pattern of responses to tDCS on the LIFG broadly matched predictions based on the multi-node framework, at least more robustly for JW. Response in the speech production task (WN), which posed a higher task load for the LIFG than speech perception tasks, was the most prominent. The contrast between JW and controls in whole brain analyses showed higher activation on right frontal and right temporo-parietal regions for JW than for controls under cathodal tDCS, and on the right temporo-parietal regions under anodal tDCS. This suggests that the right hemispheric activation in JW might serve the purpose of compensating the

damage in the left hemisphere beyond the role of handling task difficulty and tDCS perturbation observed in controls (c.f. chapters 7 and 8). Anodal tDCS, known to be facilitatory, also induced right hemispheric overactivation. It could be therefore interpreted that the right hemispheric participation in phonological processing is not maladaptive for JW. Results also suggest that for JW, the right supramarginal gyrus might serve an important role in compensating the function loss of the LIFG. At baseline (see section 7.3.1.3 of chapter 7), the right supramarginal gyrus had shown a significant lower activation compared to controls, whereas under anodal tDCS and cathodal tDCS its activation was significantly higher than that of controls. Regarding the activation of a right inferior frontal region under cathodal tDCS on the LIFG, this is indicative of the use of a frontal strategy to deal with the extra cognitive effort (Churchill et al., 2016; Davis et al., 2008; Meinzer et al., 2009) posed by the downregulation of an area highly relevant for the task .

Results of the tDCS stimulation on the LIFG during CP may also be considered revealing of the strategies of recovery from aphasia that took place for JW. The contrast controls > JW for CP under anodal tDCS showed significant brain activation, but none on language areas associated with phonological processing (particularly the LIFG and LSTG on the dorsal pathway and their right homologues RIFG and RSTG in this thesis). This could indicate that language areas for phonological processing are functional in JW, with a level of activation compared to that of controls, at least under the effect of anodal tDCS. From JW's profile of response to cathodal tDCS on the LIFG during CP, it could be inferred that communication between the endpoints of the canonical pathway of phonological processing (i.e., LIFG and LSTG) may still be satisfactory to some extent. The contrast JW > controls under cathodal tDCS showed significant activation of left temporo-parietal areas that included the LSTG, suggesting that the LSTG was overactivated to respond to the downregulation of the LIFG.

Findings for MB suggest that MB's pattern of recovery from aphasia might be different from that observed in JW. No language area associated with phonological processing has been shown to be modulated by tDCS. On the contrary, the left supramarginal gyrus, which would have a function in phonological processing as an intermediate between the LIFG and the LSTG (Gow, 2012; Rauschecker & Scott, 2009; Turkeltaub & Coslett, 2010) has shown lower activation in MB than in controls under cathodal stimulation for nonwords in WN. This result might indicate that compensation was not trigged by cathodal tDCS on the LIFG, or that it could not take place due to the low responsivity of the perilesional area or to some deficit in inter-region communication. Another possibility is that the tDCS modulation of brain activity during the experimental tasks did not differ between MB and controls in language areas involved in phonological processing because their pattern of brain activity to perform phonological processing under tDCS stimulation was somehow similar. In other words, left and right regions involved in phonological processing were not significantly recruited in MB to a higher level than that required in controls to handle both task difficulty and tDCS perturbation. That is, overactivation to compensate for the brain lesion was not noticeable in MB.

CHAPTER 12:

GENERAL DISCUSSION

12.1 INTRODUCTION

In this thesis, seven experimental studies were conducted to investigate the behavioural and neural correlates of task load modulation of tDCS effects in phonological processing. Task load modulation of tDCS effects was investigated in healthy young adults and in populations who presented a deficit in phonological processing: PWD and PWA with a frontal profile of aphasia. The multi-node framework that was proposed for this thesis was shown to be a suitable theory to interpret tDCS effects as the effects of tDCS were observed beyond the target. Predictions on the outcomes of tDCS stimulation were made for healthy young adults based on the multi-node framework, and deviations from those predictions were anticipated for the groups which presented a deficit in phonological processing.

According to the multi-node framework, responses to tDCS are directly related to the task load posed to the target during stimulation (Bikson et al., 2013; Nozari, Woodard, & Thompson-Schill, 2014; Pope et al., 2015). The experiments conducted in this thesis used tasks that involved phonological processing in a range from speech perception to speech production, as well as the word and nonword stimulus types (for LD and WN). Some of the experimental studies had the LIFG as target, and others had the LSTG. These range of tasks and stimulus types were assumed to pose an increasingly higher task load for the LIFG and a decreasingly lower task load for the LSTG. Anodal tDCS was thus expected to cause increasingly higher facilitation across the range of tasks and stimulus types used when the target was the LIFG, whilst a decreasingly lower facilitation should be observed when the target was the LSTG. Conversely, cathodal tDCS was expected to cause increasingly higher inhibition across the range of tasks and stimulus types used for the target LIFG, whilst a decreasingly lower inhibition should be observed for the target LSTG. Last, cathodal tDCS facilitation via network compensation was also expected, and should be

negatively related to the cathodal tDCS inhibitory effect. This means, the less the inhibition undergone, the more the target could be compensated by other areas.

Predictions for the populations with a deficit in phonological processing were that the effects would be at least weaker and dependent on the altered pattern of brain activation that subserved phonological processing. For example, PWD typically present a pattern of brain activation in which the LSTG is hypoactivated and the LIFG is hyperactivated (Brunswick et al., 1999; Georgiewa et al., 1999; Hoeft et al., 2006; Ruff et al., 2003). The downregulation of the LIFG in a condition of low task load could therefore not be robustly compensated, as the hypoactivation of the LSTG would restrict the possibilities of compensation available. PWA with a frontal profile of aphasia, on the other hand, presented with a lesion on the LIFG. Their possibilities of responding to tDCS stimulation on the LIFG would depend on their pattern of recovery from aphasia (Torres et al., 2013). Their perilesional area should be able to respond to tDCS in the first place. The mechanisms used by the brain to respond to the tDCS perturbation would then further depend on how efficiently the perilesional region performed, as well as the compensatory role of its right homologue regions.

