Language impairments in neurodegenerative diseases : function, dysfunction and modulation with transcranial stimulation

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Language impairments in neurodegenerative diseases: function, dysfunction and modulation with transcranial stimulation

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Thèse de doctorat en Neurosciences

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Para ser grande, sê inteiro: nada

Teu exagera ou exclui.

Sê todo em cada coisa. Põe quanto és

No mínimo que fazes.

Assim em cada lago a lua toda

Brilha, porque alta vive.

Ricardo Reis, 14-2-1933

To be great, be whole; don't exaggerate

Or leave out any part of you,

Be complete in each thing. Put all you are

Into the least of your acts.

So too in each lake, with its lofty life,

The whole moon shines.

Ricardo Reis, 14-2-1933

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Publications

Manuscripts in international peer-reviewed journals:

- **Sanches C**, Routier A, Colliot O, Teichmann M. (2018). The structure of the mental lexicon: what primary progressive aphasias reveal. *Neuropsychologia, 109, 107-115.*

- Valero-Cabré A*, **Sanches C***, Godard J, Fracchia O, Dubois B, Levy R, et al. (2019). Language boosting by transcranial stimulation in progressive supranuclear palsy. *Neurology, 93(6), e537-e547.* (*equally contributed)

- **Sanches C**, Levy R, Benisty S, Volpe-Gillot L, Habert, M-O, Kas A, et al. (2019). Testing the therapeutic effects of transcranial direct current stimulation (tDCS) in semantic dementia: a double blind, sham controlled, randomized clinical trial. *Trials, in press.*

- Teichmann M*, **Sanches C***, Moreau J, Ferrieux S, Nogues M, Dubois B, et al. (2019). Does surface dyslexia/dysgraphia relate to semantic deficits in the semantic variant of primary progressive aphasia? *Neuropsychologia, in press. (*equally contributed)*

Submitted manuscripts:

- **Sanches C**, Stengel C, Godard J, Mertz J, Teichmann M, Migliaccio R, et al. Past, present and future of non-invasive brain stimulation approaches to treat cognitive impairment in neurodegenerative diseases: time for a comprehensive critical systematic review. *Submitted.*

Manuscripts in preparation:

- **Sanches C**, Amzallag F, Dubois B, Levy R, Truong DQ, Bikson M, Teichmann M, Valero-Cabré A. Modulation of language impairments in behavioral variant of Frontotemporal Dementia after transcranial direct current stimulation of the prefrontal cortex. *In preparation.*

- **Sanches C**, Bourbon A, Dubois B, Levy R, Truong DQ, Bikson M, Teichmann M, Valero-Cabré A. Using transcranial direct current stimulation to modulate language deficits in logopenic Primary Progressive Aphasia. *In preparation.*

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Oral Communications in scientific meetings:

- 6th Scientific and clinical meeting, Fondation Plan Alzheimer, December 2017. “The array of non-invasive brain stimulation methods and technologies”.
- 4th European Congress of NeuroRehabilitation, Lausanne, October 2017. “Improvements of language induced by prefrontal transcranial direct current stimulation in Progressive Supranuclear Palsy patients”.
- 10th International Conference on Frontotemporal Dementias, Munich, August 2016. “Anatomo-functional segregation of the mental lexicon: the model of primary progressive aphasia”.
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Poster Communications:

- 10th International Conference on Experimental Linguistics, Lisbon, September 2019. “Neurodegenerative language impairments and transcranial stimulation”.
- 5th Annual Brain Stimulation and Imaging Meeting, Rome, 2019. “Do modelled tDCS cortical fields predict variability of language outcomes in semantic Primary Progressive Aphasia?”
- 2018 NYC Neuromodulation Conference and NANS Summer Series, New York, August 2018. “Language modulation induced by prefrontal transcranial direct current stimulation in Progressive Supranuclear Palsy patients”.
- 36th European Workshop on Cognitive Neuropsychology, Bressanone, January 2018. “Language modulation induced by prefrontal transcranial direct current stimulation in Progressive Supranuclear Palsy patients”.

Table of Abbreviations

ATL	Anterior Temporal Lobe
Bv-FTD	Behavioral variant of Frontotemporal Dementia
CSF	Cerebrospinal Fluid
DLPFC	Dorsolateral Prefrontal Cortex
DRC	Dual Route Cascaded
EEG	ElectroEncephaloGram
EF	Electric Field
FEM	Finite Element Model
fMRI	functional Magnetic Resonance Imaging
FTD	Frontotemporal Dementia
Lv-PPA	Logopenic variant of Primary Progressive Aphasia
LTD	Long-Term Depression
LTP	Long-Term Potentiation
MRI	Magnetic Resonance Imaging
MEG	Magnetoencephalogram
NIBS	Non-Invasive Brain Stimulation
Nfv-PPA	Non-fluent variant of Primary Progressive Aphasia
PDP	Parallel Distributed Processing
PET	Positron Emission Tomography
PHRC	Programme Hospitalier de Recherche Clinique
PPA	Primary Progressive Aphasia
PSP	Progressive Supranuclear Palsy
rTMS	repetitive Transcranial Magnetic Stimulation
Sv-PPA	Semantic variant of Primary Progressive Aphasia
tACS	transcranial Alternating Current Stimulation
tDCS	transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
TPJ	Temporoparietal Junctio

Summary

Language is one of the most defining features of human beings and an important part of our identity. It denotes who we are and it influences how others perceive who we are. Language is also the code by which we express our experiences and memories throughout our life, and through which we convey thoughts and feelings to others, arousing in them ideas, subtle perceptions and judgments. For centuries, researchers have been interested on the functional organization of language, notably on how words and information associated to them are stored and accessed in the human brain, and which neural substrates subtend such complex processes. Several studies have suggested that three main types of word-related information, semantic, syntactic and phonological/orthographic information are stored in what is called the mental lexicon. A breakdown of mechanisms subtending access to information hosted in the mental lexicon characterizes different neurodegenerative conditions. For this reason, these diseases have become fit models to study the neural basis and mechanisms of language processing. The study of language breakdown in the context of neurodegenerative models serves two purposes: first, it allows us to learn about language in healthy conditions; second, it provides insight into the mechanisms subtending language pathologies and, on such basis, guide the development of efficient and specific therapies for these conditions. In the absence of effective treatments for language deficits in different neurodegenerative diseases, non-invasive brain stimulation approaches have been gaining momentum, showing promise as novel effective therapies. Among them, transcranial Direct Current Stimulation (tDCS) modulates neural activity via the induction of weak electrical intracranial currents, showing benefit in post-stroke and neurodegenerative aphasic patients. In this context, the studies included in this thesis analyzed neurodegenerative lesion models to (1) characterize the behavioral mechanisms of word access and processing, (2) address their impact on language abilities, (3) explore the modulation of language impairment of different sorts and basis by means of tDCS to define its clinical value and indications.

In the Introduction (*Chapter I*) we present the rational of our work and the main pursued questions justifying their relevance and motivation. We first address how our brain accesses the different types of information carried by words, and provide an overview of the theoretical models that could best represent underlying mechanisms. We then review the anatomical, physiological

and clinical features of language breakdown in neurodegenerative diseases, covering existing evidence supporting therapeutic approaches such as tDCS. We finally present recent evidence supporting variability of behavioral outcomes following stimulation and the implication of the individual clinical/anatomical characteristics of each patient to such variability. We complete the Introduction by presenting the specific Aims pursued by each study included in this dissertation. The work presented here is organized along three main axes: (1) fundamental research on language (2) clinical research on language breakdown and therapies and (3) impact of individual factors on the variability of the response to such therapies.

The Fundamental research on language chapter (*Chapter II*) integrates two scientific papers accepted in peer-reviewed journals. Both articles explore the deficits of Primary Progressive Aphasia patients (PPA) with rigorously constructed experimental tasks based on different linguistic paradigms, to explore how the fundamental unit of language, the word, and the information these carry is stored and organized in our mental lexicon. Our main findings provide evidence for the existence of distinct syntactic, semantic and word-form representations in the mental lexicon, that can be accessed independently of each other and provide support for symbolic models of word reading.

Chapter III explores language breakdown caused by three neurodegenerative diseases, Progressive Supranuclear Palsy (PSP), behavioral variant of Frontotemporal Dementia (bv-FTD) and logopenic variant Primary Progressive Aphasia (lv-PPA), and the effects of tDCS on language impairments specific to each of these three diseases, compared to matched healthy controls. This chapter incorporates an accepted publication and two scientific papers in preparation to be submitted to peer-reviewed journals. On each of these cohorts, we test and asses the effects of a single session of tDCS on language deficits. Our results provide support for different types of language impairments depending on the specific brain regions affected by neurodegeneration on each disease and also disease specific tDCS outcomes.