Overall, the results of the studies reported in this thesis support predictions made under the multi-node framework. Effects of tDCS in phonological processing were task load modulated. However, as expected, results from populations with deficit in phonological processing deviated from those of healthy young adults to some extent, which has been observed for PWD. The main conclusions and particularities of the studies are outlined next.

12.2 SUMMARY OF MAIN EXPERIMENTAL FINDINGS AND GENERAL CONCLUSIONS

Task load modulation of tDCS effects was observed in the behavioural and fMRI experiments. Instances where task modulation was quite evident were especially noticeable for the CP and the WN tasks for both targets, the LIFG and the LSTG. For example, anodal tDCS of the LIFG produced larger facilitatory effects (with decreased reaction times) for the WN task than for the CP task (chapter 5), whilst the reverse pattern was observed when the LSTG was targeted instead (chapter 6). This outcome supports the assumption that the range from speech perception to speech production, or at least more robustly its endpoints, has opposite task loads for the LIFG and the LSTG, which consequently has an influence on tDCS effects. Results of cathodal tDCS also showed to be in line with these assumptions. For example, cathodal tDCS of the LIFG induced more compensation for the CP task than for the WN task (chapter 8), whilst the reverse pattern was observed for LSTG as the target (chapter 9). Not all predictions were closely met however. For example, compensation of cathodal tDCS-induced downregulation was expected to be primarily resolved within the dorsal pathway of phonological processing. Nonetheless, recruitment of the right homologues (RIFG and RSTG) was considerably high. These discrepancies could be due to particularities of the baseline profile of brain activation for each task and population.

The results from the tDCS studies performed with healthy young adults allow a qualitative comparison of the effects of tDCS on behaviour (chapters 5 and 6) and on neural correlates (chapters 8 and 9) in a single population for two targets of stimulation, the LIFG (chapters 5 and 8) and the LSTG (chapters 6 and 9). Application of tDCS showed a differential effect on the connectivity between the network nodes rather than on the BOLD signal change alone per node, which mostly showed non-significant results. Henceforth, the fMRI findings will be referred to

here as only the results of tDCS stimulation on connectivity. Behavioural and fMRI findings in general agreed, especially for the CP and WN tasks. These tasks were the endpoints of the range of tasks from speech perception to speech production used in the studies of this thesis. With the LIFG as a target, both anodal tDCS and cathodal tDCS improved behavioural performance in CP (with decrease in reaction times), but the improvement induced by cathodal tDCS was qualitatively higher (with a non-significant trend). Higher improvement induced by cathodal stimulation suggests that a successful facilitatory compensation took place. The expected neural counterpart was higher strengthening of connectivity within the network of interest during cathodal stimulation than during anodal stimulation, as observed by a larger number of significant correlations between network nodes for higher strengthening. This was indeed observed in the fMRI results. Cathodal tDCS induced three significant correlations between network nodes, whilst anodal tDCS induced only one significant correlation between network nodes. This result matched the expectation for the effect of cathodal when the task load for the target was low, as well as the expectation that improvement induced by the need for compensation would be stronger than the improvement caused by facilitatory (anodal) tDCS on a target for which the task load was low. When the WN task was used with the LIFG as target, a differential effect of anodal tDCS and cathodal tDCS was also expected, but with the reverse pattern of that for CP, since now the task load was high. The prediction on a differential effect was not matched, as both anodal and cathodal tDCS induced a large improvement in performance. However, behavioural and fMRI results converged. Both tDCS polarities induced only one significant correlation between nodes, with the same nodes involved. It may be that cathodal stimulation of the LIFG during WN was compensated by other brain regions outside the network of interest for phonological processing.

With the LSTG as target of stimulation, both anodal and cathodal tDCS improved behavioural performance in CP, but anodal tDCS induced the highest improvement, with a marginally significant trend. This matches the expectation where anodal tDCS should induce large improvement in conditions of stimulation with a high task load for the target, whereas compensation would be less satisfactory and cause only a modest improvement in performance, if any. The fMRI findings showed that the neural correlates matched the behavioural findings. Only anodal stimulation induced significant correlations between network nodes, suggesting that compensation of cathodal stimulation was rather unsuccessful. With the WN task, cathodal tDCS induced significantly larger behavioural improvement than anodal tDCS did. This matched the predictions of a successful compensation of cathodal stimulation and a modest improvement induced by anodal stimulation in a condition of low task load. The fMRI findings seem to support the view that strengthening of connectivity is larger for successful compensation induced by cathodal tDCS than for ordinary overall improvement of network connectivity induced by anodal tDCS. Only cathodal tDCS induced significant correlations between network nodes.

For the LD, a task whose task load was intermediate, rather than low or high, for both LIFG and LSTG, results were less consistent between behavioural and fMRI findings, and therefore less interpretable. For both LIFG and LSTG as target of stimulation, anodal and cathodal tDCS produced non-significant results on behavioural performance (reaction times). Non-significant results may be due to lack of effect or lack of power to detect a potential effect, therefore no definitive conclusion can be made. However, the fMRI results for LD with the LIFG as a target showed that only cathodal tDCS induced significant correlations between network nodes. This matches the aforementioned rationale that connectivity strengthening induced by a need for compensation of cathodal stimulation is stronger than the connectivity strengthening induced by

anodal stimulation. If that is the case, one could interpret that cathodal downregulation of the LIFG during LD was partially compensated, just enough to avoid performance to deteriorate, but not enough to show an improvement in performance. Cathodal showed a non-significant trend for improvement in behavioural performance that is higher than that induced by anodal stimulation. fMRI results for LSTG as a target, on the other hand, showed no difference between tDCS polarities in the strengthening of network connections (as per number of significant network node correlations). This indicates a non-successful compensation. Cathodal showed a non-significant trend to deteriorate behavioural performance that is higher than that of anodal tDCS. Following this interpretation and based on the different trends for compensation of cathodal tDCS shown in the fMRI results for LIFG and for LSTG as a target, LD could be considered to have an intermediate task load rather shifted to the low end for the LIFG and rather shifted to the high end for the LSTG.

Similarly, results for words and nonwords of LD and WN had some inconsistencies between the behavioural and the fMRI studies. However, since for the analyses of words and nonwords, carried out per task, the number of stimuli was half the number used for the analyses of tasks, null results and inconsistencies could be partially explained by lack of statistical power. For example, nonwords, considered to have high task load for the LIFG, were expected to show higher behavioural improvement under anodal than under cathodal tDCS, which should induce rather unsuccessful compensation. In the fMRI results, anodal tDCS should induce larger number of significant network node correlations than cathodal tDCS to support this prediction. Words should reverse this pattern and show satisfactory compensation. However, words and nonwords differed behaviourally for LD and WN. In the LD task, significant decrease in performance caused by anodal tDCS was observed for nonwords, whilst cathodal tDCS showed a non-significant trend for improvement and was significantly different from anodal tDCS. Although the predictions based on

task load were not met, fMRI results showed some convergence with the behavioural results. Cathodal stimulation induced more significant network node correlations than anodal tDCS, suggesting a trend for satisfactory compensation. In the WN task, only words had significant improved performance, that was similar under anodal and cathodal tDCS. In the fMRI results, anodal and cathodal tDCS induced similar number of significant network node correlations. Since words were assumed to have low task load for the LIFG, improvement induced by anodal tDCS was expected to be less expressive.

For the LSTG as a target, larger behavioural improvement was expected for words under anodal tDCS, whilst compensation of cathodal stimulation was expected to be unsuccessful. In the fMRI results, anodal was expected to induce stronger network connectivity than cathodal tDCS. Nonwords should reverse this pattern, with a successful compensation of cathodal tDCS expected. Behavioural results differed for LD and WN. In LD, cathodal tDCS significantly deteriorated performance for words. In the fMRI results, a single significant network node correlation under cathodal tDCS matched the behavioural result, suggesting that compensation was not successful. In the WN task, cathodal tDCS induced improved behavioural performance for nonwords, consistent with the prediction of a satisfactory compensation. The fMRI results showed that cathodal tDCS induced more significant network node correlations for nonwords than anodal tDCS did, suggesting that a satisfactory compensation indeed took place and that cathodal tDCS induced larger connectivity strengthening than anodal tDCS, as expected. However, unexpectedly, cathodal tDCS induced similar improved behavioural performance for words. Since in the fMRI results the number of significant network node correlations for words was equal under anodal tDCS and cathodal tDCS, it may be that successful compensation was carried out for words by other brain regions outside the network of interest for phonological processing.

Chapter 7 provided an overview of the baseline brain activation for all the tasks and stimulus types used in the tDCS experiments in healthy young adults, PWD and PWA. Some findings were unexpected. The main unexpected finding was the robust participation of the right homologues (RIFG and RSTG) of the nodes of the dorsal pathway for phonological processing in healthy young adults. This could be attributed to the high difficulty level posed by the experimental tasks and stimulus types used, as the difficulty of the task has been found to induce the participation of the right homologues in language functions in the literature (Gur et al., 2000). It was also surprising that there was a similar high level of brain activation for the frontal and temporal regions of the dorsal pathway and their right homologues in WN when the recruitment of the frontal regions was assumed to prevail. The canonical role of the LIFG in speech production seems supported by findings in this thesis, as discussed in the previous paragraph, which is in line with previous findings (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011). However, overactivation of regions other than the LIFG possibly explains otherwise inconsistent results such as, for example, the successful compensation of cathodal tDCS-induced downregulation of the LIFG during WN, with improved reaction times, reported in chapter 5.

Neural correlates of anodal tDCS of the LIFG were also surprising (chapter 8). Outcomes did not closely match the predictions based on task load, as a clear pattern of response in terms of significant correlations between network ROIs or of level of brain activation could not be apprehended. In other words, no clear distinction could be made between conditions of high and low task load. Rather, anodal tDCS of the LIFG seemed to have had a role to optimise the network functioning for all the tasks. As such effect of the anodal tDCS has not been observed when the LSTG was target of stimulation (chapter 9), it may be that this is a particular role of anodal tDCS that might only or predominantly arise from frontal stimulation (e.g., Baxter et al., 2017; Meinzer

et al., 2012). This effect of anodal tDCS of the LIFG for the optimisation of network functioning suggests that the LIFG functions as a network manager.

Finally, effects of tDCS stimulation for PWD (chapter 10) and for PWA (chapter 11) were different from effects for healthy young adults (chapter 8), as expected. In general, effects were weaker for both PWD and PWA. In PWA, effects of tDCS were only noticeable in the WN task, the one with the highest task load for the target (LIFG) (Amunts et al., 1999; Eickhoff et al., 2009; Indefrey, 2011; Liakakis et al., 2011). This shows that the outcomes broadly followed task load based predictions, since stronger effects were expected to arise in conditions of high task load. Furthermore, this finding revealed that the perilesional area of the PWA recruited, who presented a lesion on the LIFG, was still able to respond. Results in the PWA study therefore had the additional benefit of supporting the notion of tDCS as a diagnostic tool and also a potential tool for treatment (Hamilton et al., 2011).