Our third section (*Chapter IV*) was to explore inter-individual differences of tDCS cortical and behavioral impact on language correlates. We tackle this issue by means of Magnetic Resonance Imaging (MRI) customized computational biophysical models from individual sv-PPA patients analyzing the influence of individual anatomical features and current parameters on clinical outcomes driven by single tDCS sessions. Our data suggest that individual anatomical features (e.g. cortical thickness, volume of cerebrospinal fluid) influence peak electric field values

and consequently, clinical outcomes. The preliminary results of this study are presented in a paper draft on this matter.

Finally, in *Chapter V* we pre-register the methodological details of our ongoing clinical trial, the 'PHRC National STIM-SD', evaluating long-term effects of repetitive sessions of tDCS in a large cohort of patients with the semantic variant of Primary Progressive Aphasia.

The dissertation is completed by a General discussion (*Chapter VI*) section with a summary of main findings and a critical discussion of their anatomical, cognitive and clinical implications. We finally provide future perspectives in the specific topic of the dissertation and the field. We emphasize the importance of our work providing evidence for the ability of tDCS to drive improvements in language impairments in neurodegenerative diseases. However, we highlight that the understanding of tDCS mechanisms and disease characterization through the combination of neuroimaging and neurophysiological measures along with the application of stimulation protocols is critical for the future development of non-invasive brain stimulation techniques in clinical settings and for the adequate use of the new techniques being developed.

Résumé (Français)

Le langage est une caractéristique déterminante de l'être humain et constitue une partie importante de notre identité, de qui nous sommes et de la façon dont les autres perçoivent qui nous sommes. La langue est le code par lequel nous exprimons nos expériences et nos souvenirs à travers la vie, par lequel nous transmettons nos pensées et nos sentiments aux autres, en suscitant en eux des idées nouvelles ainsi que des perceptions et des jugements subtils. Depuis des siècles, les chercheurs s'intéressent à l'organisation fonctionnelle du langage, notamment à la manière dont les mots et les informations qui leur sont associés sont stockés et accédés dans le cerveau humain, et sur quels substrats neuronaux sous-tendent le fonctionnement normal de ces complexes processus. Plusieurs études ont maintenant suggéré le stockage de trois types principaux d'informations relatives aux mots, les informations sémantiques, syntaxiques et phonologiques / orthographiques, dans ce qu'on appelle le lexique mental. Le dysfonctionnement des mécanismes permettant un bon accès aux informations du lexique mental est présent dans différentes maladies neurodégénératives, devenues ainsi un modèle majeur pour explorer les capacités langagières. L'étude de la dégradation du langage par le biais de modèles neurodégénératifs peut être abordée sous deux angles différents : celui de l'apprentissage sur des processus normaux et celui de la compréhension de la pathologie pour la mise en place de traitements plus ciblés.

En l'absence de traitement efficace pour les troubles du langage dans différentes maladies neurodégénératives, les techniques non invasives de stimulation cérébrale gagnent du terrain et de nombreuses études ont montré leur potentiel en tant que thérapies innovantes. Parmi ces techniques, on trouve la stimulation transcrânienne à courant continu (STCC), qui module l'activité neuronale via l'induction de faibles courants électriques dans le cerveau, et dont les effets bénéfiques ont été démontrés à la fois chez les patients aphasiques victimes d'accidents vasculaires cérébraux et les patients neurodégénératifs.

Les études incluses dans cette thèse ont utilisé des modèles de lésions neurodégénératives pour (1) étudier les mécanismes comportementaux de l'accès et du traitement des mots, (2) étudier leur impact sur les capacités langagières, (3) explorer la possibilité de moduler le langage à travers la STCC afin de définir sa valeur en tant qu'outil thérapeutique pour les troubles du langage.

Dans l'Introduction (*Chapitre I*), nous présentons les questions posées dans notre travail, ainsi que leur pertinence et leur motivation. Nous abordons d'abord comment nous accédons aux différents types d'informations véhiculées par les mots, et nous donnons un aperçu des modèles théoriques se rapportant à cette question. Nous passons ensuite en revue les caractéristiques anatomiques, physiologiques et cliniques de la dégradation du langage dans les maladies neurodégénératives, en examinant les données existantes soutenant de nouvelles approches thérapeutiques, telles que la stimulation transcrânienne en courant continu (STCC). Enfin, nous présentons des preuves récentes de la variabilité des résultats comportementaux en réponse à la stimulation transcrânienne et de l'implication des caractéristiques cliniques / anatomiques individuelles de chaque patient pour une telle variabilité. Nous complétons l'Introduction en présentant les objectifs spécifiques poursuivis par chaque étude présentée dans cette thèse. La thèse s'articule ensuite autour de trois axes principaux : (1) recherche fondamentale sur le langage, (2) recherche clinique sur le dysfonctionnement du langage et approches thérapeutiques et (3) impact de facteurs individuels sur la variabilité de la réponse à ces thérapies.

Le chapitre Recherche fondamentale sur le langage (*Chapitre II*) intègre deux articles scientifiques acceptés dans une revue à comité de lecture. Les deux articles explorent les déficits des patients atteints d'Aphasie Primaire Progressive avec des tâches expérimentales rigoureusement construites, basées sur différents paradigmes linguistiques, afin d'explorer comment l'unité fondamentale du langage, le mot, et des informations le concernant sont stockées et organisées dans notre lexique mental. Nos principaux résultats suggèrent l'existence de représentations syntaxiques, sémantiques et phonologiques/orthographiques dans le lexique mental, informations qui peuvent être accédées indépendamment les unes des autres.

Le *Chapitre III* explore la dégradation du langage due à trois conditions neurodégénératives, la Paralysie Supranucléaire Progressive, la variante comportementale de la Démence Frontotemporale et la variante logopénique de l'Aphasie Primaire Progressive, ainsi que les effets de la STCC sur les troubles du langage spécifiques à chaque condition. Ce chapitre comprend un article scientifique accepté et deux articles scientifiques en préparation pour être soumis à des revues à comité de lecture. Sur chacune de ces cohortes, nous testons et évaluons les effets d'une session unique de STCC sur les déficits langagiers. Nos résultats montrent l'existence de différents types de troubles du langage en fonction des régions du cerveau affectées par la

neurodégénérescence dans chaque condition ainsi que des effets de la STCC spécifiques et différents pour chaque maladie.

Notre troisième objectif, *Chapitre IV*, était d'explorer les différences interindividuelles de l'impact cortical et comportemental de la STCC sur les corrélats du langage. Nous abordons ce problème en produisant des modèles biophysiques informatiques personnalisés, en utilisant de l'Imagerie par Résonance Magnétique (IRM) de patients atteints de la variante sémantique de l'Aphasie Primaire Progressive, analysant ainsi l'influence des caractéristiques anatomiques individuelles et des paramètres du courent électrique sur les résultats cliniques entrainés par une seule session de STCC. Nos données suggèrent que les caractéristiques anatomiques individuelles (comme l'épaisseur corticale, le volume de liquide céphalo-rachidien) influencent la magnitude du courant dans le cerveau et, par conséquent, les résultats cliniques. Les résultats préliminaires de cette étude sont présentés dans un manuscrit scientifique en préparation sur ce sujet.

Finalement, dans le *Chapitre V*, nous avons préenregistré les détails méthodologiques de notre essai clinique en cours, le «PHRC National STIM-SD», qui évalue les effets à long terme de séances répétitives de STCC dans une large cohorte de patients atteints de la variante sémantique de l'Aphasie Primaire Progressive.

La thèse est complétée par une section de Discussion générale (*Chapitre VI*) avec un résumé des principales conclusions, une discussion critique de celles-ci et leurs implications anatomiques, cognitives et cliniques. Nous fournissons enfin des perspectives sur le sujet spécifique de la thèse et du domaine. Nous soulignons l'importance de nos travaux pour fournir des preuves de la capacité de la STCC à entrainer à des améliorations des déficits du langage dans les maladies neurodégénératives. Cependant, nous soulignons que la compréhension des mécanismes de la STCC et la caractérisation de chaque maladie par la combinaison de mesures de neuroimagerie et neurophysiologiques et l'application de protocoles de stimulation sont essentielles pour le développement futur des techniques non-invasives de stimulation du cerveau en milieu clinique et pour l'utilisation adéquate des nouvelles techniques en cours.

CHAPTER I

Introduction

'Philosophy means *love of wisdom*. […] It is, as the Greeks put it, a kind of sightseeing adventure undertaken for its own sake. […] Philosophy begins when someone asks a general question, and so does science.' (Russell, 1959). Questioning, systematic presenting and critically discussing are some of the methods used in philosophy, as well as in science.

In this *Chapter I – Introduction*, we present the rational for our work, giving the basis for a good understanding of the questions we try to answer later on, the pertinence of these questions and what motivated them and motivated us to pursue research on this field. We start by asking about language, how do we have access to the different information about words and what theoretical models can best represent how we recognize them. Having focused on language itself in the first place, we then proceed by asking about the impact of neurodegenerative diseases on language breakdown and on the efficacy of a potential new therapeutic approach, transcranial direct current stimulation (tDCS), on such deficits in patients for whom currently there is no validated therapy. Transcranial DCS is a promising non-invasive technique that uses electric current delivered to the brain in order to modulate neurons' activity. However, different individuals respond differently to the application of stimulation, a fact that raises the question of how the individual anatomical characteristics of each patient can affect the amount of electrical current entering the brain and the impact of this on clinical outcome measures.

Besides exploring these scientific questions with rigorous approaches and methodologies, our work has also a more fundamental purpose, that should be present, if subtly, in any effort conducing to a PhD. As Schelling puts it, 'the beginning and end of all philosophy is freedom' (1936). The end of this PhD is to explore a way of giving those who lost the ability to express themselves through language a way to do it again. Being able to understand the world around, to show how we identify with it, what we think about it how it influences us is fundamental for our feeling of freedom. Freedom also comes with responsibility and in nowadays society it is our responsibility to share our knowledge in a factual way, to provide others with the means of

constructing their own well-informed ideas and importantly to answer prominent questions that impact peoples' lives.

I.1. Language

'Human language is a system of remarkable complexity' (Chomsky, 1975). But why is it so noteworthy and what makes it so specific to humans? Language is an important part of our identity, of who we are and of how others perceive who we are. Identity refers to how people understand their relationship to the world and how this relationship is constructed across time and space (Norton, 1997). In the social sciences, it is defined as the way in which people label themselves as members of a group, whereas in psychology it is described as an individuals' self-image (Fishman, 1999). Our culture is a defining aspect of our identity. Shared values, customs, history and language strongly influence how we conceive the world (Norton, 1997). Benjamin Whorf (1987-1941) hypothesized that the language available to describe perceptual experiences is able to influence the experience itself (Carrol, 1956). Russian speakers, for example, have more words than English ones to refer to the spectrum of the blue color and were shown to be able to better discriminate different shades of blue (Winawer et al., 2007). Goldstein and Davidoff (2008) studied the Himba culture to analyze the effects of vocabulary on perceptual classification. This culture has a rich vocabulary of animal patterns and show a high recognition accuracy for animal stimuli (Goldstein & Davidoff, 2008). However, language does not only influence how we see the world but is also influenced by what we see in the world. A simple and very well-known example are Eskimo languages, which have words for different types of snow that do not exist in other languages (Regier et al., 2016). In this case, the physical environments we are all embedded in, shape the local cultural communication needs, but many other aspects of language are influenced by the specific needs and habits of our culture (Regier et al., 2016). The way we speak, the words we know, the concepts we can describe and the different ways in which we can describe them reflect the culture we grew up in. Language is the code by which we express our experiences and memories through life, by which we convey our thoughts and feelings to others, arousing in them novel ideas and subtle perceptions and judgments (Chomsky, 1975). As wrote by the poet (educator and writer) Sabine Ulibarrí 'The language, the word, carries within it the history, the culture, the traditions, the very life of a people […]. Language is the people. We cannot conceive of a people without a language, or a language without a people.' (cited in Melinte, 2012).

Language is indeed a remarkable and unique capacity of humankind. Despite its complexity, children develop this highly specialized skill spontaneously, without conscious effort or formal instruction (Pinker, 1994). Many aspects seem to be special to language, even if some of them can be present in different cognitive processes or can be found in other species than humans. The debate on which characteristics of language are unique to it and exclusive to human species is ongoing, however, one aspect that seems to consensually make language a unique human capacity is recursion (Corballis, 2011; Hauser et al., 2002; Pinker & Jackendoff, 2005; van der Hulst, 2010). This phenomenon is based on a constituent that contains a constituent of the same type, as in the sentence '*a question [that was made by the woman [that wrote the book [that you bought in the book-store [that belongs to my friend [that is a scientist [that…]]]]]]*' (Pinker & Jackendoff, 2005). In this example, it is the recursive property of grammar that allows us to build meaningful sentences with multiple phrases in it, by respecting a set of combinatorial rules, and, in the same way, it is this feature that allows us to compose an infinite number of sentences (Chomsky, 1980). Morphology, relating to the internal structure of words (e.g. *anti + dis + establish + ment + ari + an + ism*), and syntax, relating to how words are combined together in phrases and sentences, integrate the classical domain of recursion (Hauser et al., 2002).

Words are an essential element of language which will be studied in this dissertation. Although it could appear more relevant to study how we process complex structures like sentences, active research is carried out at the word level because words are relatively well-defined minimal units that carry many codes of analysis (orthography, phonology, semantics, syntax), and processing distinctions (automatic vs. attentional) (Balota et al., 2006). Words are shared, organized linkages of phonological, conceptual, and grammatical structures, becoming unique language-specific elements of human knowledge (Pinker & Jackendoff, 2005). Nagy and Anderson (1984) estimated that a high-school level child might know around 45,000 basic words (meaning words that cannot be derived from any other word), and these words can describe a vast range of concepts and provide specific information with unique precision (Pinker & Jackendoff, 2005). The information about a given word, that is considered somewhat distinctive and therefore must be learned and stored in the lexicon, determines how the word enters into the recursive components of grammar (morphology and syntax) (Pinker & Jackendoff, 2005). The association, in long-term memory, about syntactic, semantic and phonological/orthographic information associated to words is referred to as the mental lexicon (Jackendoff, 2002). The concept of mental

lexicon was first introduced by Oldfield (1966) who suggested that we could have a 'mental dictionary' and raised the question of how is the information about a word meaning retrieved. This question can now be extended to the access to information about the other components of a word, as for example how we access lexical information, a task that we spontaneously perform every day while speaking or writing to other people, even about trivial topics such as describing what we just saw in a shop window.

Some models have been proposed to answer the above question, like the model by Levelt (1992) suggesting that lexical access occurs in two stages: first, the selection of semantic and syntactic representations; secondly, the selection of its phonological associated content. In support of such a two-stage model comes the study of anomic patients that are able to give lexical-syntactic information, like gender, of words which they were unable to produce or to give any phonological information about (Badecker et al., 1995). However, Caramazza and Miozzo (1997) studied the « tip-of-the-tongue » phenomenon analyzing the correlation between correct retrieval of lexical-syntactic information and phonological information, like the first phoneme of words that subjects were unable to fully retrieve. They failed to find a positive correlation between these two abilities and showed that access to phonological information is possible regardless of access to syntactic information (Caramazza & Miozzo, 1997). Thus, authors proposed an independent network model, in which the semantic, syntactic and phonological features of a word can be independently accessed. In support of this model, Kavé and Levy (2003) also showed that patients with Alzheimer's disease presenting major linguistic deficits on semantic-conceptual tests of naming are able to detect gender agreement violations, revealing an intact access to syntactic information despite deficits accessing semantic information. The opposite pattern, notably patients with post-stroke aphasia who were able to access semantic information, by correctly naming pictures, but were unable to provide syntactic information (gender) also suggests that lexical-syntactic information is stored separately from lexical-semantics (Biran & Friedmann, 2012).

Another important question when it comes to words is how are these recognized and processed and, importantly, how we process different types of words, namely regular words - for which the phoneme-grapheme correspondence is transparent (e.g., 'cat') - irregular words - for which this correspondence is non-transparent (e.g., 'plaid' incorrectly read as '/pleId/' and written as 'plad') - or even non-words - strings of letters that are orthographically/phonologically correct but have no meaning. Two influential models of reading, the connectionist and symbolic accounts,

postulate two different mechanisms for the processing of different types of words (Figure 1). The prototype of connectionist accounts is the triangular Parallel Distributed Processing (PDP) model (Plaut et al., 1996), in which semantic, phonological and orthographical patterns are interconnected via an associative network (Figure 1A). The model claims that the processing of irregular words necessarily depends on a reading/writing route involving semantics, while regular words can also be processed via a direct route from orthographical to phonological patterns (or vice-versa for writing). This route is also crucial for novel or non-words which are exclusively processed via this direct pathway. Conversely, symbolic reading models and more particularly the Dual Route Cascaded (DRC) model (Coltheart et al., 2001) state that, in addition to semantic, phonological and orthographical representations, there is an intermediate level referred to as the mental lexicon which contains whole word forms (Figure 1B). According to DRC models, this lexical level is critical to the processing of irregular words, mapping word entries in the orthographic lexicon directly onto word entries in the phonological lexicon, during reading, and vice versa during writing.