Results of tDCS stimulation in PWD were both weaker and inconsistent with task load predictions. For example, anodal and cathodal tDCS effects for CP and WN were contrary to the expectations. Larger facilitation was induced by the anodal tDCS of the LIFG on the CP task than on the WN task, and more compensation was observed under cathodal tDCS of the LIFG for WN than for CP. For all other conditions where cathodal tDCS was applied, no compensation was observed. Phonological processing in PWD is known to rely on a hypoactivated LSTG and a hyperactivated LIFG (Brunswick et al., 1999; Georgiewa et al., 1999; Ruff et al., 2003). It could be interpreted, therefore, that findings where the LIFG in PWD reacted to tDCS as predicted for the LSTG in the healthy brain seem to suggest that the functions of the LSTG in phonological processing have at least partly been transferred to the LIFG in PWD. In turn, findings where the LIFG in PWD did not react as expected according to its original attributions in phonological

processing (or task load with the healthy brain as a reference) suggest that these attributions are currently less satisfactorily accomplished as a result of the transfer. This interpretation highlights the potential of tDCS as a diagnostic tool in dyslexia.

The potential of tDCS as a tool for treatment of dyslexia is also supported by findings reported in chapter 10. Some of the anodal tDCS-induced facilitation and cathodal tDCS-induced compensation results in PWD have shown the involvement of both the LSTG and the RSTG. This indicates that temporal areas, typically hypoactivated (the LSTG), are able to assume a function in phonological processing. It seems that the possibility of counting on temporal areas for phonological processing already identified at baseline (chapter 7) can be improved with the direct current. Improvement in language abilities that involve phonological processing by targeting the LSTG with tDCS has been reported in the literature (Costanzo et al., 2016a, 2016b).

12.3 LIMITATIONS

The generalizability of results and the possibilities of further investigation of complementary research questions are briefly discussed in this section. Small sample size restricts the generalizability of the results obtained in the studies with PWD and PWA. Conclusions from these studies, therefore, are only indicative and should be considered cautiously. The study with PWD (chapter 10) should be appreciated as a pilot study, due to the small sample size. Nevertheless, the study overall shows promise, as some of the results are in line with findings in the literature. An increase in sample size would allow to investigate whether the effects outlined would remain. The study with PWA (chapter 11), in turn, was ultimately designed as case studies due to the unavailability of more PWA who met the inclusion criteria to be included in the sample. Singleton analyses were used to compare the profile of brain activation of each PWA with that of

healthy adult controls. This is a strength of this study in terms of its diagnostic power compared to studies where individual PWA data were analysed alone (e.g., Ulm et al., 2015). However, to better understand the task modulation of tDCS effects during phonological processing in PWA, an increase in sample size would be needed. The particular pattern of recovery from aphasia undergone by each PWA (Torres et al., 2013) should be considered, as it is determinant for the PWA's ability to respond to tDCS in the first place. Many other factors, as discussed in chapter 2, might need to be considered to increase the homogeneity of the sample as much as possible.

In this thesis, fMRI was used to investigate the neural correlates of task load modulation of the effects of tDCS of the LIFG and of the LSTG in phonological processing. In particular, partial correlation was used to understand how the brain network that subserves phonological processing handles task load differences and tDCS perturbations. This approach unveiled that tDCS had an effect in determining the most prominent node connections that manages each experimental condition. Partial correlation is thought to be a reasonable standard technique for connectivity analyses when prior information on the temporal dynamics between nodes is not available to allow investigation of causal relationships (Marrelec et al., 2006). Although fMRI has low temporal resolution, recent advances such as dynamic causal modelling and the use of both fMRI and tDCS show promise and may help to explore the causal relationships between the network nodes involved in phonological processing in the healthy brain and in the presence of a phonological processing impairment, such as in aphasia or dyslexia.

The potential of fMRI to explore the network mechanisms used by the brain to handle phonological processing under tDCS could be further expanded with the incorporation of structural imaging data, such as white matter information from diffusion tensor imaging (DTI). This should increase the predictive power for the effects of tDCS in PWD and PWA. Since both populations

are known or expected to have some degree of white matter degradation in the dorsal pathway of phonological processing (Basilakos et al., 2014; Carter et al., 2009; Klingberg et al., 2000; Li et al., 2017; Rimrodt et al., 2010; Schlaug et al., 2009), predictions based on a healthy adult well-functioning network could be more accurate if adjusted to account for any underlying structural damages. Consideration of white matter integrity has been shown to contribute to our understanding of group differences for participants with a neurological impairment (Chechlacz et al., 2010; Li et al., 2017).

12.4 CONCLUSIONS

The seven experiments described in this thesis were designed to investigate task load modulation of tDCS effects during phonological processing in healthy young adults, PWD and PWA. Conceptually, the overall aim of this thesis was to contribute to the brain-state-dependent stimulation framework (Bikson et al., 2013; Gharabaghi et al., 2014; Sergeeva et al., 2014; Silvanto et al., 2008), which advocates that the state of the brain under stimulation is crucial for the outcomes. The present research accomplished this aim by particularly focusing on the task load modulation of tDCS effects. Results demonstrated that task load shaped the effects of tDCS. Different neural network strategies and behavioural performances were observed for different combinations of task and tDCS condition. Furthermore, the studies with PWD and PWA enabled an additional brain state factor relevant for the outcomes of tDCS stimulation to be explored: how function impairment, and its particular altered pattern of brain activity, modifies predictions for the healthy brain.