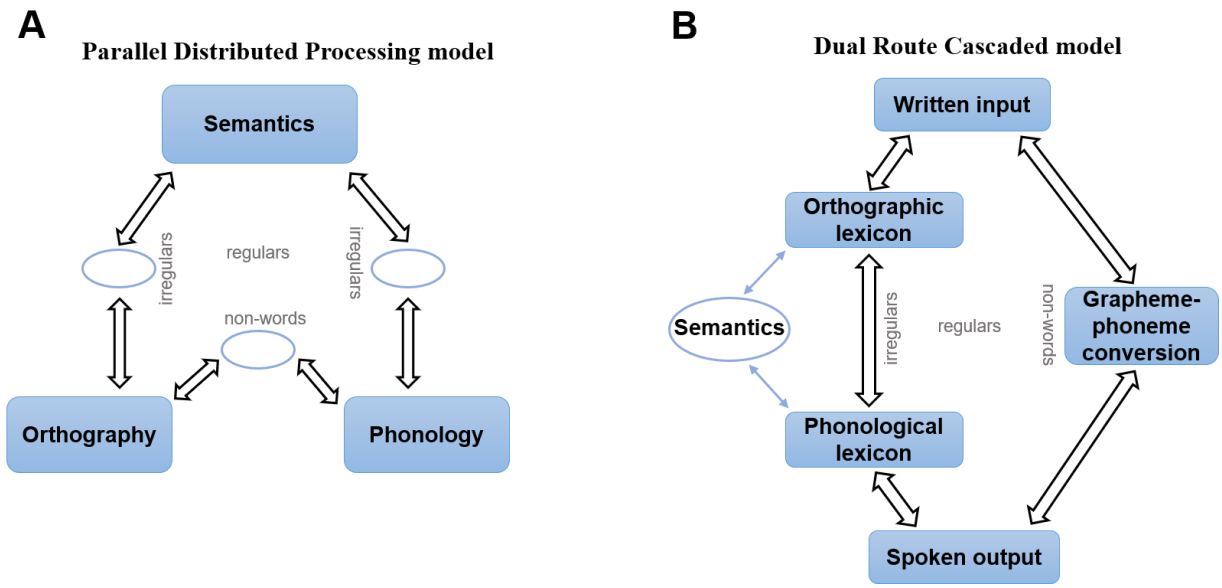

Figure 1. Connectionist (A) and symbolic (B) models of Reading. **A)** The Parallel Distributed Processing (PDP) model states that semantic, phonological and orthographical patterns of a word are interconnected via an associative network, claiming that the processing of irregular words necessarily depends on a reading/writing route involving semantics, while regular words can also be processed via a direct route from orthographical to phonological patterns. **B)** The Dual Route Cascaded (DRC) model states that in addition to semantic, phonological and orthographical representations, there is an intermediate level

referred to as the mental lexicon that contains whole word forms which is critical to the processing of irregular words, mapping word entries in the orthographic lexicon directly onto word entries in the phonological lexicon.

As we saw, language is a complex system and the access to the lexicon involves a number of relatively distinct (but interacting) mental representations and cognitive processes that recruit an extended neural system including several brain regions and white matter projections. Language was one of the first cognitive functions to be characterized from a biological perspective, since Paul Broca, in the 19th century, observed the dissimilar effects of damage to different brain regions and described the asymmetrical roles of the left and right hemispheres in language processing (Albright & Neville, 1999). There is still no absolute consensus on the role of different brain structures on the diverse language processes. However, it has been shown that distinct language features, as phonology, syntax and semantics, rely each on different neural structures. Functional magnetic resonance imaging (fMRI) studies exploring processes of lexical retrieval have shown activation in various brain areas including the middle temporal and the superior temporal gyrus, the anterior temporal lobe (ATL), the inferior frontal gyrus and the inferior parietal lobe (e.g., Kuperberg et al., 2008; Lau et al., 2013; Ruff et al., 2008). A growing body of evidence has been showing the important role of the ATL in the representation and processing of lexical semantic information (Wilson et al., 2014). Recognizing a word involves a process of matching an orthographic or phonologic input with stored representations in lexical memory (Adelman et al., 2014), with different brain regions like the left inferior frontal gyrus and the middle temporal gyrus being associated to this function (Graves et al., 2010; Pillay et al., 2014). With regards to syntactic information, Snijders et al. (2009) have suggested that the left inferior frontal gyrus contributes to syntactic unification whereas the left posterior temporal gyrus subtends the retrieval of lexical-syntactic information. Finally, language comprehension and production also require control and working memory resources, that are subtended by prefrontal regions such as the dorsolateral prefrontal cortex (Klaus & Schutter, 2018).

A fundamental condition for the effectiveness of the neural circuits supporting language functions is the information transfer between the different brain language-relevant regions (Friederici & Gierhan, 2013). This is done via fiber bundles that connect these regions, the major ones involved in language being the uncinate and the arcuate fasciculi (Figure 2). The uncinate

fasciculus (Figure 2A) is a major white-matter tract that connects the anterior inferior frontal and anterior temporal cortices and is suggested to be an indirect path of the 'semantic ventral pathway', that supports lexical retrieval (Parker et al., 2005). The arcuate fasciculus (Figure 2B) connects the perisylvian cortex, including the pars opercularis/pars triangularis sections of the inferior frontal gyrus (known as Broca's area) with the posterior/middle superior temporal gyrus (known as Wernicke's area) with fibers also extending into the inferior parietal lobe (Catani & Mesulam, 2008).

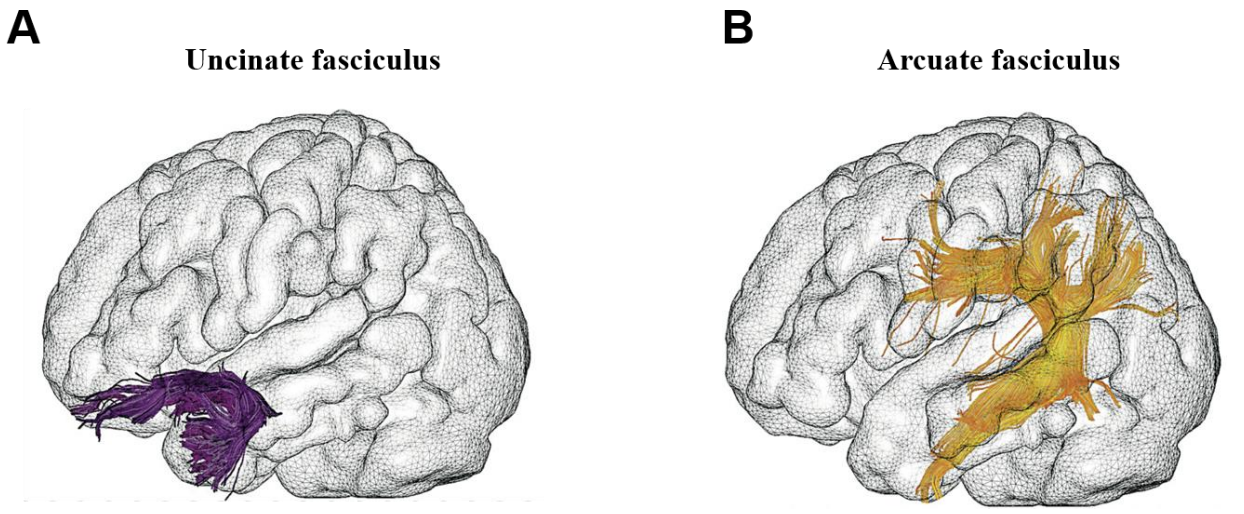

Figure 2. White-matter tracts connecting language-relevant regions. **A)** The uncinate fasciculus connects the anterior inferior frontal and anterior temporal cortices. **B)** The arcuate fasciculus connects the perisylvian cortex, including the pars opercularis/pars triangularis sections of the inferior frontal gyrus (known as Broca's area) with the posterior/middle superior temporal gyrus (known as Wernicke's area) with fibers also extending into the inferior parietal lobe. *Adapted from Catani & de Schotten, 2008.*

Taken together, the core nodes of the complex and highly specialized language network seem to be located in the left frontal, temporal and inferior parietal cortices (Figure 3). The breakdown of this complex language system is present in different neurodegenerative diseases and at different levels. The study of language breakdown through neurodegenerative models can be looked at from two different perspectives: that of understanding the pathology to have insight into more targeted therapies and that of learning about the normal processes (Levy & Kavé, 1999).

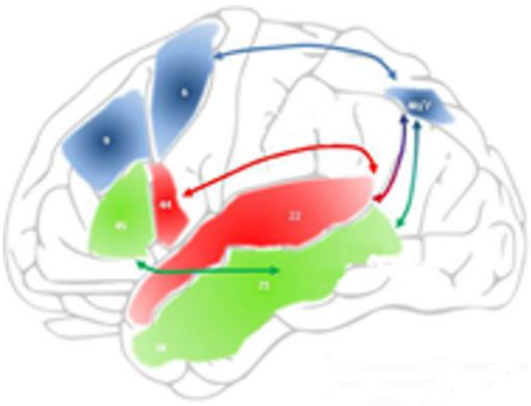

Figure 3. Simple schematic representation of brain regions and connections that are part of the language network. Regions of the left frontal, temporal and parietal cortices are differently involved in language processing and are connected via white-matter fiber tracts. *Adapted from Majerus, 2013.*

I.2. Neurodegenerative diseases

Due to low birth rates and increasing life expectancy, developed societies are facing rapid population aging. Consequently, private or state-funded welfare and health systems have to deal with dramatic increases of the incidence and prevalence of cognitive decline and aging related conditions. Neurodegenerative diseases generating cognitive disability, popularly referred to as dementia syndromes, are evolving conditions impacting high-level brain functions, which significantly impacts daily life (Przedborski et al, 2003). Aging is the most well-known risk factor in most neurodegenerative diseases (Przedborski et al., 2003). Yet genetics (see Bettens et al., 2013; Karch et al., 2014; Mesulam et al., 2008; Seeley et al., 2009 for review) and environmental factors (Kivipelto, 2001; Lau & Breteler, 2006; Qiu et al., 2007; Reitz & Mayeux, 2014) may also play a major role.

Depending on the disease, patients can present with impairments of memory, language, reasoning, judgment and visuospatial skills (Albert et al., 2011). Cognitive symptoms get gradually worse, affecting patients' ability at work and in daily-life activities, which generates dependency (McKhann et al., 2011). Cognitive deficits are caused by progressive neuronal loss, and the subsequent gray matter atrophy of the brain areas in which such processes take place. White matter is also impacted (Good et al., 2002; Mahoney et al., 2013; Rohrer et al., 2010; Zhang et al., 2009), not only as the consequence of neuronal loss (by axonal Wallerian degeneration), but also likely by direct damage conveying altered intracellular cellular protein aggregates and neuroinflammatory processes (Caso et al., 2016). Neurodegeneration generally starts long time before the onset of clinical manifestations, during the so-called "asymptomatic" stage (Hampel et al., 2010). The subtending pathological mechanisms impact specific sets of regions and the

distribution of anatomical damage evolves dynamically from early to later stages depending on the disease spreading (Przedborski et al., 2003).

Language impairments are found in numerous neurodegenerative diseases, sometimes as the most prominent symptom, as in Primary Progressive Aphasia (PPA), and sometimes covered by other cognitive and non-cognitive deficits (Boschi et al., 2017), as is the case in Progressive Supranuclear Palsy (PSP). Since Pick first described, in 1892, a progressive language disorder derived from a degenerative brain disease (Pick, 1892), our knowledge about the individual linguistic variables identifying language deficits related to different neurodegenerative diseases as greatly improved and language characterization and assessment has a crucial role in the diagnosis of many of these pathologies (Boschi et al., 2017).

The study of neurodegenerative diseases has not only improved our knowledge of the disease in itself but also allowed for a greater understanding of language processing and, due to imaging techniques, a better knowledge of the language network, from which different regions are targeted by each disease (Graff-Radford et al., 2014). For a long time, and due to the important works of Paul Broca (Broca, 1863) and Carl Wernicke (Wernicke, 1874), the locus of research when studying the neurology of language was aphasias following a stroke. However, despite the crucial advances they allowed, studies with post-stroke patient cohorts as a method of identification of brain regions associated with specific deficits may be biased, because there are brain regions that are more vulnerable to ischemia and these areas are, therefore, more likely to be revealed as associated with deficits than less vulnerable areas (Race et al., 2013). Neurodegenerative diseases affect brain regions that are less frequently affected by stroke, in addition to areas often affected by stroke (Mesulam et al., 2014; Race et al., 2013), and have thus been providing new insights into the regions of the brain that interact in a normally functioning language network. The study of neurodegenerative diseases affecting language has thus a double value by allowing: (1) a better knowledge of the mechanisms of language processing and the neural components of the language network and, (2) a better detection and characterization of language impairments in such diseases, which should lead to a better targeting of such deficits with improved therapies.

Below are described the main anatomical and clinical characteristics of the pathologies that were the subject of study during this thesis.

I.2.1. Progressive Supranuclear Palsy

Progressive Supranuclear Palsy (PSP) affects relatively young patients (~65 years) (Golbe, 1994) and is strongly linked with the presence of tau pathology and a loss of striatal dopamine, as well as deficits in cholinergic markers and basal forebrain cholinergic neurons (Dickson et al., 2007). Anatomically, it impacts mainly the basal ganglia, specifically the caudate nucleus and putamen, the midbrain, and the superior cerebellar peduncle (Kato et al., 2003; Looi et al., 2011; Paviour et al., 2006) but damage in prefrontal cortical regions (Brenneis et al., 2004; Cordato et al., 2005, 2002; Paviour et al., 2006) has also been observed (Figure 4).

Its most characteristic clinical features are parkinsonism, postural instability, axial and limb rigidity, an impairment of vertical eye saccades (Litvan et al., 2003; Maher & Lees, 1986). Additionally, several investigations have shown important cognitive and behavioral disorders including a breakdown of executive function and language capacities (Daniele et al., 2013; Schofield et al., 2012). In the language domain, patients suffer deficient lexical access and hampered access to semantic representations, causing a profound diminution of language initiation/fluidity (Josephs & Duffy, 2008; Paviour et al., 2006; Rohrer et al., 2010). Accordingly, PSP patients perform significantly worse than healthy controls on tasks assessing access to lexical and semantic information and the fluidity/initiation of word production (Daniele et al., 2013; Esmonde et al., 1996; Rosser & Hodges, 1994). Likewise, PSP patients demonstrate impaired performance on a wide range of lexical/semantic tests such as synonym judgment, semantic associations, single-word comprehension and naming tasks (Cotelli et al., 2006; Daniele et al., 2013; van der Hurk & Hodges, 1995). Importantly, neuroimaging studies in PSP patients have also demonstrated a correlation between language disorders and atrophy levels in the left Dorsolateral Prefrontal Cortex (DLPFC) (Paviour et al., 2006; Schofield et al., 2012).

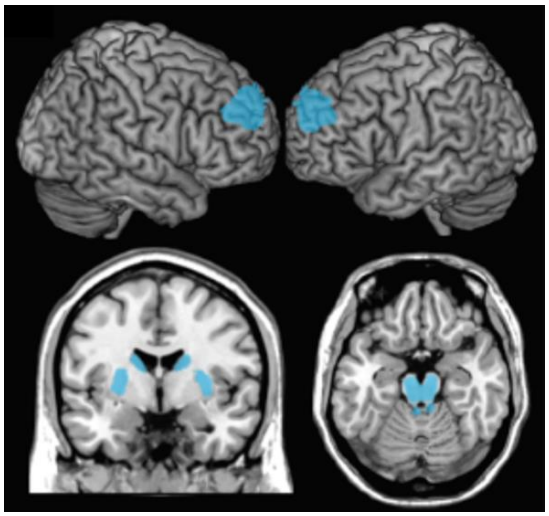

Figure 4. Brain image showing on a standard cerebral volume the cortical and subcortical regions affected by neurodegenerative damage in patients with Progressive Supranuclear Palsy - bilateral caudate, putamen, midbrain and pons and bilateral circumscribed regions of the prefrontal cortex.