Taken together, findings of the studies of this thesis corroborate the claim that the state of the brain is crucial in defining outcomes of brain stimulation, particularly tDCS in the current

research. Task load modulated the effects of tDCS, which could be observed on both behavioural and neural correlates of phonological processing. The overall consistency of results on the behavioural and neural domains, with different populations, shows that the approach used was at least adequate to ensure a fair extent of reproducibility of findings. This is a valuable contribution, since reproducibility is an important issue in the tDCS literature as the results tend to be either contradictory or null (Jacobson et al., 2012). The proposed multi-node framework, used to predict network brain strategies to handle differences in task load under the perturbation of tDCS, has been shown to be suitable. Adjustments to this model to incorporate altered patterns of brain activation, such as those observed in PWD and in PWA, seem possible. Results in the studies with PWA and PWD not only supported previous knowledge on these altered patterns, but expanded our understanding on them by providing evidence for brain strategies used in aphasia and in dyslexia to handle phonological processing.

The brain-state-dependent stimulation approach used in this thesis ultimately allowed the interpretation of tDCS results in reverse inference for diagnostic purposes (Hamilton et al., 2011). These inferences helped to interpret the pattern of recovery from aphasia used by PWA and to deepen the understanding of the processing strategies used by PWD to perform phonological processing. As both populations responded to tDCS, results support the idea that this tool has a promising potential for treatment (Hamilton et al., 2011; Vicario & Nitsche, 2013).

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APPENDIX 1:

WHOLE BRAIN ANALYSES – TASK LOAD MODULATION OF BRAIN ACTIVATION FOR PHONOLOGICAL PROCESSING IN HEALTHY YOUNG ADULTS AND PWD

Results of whole brain analyses are presented in this appendix by task and stimulus type for healthy young adults and PWD.

1 CP

1.1 Healthy young adults

Table 1 shows regions of the cerebral cortex where CP induced significant activation in healthy young adults for the contrast CP > rest. The highest cluster peaks were observed in areas of auditory processing bilaterally, what was expected from a task that involved listening.

Table 1. Cluster peaks of activated cortical regions for the contrast CP > rest

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
Heschl's Gyrus	R	3803	54	-18	6	9.07
Heschl's Gyrus	L	3019	-46	-24	8	9.01
Precentral Gyrus	R	4069	28	-22	76	6.37
Frontal Pole	R	2064	42	50	8	6.28
Paracingulate Gyrus	R	881	4	18	48	5.65
Cingulate Gyrus, posterior division	R	853	6	-22	26	5.05
Precuneous Cortex	R	635	6	-76	44	4.76
Intracalcarine Cortex	R	1377	4	-74	12	4.32

T-contrast with $Z > 2.3$, $p_{corr} < 0.05$.

1.2 PWD

Table 2 shows regions of the cerebral cortex where CP induced significant activation for the contrasts of CP > rest, PWD > controls and controls > PWD. Different from healthy young adults, the highest cluster peaks in PWD were observed in frontal areas. This is consistent with the altered pattern of brain activation underlying phonological processing in PWD, that typically shows overactivation of frontal regions and hypoactivation of temporal regions (Brunswick et al., 1999; Georgiewa et al., 1999; Ruff et al., 2003).

Table 2. Cluster peaks of activated cortical regions for CP

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
CP > rest						
Frontal Orbital Cortex	R	1732	40	22	-8	6.37
Angular Gyrus	R	702	46	-46	52	5.63
Insular Cortex	L	638	-36	22	-2	4.7
Frontal Pole	R	1523	30	50	30	4.43
Parietal Operculum Cortex	L	425	-44	-42	22	4.1
Paracingulate Gyrus	R	603	2	10	48	4.01
PWD > controls						
Frontal Orbital Cortex	R	634	40	22	-10	5.65
Precentral Gyrus	L	442	-50	4	16	4.11
controls > PWD						
Middle Temporal Gyrus, temporooccipital part	L	689	-44	-62	4	4.35
Lateral Occipital Cortex, inferior division	R	1035	46	-78	4	3.97
Postcentral Gyrus	R	367	20	-42	62	3.79
Lateral Occipital Cortex, superior division	L	504	-18	-86	26	3.63
Precentral Gyrus	R	963	10	-30	64	3.52

T-contrasts with $Z > 2.3$, $p_{corr} < 0.05$.

2 LD

2.1 Healthy young adults

Table 3 shows regions of the cerebral cortex where LD induced significant activation in healthy young adults for the contrast LD > rest.

Table 3. Cluster peaks of activated cortical regions for the contrast LD > rest

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
Insular Cortex	R	14990	38	20	-2	10.4
Precentral Gyrus	L	26766	-58	6	20	10.2

T-contrast with Z > 2.3, $p_{corr} < 0.05$.

2.2 PWD

Table 4 shows regions of the cerebral cortex where LD induced significant activation in PWD for the contrasts of LD > rest, PWD > controls and controls > PWD.

Table 4. Cluster peaks of activated cortical regions for LD

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
LD > rest						
Insular Cortex	R	1409	34	24	2	7.65
Occipital Pole	L	6076	-16	-90	-4	7.1
Lateral Occipital Cortex, superior division	L	474	-30	-62	50	7.03
Angular Gyrus	R	493	36	-52	40	6.66
Insular Cortex	L	1923	-34	22	2	6.47
Precentral Gyrus	R	1513	46	10	26	5.59
Supplementary Motor Cortex	L	1675	-4	-2	68	5.42
Intracalcarine Cortex	L	340	-24	-62	4	4.02
PWD > controls						
Occipital Pole	R	435	28	-92	4	5.2
Occipital Pole	L	338	-22	-94	10	4.6
Insular Cortex	R	305	34	26	2	3.99
controls > PWD						
Angular Gyrus	R	1797	54	-58	22	5.13
Inferior Frontal Gyrus, pars triangularis	L	417	-58	30	4	4.94
Angular Gyrus	L	2056	-52	-60	14	4.74
Frontal Pole	R	340	38	44	8	4.22
Central Opercular Cortex	L	330	-44	4	2	4
Superior Frontal Gyrus	R	492	18	18	66	3.95

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

3 WN

3.1 Healthy young adults

Table 5 shows regions of the cerebral cortex where WN induced significant activation in healthy young adults for the contrast WN > rest.

Table 5. Cluster peaks of activated cortical regions for the contrast WN > rest

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
Paracingulate gyrus	L	121148	-2	8	50	14

T-contrast with Z > 2.3, $p_{corr} < 0.05$.

3.2 PWD

Table 6 shows regions of the cerebral cortex where WN induced significant activation in PWD for the contrasts of WN > rest, PWD > controls and controls > PWD.

Table 6. Cluster peaks of activated cortical regions for WN

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
WN > rest						
Lateral Occipital Cortex	L	50486	-30	-62	50	8.99
Supplementary Motor Cortex	R	5319	2	-2	68	9.49
Precentral Gyrus	R	580	16	-32	62	6.33
Frontal Pole	L	495	-26	52	36	5.1
Cingulate Gyrus	L	419	-6	-20	28	4.96
PWD > controls						
Lateral Occipital Cortex, superior division	L	340	-30	-62	50	6.15
Precentral Gyrus	L	425	-40	-22	64	5.63
Precentral Gyrus	R	593	62	14	30	4.63
controls > PWD						
Central Opercular Cortex	L	2874	-38	4	12	5.26
Lateral Occipital Cortex, superior division	R	1371	56	-60	18	5.2
Frontal Pole	R	2707	38	44	10	5.1
Frontal Pole	L	460	-50	40	14	5.07
Precuneous Cortex	R	1601	12	-52	38	4.97
Superior Frontal Gyrus	R	1005	26	20	58	4.38
Middle Frontal Gyrus	L	579	-34	14	50	3.91

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

4 ANALYSIS OF WORDS AND NONWORDS OF LD

4.1 Healthy young adults

Table 7 shows regions of the cerebral cortex where stimulus types of words and nonwords of LD induced significant activation in healthy young adults for the contrasts of stimulus type > rest.

Table 7. Cluster peaks of activated cortical regions for the contrasts words > rest and nonwords > rest in LD

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
words						
Insular Cortex	R	5021	36	22	0	10.1
Precentral Gyrus	L	27531	-58	6	20	10
Paracingulate Gyrus	R	10065	2	16	48	9.9
nonwords						
Paracingulate Gyrus	L	12977	-2	8	50	10.1
Precentral Gyrus	L	6199	-54	6	20	9.93
Lateral Occipital Cortex, inferior division	L	17225	-44	-66	-12	9.31

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

4.1 PWD

Table 8 shows regions of the cerebral cortex where stimulus types of words and nonwords of LD induced significant activation in PWD for the contrasts of stimulus type > rest, PWD > controls and controls > PWD. No significant activation was induced by the contrast PWD > controls for nonwords.

Table 8. Cluster peaks of activated cortical regions for words and nonwords in LD

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
words						
words > rest						
Occipital Pole	L	3501	-16	-90	-4	7.37
Insular Cortex	R	814	36	22	0	7.17
Occipital Pole	R	1939	18	-92	2	7.06
Angular Gyrus	R	406	36	-52	40	6.51
Lateral Occipital Cortex, superior division	L	371	-30	-62	50	6.38
Insular Cortex	L	1760	-34	22	2	5.85
Precentral Gyrus	R	884	36	-16	72	5.36
Precentral Gyrus	R	302	46	10	26	5.08
Supplementary Motor Cortex	L	1419	-4	-2	70	4.97
Intracalcarine Cortex	L	345	-24	-62	4	3.98
Intracalcarine Cortex	R	286	24	-68	8	3.73
PWD > controls						
Occipital Pole	R	386	28	-92	2	5.07
Occipital Pole	L	396	-22	-94	10	4.54
controls > PWD						
Angular Gyrus	R	1683	54	-58	20	4.69
Inferior Frontal Gyrus, pars triangularis	L	299	-58	30	4	4.64
Superior Frontal Gyrus	R	610	18	18	66	4.23
Angular Gyrus	L	1779	-52	-60	14	4.18
Frontal Pole	R	287	36	42	8	3.78
Precuneous Cortex	R	603	2	-56	46	3.7
nonwords						
nonwords > rest						
Insular Cortex	R	1467	34	24	2	7.45
Lateral Occipital Cortex, superior division	L	517	-30	-62	50	6.96
Occipital Pole	R	5637	28	-92	4	6.51
Insular Cortex	L	1781	-32	24	2	6.5
Angular Gyrus	R	468	36	-52	40	6.39
Precentral Gyrus	R	1513	46	10	26	5.7
Supplementary Motor Cortex	L	1664	-4	-2	68	5.42

controls > PWD						
Angular Gyrus	R	1432	54	-58	22	4.78
Angular Gyrus	L	1730	-52	-60	12	4.69
Inferior Frontal Gyrus, pars triangularis	L	385	-58	30	4	4.53
Insular Cortex	L	336	-42	0	2	3.95

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

5 ANALYSIS OF WORDS AND NONWORDS OF WN

5.1 Healthy young adults

Table 9 shows regions of the cerebral cortex where stimulus types of words and nonwords of WN induced significant activation in healthy young adults for the contrasts of stimulus type > rest.

Table 9. Cluster peaks of activated cortical regions for the contrasts words > rest and nonwords > rest in WN

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
words						
Postcentral Gyrus	L	121215	-50	-14	42	13.4
nonwords						
Paracingulate Gyrus	L	114763	-2	8	50	13.9

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

5.2 PWD

Table 10 shows regions of the cerebral cortex where stimulus types of words and nonwords of WN induced significant activation in PWD for the contrasts of stimulus type > rest, PWD > controls and controls > PWD.