I.2.2. Behavioral variant of Frontotemporal Dementia

The behavioral variant of frontotemporal dementia (bv-FTD) is a neurodegenerative disease with early onset (frequently before 65 years of age) (McKhann et al., 2011) generating major repercussions on patients' quality of life (Knopman & Roberts, 2011). Nearly all bv-FTD cases fall within one of three neuropathological groupings: tau-positive, TAR DNA-binding protein 43-positive pathology (TDP-43, a nuclear protein implicated in exon skipping and transcription regulation), or fused-in sarcoma protein pathology (FUS, a multifunctional DNA- and RNA-binding protein, sharing functional homology with TDP-43) (Cairns et al., 2007). Anatomically, bv-FTD is characterized by bilateral atrophy of the prefrontal cortex, including dorsolateral, ventromedial and orbitofrontal regions (Rosen et al., 2002; Whitwell et al., 2009) which subtend executive functions and contribute to the regulation of behavior (Peters et al., 2006) (Figure 5). According to the revised diagnosis criteria of Rascovsky et al. (2011), bv-FTD leads to gradual deterioration of behavior resulting in apathy, diminution of social convenience, impulsivity and disinhibition. In addition, executive capacities are impaired and language production is severely diminished (Bertoux et al., 2016; Kramer et al., 2003; Le Ber et al., 2006; Rascovsky et al., 2011). More specifically, bv-FTD affects communication abilities due to the progressive breakdown of language initiation/activation and research mechanisms in the mental

lexicon as shown by impairments in naming and verbal fluency tasks (Hardy et al., 2015), which are subserved by the left DLPFC (Sanjuán et al., 2010; Valero-Cabré et al., 2019).

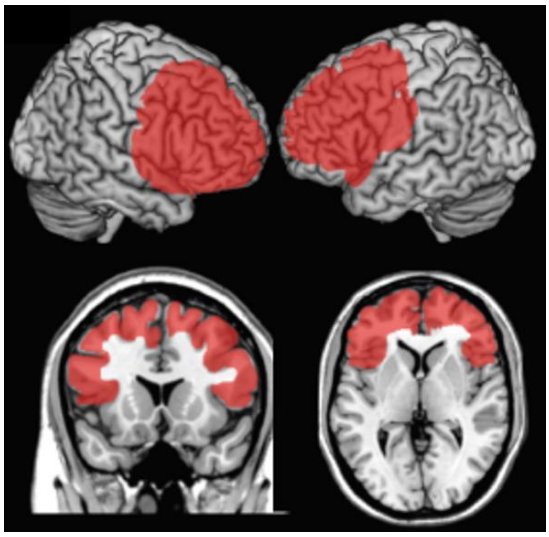

Figure 5. Brain image showing on a standard cerebral volume the cortical regions affected by neurodegenerative damage in patients with the behavioral variant of Frontotemporal dementia -bilateral prefrontal cortex.

I.2.3. Primary Progressive Aphasia

Primary Progressive Aphasia (PPA) starts generally before 65 years of age (Mesulam et al., 2014) and is characterized by progressive loss of language abilities (Mesulam, 1987). Other cognitive abilities as well as activities of daily life are relatively well preserved during approximately the first two years after diagnosis. Beyond that point, memory, praxis and executive functions can also be severely affected (Mesulam, 2001).

Three main PPA variants have been characterized: semantic (sv-PPA), logopenic (lv-PPA) and nonfluent/agrammatic (nfv-PPA). PPA has heterogeneous neuropathologic causes (Gorno-Tempini et al., 2011) but despite heterogeneity, there is some association between a specific PPA variant and an underlying pathology (Grossman, 2010). The most frequent finding in sv-PPA is ubiquitin-positive and TDP-43-positive, in lv-PPA is Alzheimer's disease pathology, with decreased amyloid beta-protein 42 (Aβ42) and increased tau in the cerebrospinal fluid (CSF), and in nfv-PPA is tau-positive pathology (Grossman, 2010). Anatomically, sv-PPA is linked to damage to both ATLs with high left side predominance (Figure 6). Clinically, it is characterized by damage

to the semantic system, with loss of conceptual knowledge, resulting in anomia and difficulties in single word comprehension (Gorno-Tempini et al., 2011). Lv-PPA mainly affects the left posterior temporal and parietal cortices, encompassing the temporo-parietal junction (TPJ) (Figure 6), and causes an impairment in the access to lexical representations, reflected by single-word retrieval difficulties, and a diminution of verbal working memory (Gorno-Tempini et al., 2011; Teichmann et al., 2013). Nfv-PPA is related to damage to the left inferior-posterior frontal cortex including Broca's area (Figure 6) (Gorno-Tempini et al., 2004) and is defined by agrammatism and difficulties in phonological and phonetic encoding leading to phonemic paraphasias, and frequently speech apraxia (Gorno-Tempini et al., 2011).

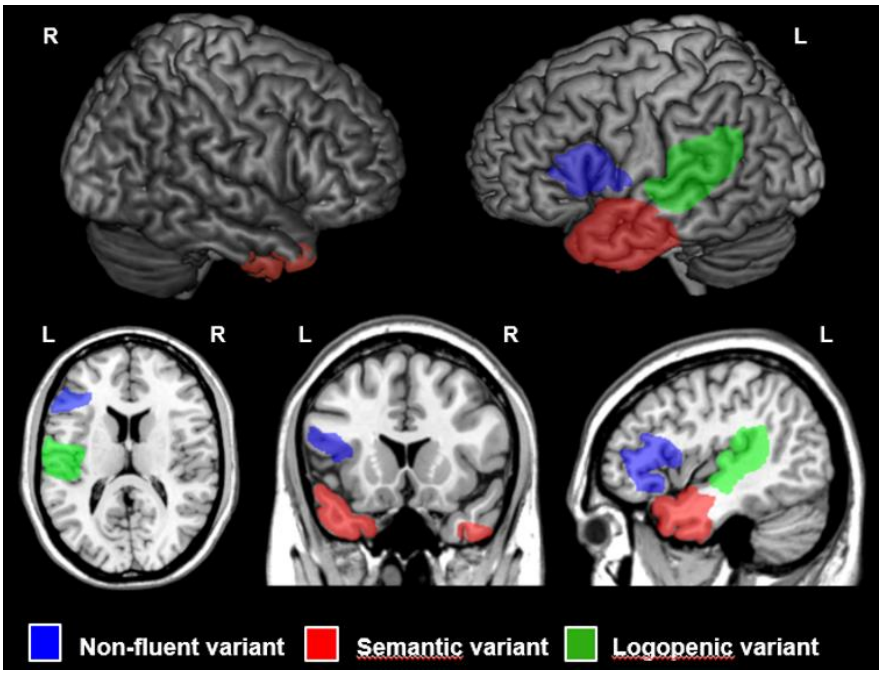

Figure 6. Brain image showing on a standard cerebral volume the cortical regions affected by neurodegenerative damage in patients with the semantic variant of Primary Progressive Aphasia (red) – anterior temporal lobe; the logopenic variant of Primary Progressive Aphasia (green) – middle/posterior temporal and inferior parietal lobes; non-fluent variant of Primary Progressive Aphasia (blue) – inferior frontal cortex.

Despite strategies to slow-down cognitive symptoms in these diseases, no effective treatment at the cellular level has proven successful to contain cognitive impairments (Kumar et al., 2015; Lamb et al., 2016; Vossel & Miller, 2008) and speech therapy shows little effects in slowing language decline (Savage et al., 2013). It has been estimated that about 24 million people

worldwide suffer from cognitive neurodegenerative diseases and their prevalence doubles every five years (Qiu et al., 2007). These pathologies are individually and socially debilitating and represent an unbearable burden for patients, and their families, especially due to the lack of effective treatments (Przedborski et al., 2003). In this context, the development of novel therapeutic approaches able to drive improvements in quality of life, and dwindle their associated clinical, social and financial burden becomes paramount.

I.3. Non-invasive brain stimulation

The electrical nature of nervous tissue has been known for centuries, since the experiments of Luigi Galvani in 1791 provided the first evidence for the electric nature of the 'fluid' involved in nerve conduction and muscle contraction (Piccolino, 1998). Despite the controversy regarding Galvani's findings at the time, consequent work carried by Carlo Matteucci in 1838 and later by Emil du Bois-Reymond established the existence of action potentials and its spreading nature in nervous tissue (Piccolino, 1998). This electrical nature of the nervous tissues is the basis of non-invasive brain stimulation (NIBS) techniques, that use an electrical or magnetic source to inject energy into a brain area to promote neural change (Paulus et al., 2013). In neurodegeneration, the two most commonly employed technologies for modulating cortical activity are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) (Figure 7). The latter was the one explored in the studies presented in this dissertation.

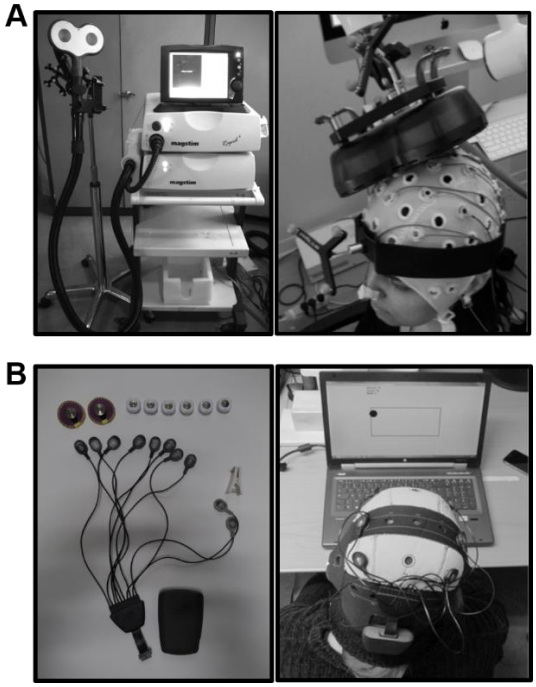

Figure 7. Technical equipment and procedure to use Transcranial magnetic stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS). **A)** TMS is a heavy non-portable equipment that charges current in a series of capacitors, delivering current through a stimulation coil. **B)** tDCS is delivered through a small light and portable rechargeable battery system often placed in a cap worn by subjects and controlled wirelessly from a computer or portable device.

I.3.1. Transcranial direct current stimulation

After having been investigated in the mid-sixties in animal models as a tool for cortical polarization (Bindmam et al., 1964; Purpura & McMurtry, 1965), tDCS was rescued 15 years ago as a cheaper, safer and more portable way to modulate brain activity than TMS. Transcranial DCS is based on passing a weak constant electrical current (1 to 2 mA) between an *active* (anode or cathode) and a *return* electrode placed on distant regions of the skull (Nitsche & Paulus, 2000) (Figure 7B), inducing a voltage gradient in the brain and a passive change in membrane potential (Rahman et al., 2013). At difference to TMS, tDCS is unable to directly trigger action potentials in cortical neurons. It aims to polarize the targeted region, generating large areas of cortical polarization. By attracting charges and distributing them with a specific topography along the areas influenced by the active vs. return electrodes, it modulates membrane resting potentials, making neurons more or less prone to generate an action potential (Paulus et al., 2013; Rahman et al., 2013).

Neurons polarize in a compartment specific manner and specific effects depend on their orientation towards the direction of the current flow (Radman et al, 2009; Rahman et al., 2013). Generally, compartments of the neuron (as apical dendrites in pyramidal cells) oriented towards the anode, where current flows in, hyperpolarize (Figure 8A), whereas compartments oriented towards the cathode, where current flows out, depolarize (Figure 8B) (Bikson et al., 2004; Radman et al., 2009; Rahman et al., 2013). Contrary, distant compartments from the anode (as the soma in pyramidal cells) will then be depolarized (Figure 8A) whereas distant compartments from the cathode will be hyperpolarized (Figure 8B) (Bikson et al., 2004; Radman et al., 2009; Rahman et al., 2013). The change in the spontaneous firing rate of a neuron reflects somatic polarization (Purpura & McMurtry, 1965; Radman et al., 2009). It is now commonly accepted that anodal stimulation renders neural cells more likely to fire when receiving an action potential through presynaptic inputs (Nitsche et al., 2005; Radman et al., 2009; Rahman et al., 2013). Inversely, cathodal stimulation usually decreases the probability to trigger an action potential (Nitsche et al., 2005; Radman et al., 2009; Rahman et al., 2013) (Figure 8).

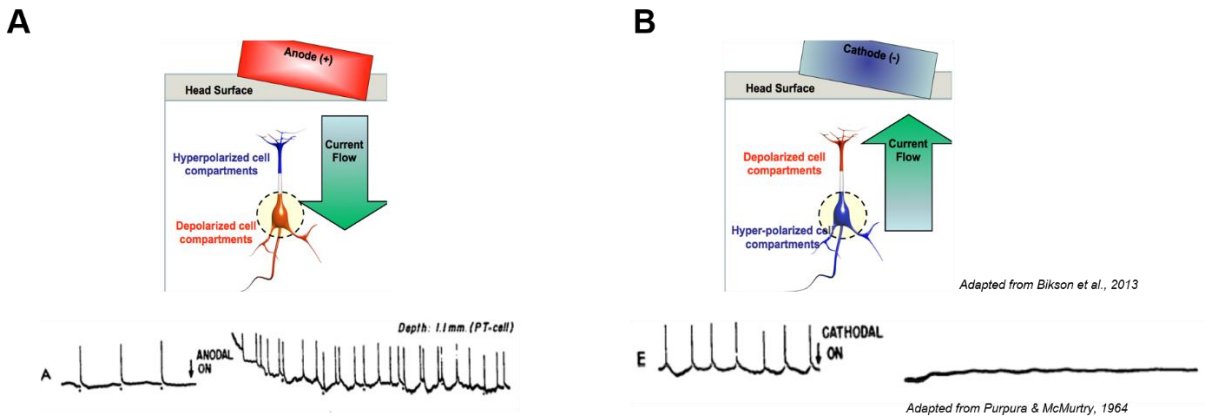

Figure 8. Effects of transcranial direct current stimulation in the brain. **A)** Anodal stimulation: the anode is placed on the scalp over the brain region intended to be modulated; depolarizes the soma of the neuron rendering neural cells more likely to fire when receiving an action potential through presynaptic inputs. **B)** Cathodal stimulation: the cathode is placed on the scalp over the region intended to be modulated; hyperpolarizes the soma of the neuron decreasing the probability of neuronal cells to trigger an action potential.

Transcranial DCS effects operate during the delivery of the stimulation (online tDCS effects) but remain active following the end of stimulation (Nitsche & Paulus, 2000), leading to responses described as long-term potentiation (LTP) or long-term depression-like (LTD) (Pelletier & Cicchetti, 2014). Long-term potentiation allows for modulation of synaptic strength that can stabilize for days, months, or years (Stagg & Nitsche, 2011) and is thought to mediate learning and memory formation in the brain (Takeuchi et al., 2014). Evidence has been provided that tDCS modulates synaptic strength within the cortex suggesting that synaptic plasticity is occurring (Kronberg et al., 2017). Moreover, different studies using neuroimaging techniques have suggested that tDCS can impact widespread distributed brain networks, influencing brain connectivity, by increasing excitability in the underlying stimulated area and in distant interconnected brain regions (Keeser et al., 2011; Lang et al., 2005; Peña-Gómez et al., 2012; Polanía et al., 2012), leading to performance improvement in cognition supported by specific networks (Pereira et al., 2013).

In stimulation protocols, the stimulation electrode i.e., either the anode or the cathode depending on stimulation modality, is placed in the skull over the region of interest, while the return is placed over a region far from the target to avoid current shunting through the skin,

favoring penetration (Bikson et al., 2012) (Figure 7B). Since the current flows from relatively large electrodes separated away, tDCS has a broad spatial resolution (~5-7 cm radius with classical 2 electrode montages), with wide current dispersion (Bikson et al., 2009; Wagner et al., 2007). Nonetheless, focality can be increased reducing electrode size or implementing additional montages with an active electrode surrounded by several returns (Minhas et al., 2010; Miranda, 2013). Intensities below 0.4 mA do not induce meaningful after-effects (Nitsche & Paulus, 2000), whereas those above 3 mA, particularly passed through small electrodes can induce skin rush and tinkling sensations (Furubayashi et al., 2008). Both exploratory and therapeutic tDCS effects have been obtained with intensities between 1-2mA delivered through rectangular or round electrodes (normally between $25cm^2$ and $35cm^2$).