Table 10. Cluster peaks of activated cortical regions for words and nonwords in WN

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
words						
words > rest						
Supplementary Motor Cortex	R	56650	2	-2	68	9.02
Frontal Pole	R	478	32	50	36	6.07
Frontal Pole	L	511	-28	50	34	5.17
Cingulate Gyrus, posterior division	L	516	-8	-20	40	4.75
PWD > controls						
Lateral Occipital Cortex, superior division	L	377	-30	-62	50	5.8
Postcentral Gyrus	L	343	-42	-22	62	5.43
Precentral Gyrus	R	383	62	14	30	4.12
controls > PWD						
Angular Gyrus	R	1432	46	-50	20	4.94
Frontal Pole	R	310	38	44	8	4.86
Superior Frontal Gyrus	R	1017	26	18	56	4.76
Supramarginal Gyrus, posterior division	L	1071	-52	-44	24	4.71
Precuneous Cortex	L	1269	-4	-74	52	4.63
Frontal Operculum Cortex	L	549	-38	10	12	4.58
Frontal Operculum Cortex	R	687	50	10	2	4.07
Frontal Pole	R	446	4	58	20	3.98
Parahippocampal Gyrus, anterior division	R	390	32	-8	-24	3.89
nonwords						
nonwords > rest						
Supplementary Motor Cortex	R	4987	2	-2	68	9.65
Lateral Occipital Cortex, superior division	L	46060	-30	-62	50	9
Frontal Pole	L	393	-26	52	36	4.75
PWD > controls						
Superior Parietal Lobule	R	308	30	-44	38	6.43
Precental Gyrus	L	411	-40	-22	64	5.37
Precental Gyrus	R	575	62	14	30	4.44

controls > PWD						
Central Opercular Cortex	L	3046	-40	2	12	5.7
Frontal Pole	L	623	-50	40	14	5.25
Precuneous Cortex	R	1444	12	-52	38	5
Lateral Occipital Cortex, superior division	R	1186	56	-60	20	4.94
Frontal Pole	R	1010	10	60	8	4.81
Parahippocampal Gyrus, anterior division	R	3219	32	-6	-24	4.62
Cingulate Gyrus, posterior division	R	400	2	-22	36	4.49
Temporal Occipital Fusiform Cortex	R	960	42	-44	-18	4.23
Frontal Pole	R	387	14	42	40	4.04
Middle Frontal Gyrus	L	414	-34	14	50	3.9

T-contrasts with $Z > 2.3$, $p_{corr} < 0.05$.

APPENDIX 2:

WHOLE BRAIN ANALYSES – TASK LOAD MODULATION OF THE EFFECTS OF TDCS OVER THE LIFG FOR PHONOLOGICAL PROCESSING IN HEALTHY YOUNG ADULTS

Results of whole brain analyses showing task load modulation of the effects of tDCS over the LIFG in healthy young adults are presented in this appendix by task and stimulus type.

1 CP

No significant results were observed in whole brain analysis of healthy young adults for CP.

2 LD

No significant results were observed in whole brain analysis of healthy young adults for LD.

3 WN

Table 1 shows regions of the cerebral cortex where significant activation was induced by tDCS during WN. Significant activation was found for the contrast WN > rest only under anodal tDCS. The highest cluster peak was observed in a frontal area.

Table 1. Cluster peaks of activated cortical regions for the contrast WN > rest under anodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
Superior Frontal Gyrus	R	664	28	22	56	3.91
Postcentral Gyrus	R	681	48	-26	52	3.69
Precuneous Cortex	L	411	-2	-52	66	3.66
Precuneous Cortex	L	457	-12	-60	40	3.35

T-contrast with Z > 2.3, $p_{corr} < 0.05$.

4 ANALYSIS OF WORDS AND NONWORDS OF LD

No significant results were observed in whole brain analysis of healthy young adults for words and nonwords of LD.

5 ANALYSIS OF WORDS AND NONWORDS OF WN

Table 2 shows regions of the cerebral cortex where significant activation was induced by tDCS for words and nonwords of WN. Significant activation was only found with the contrast words > rest and nonwords > rest under anodal tDCS. The highest cluster peaks were observed in right frontal areas for both words and nonwords.

Table 2. Cluster peaks of activated cortical regions for the contrasts words > rest and nonwords > rest in WN under anodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
words						
Precentral Gyrus	R	1454	58	-2	50	3.99
Precuneous Cortex	L	307	-2	-52	64	3.42
nonwords						
Superior Frontal Gyrus	R	415	24	24	56	3.75
Precentral Gyrus	L/R	346	0	-28	64	3.72

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

APPENDIX 3:

WHOLE BRAIN ANALYSES – TASK LOAD MODULATION OF THE EFFECTS OF TDCS OVER THE LIFG FOR PHONOLOGICAL PROCESSING IN DYSLEXIA

Results of whole brain analyses showing task load modulation of the effects of tDCS over the LIFG in PWD are presented in this appendix by task and stimulus type.

1 CP

Table 1 shows regions of the cerebral cortex where significant activation was induced by tDCS during CP. Significant activation was found with the contrast controls > PWD under both anodal tDCS and cathodal tDCS. The highest cluster peaks were observed in frontal areas.

Table 1. Cluster peaks of activated cortical regions for the contrast controls > PWD in CP under anodal tDCS and cathodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
anodal tDCS						
Supplementary Motor Cortex	L/R	446	0	-6	60	3.62
cathodal tDCS						
Middle Frontal Gyrus	R	288	52	18	40	3.36
Superior Frontal Gyrus	R	531	12	-4	68	3.4

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

2 LD

Table 2 shows regions of the cerebral cortex where significant activation was induced by tDCS during LD under both anodal tDCS and cathodal tDCS. The highest cluster peaks were

observed in visual areas of the left and the right hemispheres for both anodal tDCS and cathodal tDCS.

Table 2. Cluster peaks of activated cortical regions for LD under anodal tDCS and cathodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
anodal tDCS						
LD > rest						
Occipital Pole	L	2191	-12	-92	-6	4.02
Cuneal Cortex	R	473	2	-82	34	3.13
PWD > controls						
Occipital Pole	L	364	-12	-92	-6	3.66
Lateral Occipital Cortex, superior division	R	323	32	-62	58	3.29
Middle Frontal Gyrus	R	303	38	28	22	3.29
Lingual Gyrus	R	269	10	-72	2	3.21
cathodal tDCS						
LD > rest						
Lateral Occipital Cortex, superior division	L	357	-32	-60	52	4.06
Insular Cortex	R	1939	32	-26	16	3.72
Occipital Pole	R	3750	4	-90	-2	3.71
Postcentral Gyrus	L	558	-60	-8	24	3.53
PWD > controls						
Lateral Occipital Cortex, superior division	L	824	-32	-60	52	4.27
Cingulate Gyrus, posterior division	R	463	4	-32	24	3.91
Intracalcarine Cortex	R	5935	6	-70	8	3.82
Insular Cortex	R	3420	38	22	-4	3.78
Temporal Fusiform Cortex, posterior division	R	640	36	-38	-30	3.78
Precentral Gyrus	L	511	-42	-2	40	3.77
Occipital Fusiform Gyrus	R	404	34	-74	-18	3.28

T-contrasts with Z > 2.3, $p_{corr} < 0.05$.

3 WN

Table 3 shows regions of the cerebral cortex where significant activation was induced by tDCS during WN. Significant activation was only found with the contrast controls > PWD under anodal tDCS. The highest cluster peaks were observed in frontal areas.

Table 3. Cluster peaks of activated cortical regions for the contrast controls > PWD in WN under anodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
Precentral Gyrus	R	689	62	0	36	3.92
Precentral Gyrus	R	380	14	-32	60	3.89
Lingual Gyrus	R	1837	14	-52	-8	3.63

T-contrast with Z > 2.3, $p_{corr} < 0.05$.

4 ANALYSIS OF WORDS AND NONWORDS OF LD

Table 4 shows regions of the cerebral cortex where significant activation was induced for words and nonwords of LD under anodal tDCS and cathodal tDCS. Cluster peaks have been observed in occipital, parietal, frontal and temporal areas.

Table 4. Cluster peaks of activated cortical regions for words and nonwords of LD under anodal tDCS and cathodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
anodal tDCS						
words						
words > rest						
Occipital Pole	L	5374	-12	-92	-4	3.9
PWD > controls						
Lateral Occipital Cortex, superior division	L	257	-28	-74	24	3.87
Occipital Pole	L	293	-12	-92	-4	3.49
Precuneous Cortex	R	721	8	-80	44	3.38

Middle Frontal Gyrus	R	343	38	28	22	3.23
Intracalcarine Cortex	R	492	10	-74	4	3.22
nonwords						
nonwords > rest						
Occipital Pole	L	356	-10	-92	-6	3.64
PWD > controls						
Angular Gyrus	R	343	38	-56	44	3.4
cathodal tDCS						
words						
words > rest						
Occipital Pole	L	8598	-20	-92	22	3.84
Postcentral Gyrus	L	1375	-52	-14	34	3.84
Insular Cortex	R	4114	32	-26	18	3.81
Frontal Pole	R	452	26	48	16	3.38
Superior Parietal Lobule	R	294	36	-44	60	3.28
PWD > controls						
Lateral Occipital Cortex, superior division	L	9207	-24	-66	60	4.01
Precentral Gyrus	L	1177	-34	-10	42	3.66
Frontal Pole	R	729	26	48	18	3.52
Cingulate Gyrus, posterior division	R	254	4	-32	24	3.47
Frontal Pole	L	332	-32	52	24	3.37
nonwords						
nonwords > rest						
Occipital Pole	R	1090	4	-90	-2	3.45
PWD > controls						
Lateral Occipital Cortex, superior division	L	625	-32	-60	52	4.12
Cingulate Gyrus, posterior division	R	390	2	-32	24	3.95
Lingual Gyrus	L	1789	-2	-78	-4	3.63
Precuneous Cortex	R	887	16	-68	42	3.53
Middle Temporal Gyrus, temporooccipital part	R	396	58	-48	-6	3.45
Insular Cortex	R	328	38	22	-4	3.34
Precentral Gyrus	R	442	52	4	50	3.2

T-contrast with Z > 2.3, $p_{corr} < 0.05$.

5 ANALYSIS OF WORDS AND NONWORDS OF WN

Table 5 shows regions of the cerebral cortex where significant activation was induced by tDCS for words and nonwords of WN. Significant activation was only found with the contrast controls > PWD under anodal tDCS. The highest cluster peaks were observed in right frontal areas, followed by right occipital areas for both words and nonwords.

Table 5. Cluster peaks of activated cortical regions for the contrast controls > PWD in words and nonwords of WN under anodal tDCS

Region	Hemisphere	Cluster size (voxels)	MNI coordinates			Z-value
			x	y	z	
words						
Precentral Gyrus	R	1909	60	0	36	4.3
Temporal Occipital Fusiform Cortex	R	3848	34	-56	-20	3.94
Postcentral Gyrus	L	378	-24	-36	62	3.76
Supplementary Motor Cortex	L/R	293	0	-4	56	3.47
nonwords						
Precentral Gyrus	R	376	60	2	40	3.99
Lingual Gyrus	R	362	10	-70	-2	3.66

T-contrast with Z > 2.3, $p_{corr} < 0.05$.