The strongest assets of tDCS compared to TMS are its low cost, an outstanding safety profile (local side-effects are limited to local tinkling and/or an itching sensation under the active electrode (Iyer et al., 2005)), its portability and highly adaptable ergonomics (reviewed in Polanía et al., 2018; and Valero-Cabré et al., 2017). These advantages have developed tDCS applications in both hospitals and particular homes for bedridden patients, boosting the popularity of this technology in clinical applications (Elder & Taylor, 2014). Moreover, in contrast with TMS, tDCS allows an excellent sham condition, which cannot be easily identified from active stimulation (Gandiga et al., 2006). The main weakness of tDCS compared to TMS is its poor spatial resolution, which is paramount when specific brain areas must be stimulated selectively (Torres et al., 2013). Its limited focality may, however, prove beneficial when cortical targets are elusive or when a clinically effective application requires, such as it is often the case in neurodegenerative diseases, the stimulation of large cortical areas (Torres et al., 2013).

The use of TMS or tDCS for improving brain function is currently developing around two main strategies: (1) to enable increases of cortical excitability within areas of interest hosting specific cognitive operations (i.e., to promote improvements in performance likely by facilitating LTP-like processes between the stimulated neurons); and/or (2) to suppress networks (likely via LTD-like processes) in damage-spared brain areas that under normal conditions interfere performance (Liebetanz et al., 2002; Luber & Lisanby, 2014). The latter approach is often achieved by reducing an output of net inhibitory interactions from a healthy area located in the contralateral hemisphere, relative to the cognitively relevant homotopic region, which releases the latter from a

pathological state of excessive transcallosal inhibition (Floel, 2014; Hamilton et al., 2011; Luber & Lisanby, 2014) (Figure 9).

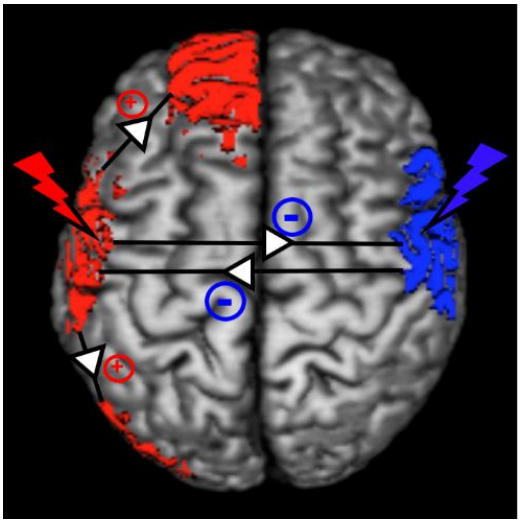

Figure 9. Schematic representation of the mechanisms of brain function modulation by TMS/tDCS. Anodal stimulation/high-frequency repetitive TMS (rTMS) (in red) increases excitability in the targeted region and connected regions, improving its functioning. Cathodal stimulation/low-frequency rTMS (in blue) decreases activity in the targeted region, reducing its influence in the contralateral homotopic region and improving its function by doing so.

I.3.2. Computational models of tDCS current magnitude and distribution

Transcranial DCS produces a complex spatial distribution of the electric current flow in the brain that hinders an accurate localization of the stimulated brain areas (Opitz et al., 2015). The precise pattern of current flow through the brain is determined not only by the stimulation dose but also by the underlying anatomy and tissue properties (Bikson et al., 2012) such as the skin-to-brain target straight distance, skull shape, cortical volume and thickness, sulcal pattern and gyri geometry and target localization (Bikson et al., 2012; Wagner et al., 2007). There is evidence that the thickness of the skull, the volume of the cerebrospinal fluid in the subdural space and the distance of the targeted region in the brain to the tDCS anode or cathode account for up to 50% of the spatial variation of the electric field strength (Datta et al., 2012; Opitz et al., 2015; Russell et al., 2013). Kim et al. (2014) found that performance improvement in a working memory task correlated with the simulated electric field strength, suggesting that inconsistent behavioral outcomes of tDCS might be partly due to individual anatomical differences.

Electric fields induced during stimulation in humans are not easy to assess directly and so modelling approaches are frequently used to study electric field distributions and magnitudes in the human brain (Alekseichuk et al., 2019). Computational Finite Element Models (FEM) can be used to estimate the spread and intensity of current fields based on individual structural magnetic

resonance imaging (MRI), to account in advance for variability and tailor individually the optimal stimulation settings and approaches (Wagner et al., 2014; Wagner et al., 2007) (Figure 10).

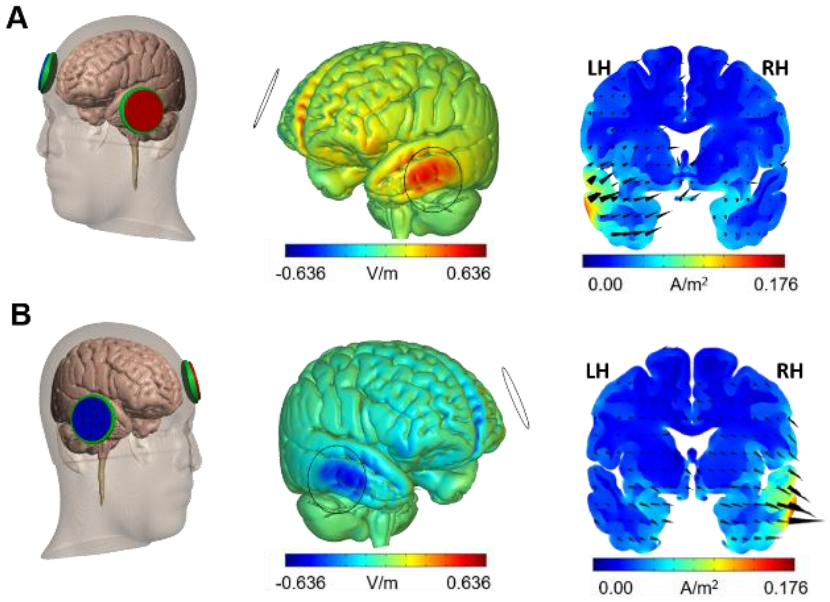

Figure 10. Finite Element Method (FEM) biophysical models of the distribution of current across the whole head and brain volume, using a tDCS montage with 25cm^2 electrodes and an intensity of 1.59 mA. **A)** Anodal left temporal pole stimulation with right supraorbital return. **B)** Cathodal right temporal pole stimulation with left supraorbital return. In each panel, from left to right: electrode position on the scalp; spatial distribution of the radial electrical field (V/m) in the cortical surface and; current density (A/m^2) and current flow direction on a coronal section of the brain. *Adapted from Teichmann et al., 2016.*

Such models consider cortical anatomical anisotropies (e.g. sulci, gyri, or areas of atrophy and lesions etc.), the biophysical properties (conductivity) and the volume of the layers of tissue that TMS/tDCS fields need to go through before reaching a cortical target. On that basis, they estimate the cortical site of peak electric field strength, the radial spatial distribution of the electric fields, which determine focality and current peak density. Off-the-shelf biophysically-based computational models for TMS and/or tDCS (simNIBS 2.0, www.simnibs.de, Thielscher et al., 2015; BONSAI, www.neuralengr.com/bonsai/, Truong et al., 2014; or ROAST, www.parralab.org/roast/, Huang et al., 2019) are now freely available for users. A computational

approach of modeling should help defining if and how tDCS current magnitude and distribution in an individual head differ and allowing the study of how these differences can affect clinical outcomes.

I.4. Non-invasive brain stimulation in neurodegenerative diseases

Effective therapeutic approaches in neurodegeneration should be able to operate on the degenerative process itself or, alternatively on life-long active plasticity processes to generate enduring modulations of excitability, on anatomical systems impacted by the disease or on spared neural networks interconnected with the former (Gutchess, 2014). In this vein, NIBS approaches have been shown to enable plastic reorganization processes and have been extensively used for more than a decade on healthy participants to modulate performance in different cognitive domains.

In order to understand the potential of NIBS on cognitive symptoms of neurodegenerative diseases, some recent key advances need to be summarized. For many decades, neurodegenerative diseases have been conceived under a purely topological view as impacting focal brain regions, and progressing nonspecifically across brain areas, not following a specific spatial pattern. The advent of advanced brain imaging techniques has shown, however, that their spatial spread impacts brain sites organized in networks (Seeley et al., 2009) by following specific white matter pathways (Clavaguera et al., 2013; Maruyama et al., 2013; Pievani et al., 2014). Accordingly, damage translates into sets of symptoms in coherence with anatomical damage reached at each clinical stage of the disease (Saxena & Caroni, 2011).

According to the network degeneration hypothesis reported above, neurodegenerative diseases can be conceptualized as connectivity disorders (Seeley et al., 2009) originating in small focal networks to progressively spread to interconnected areas (Gomez-Ramirez & Wu, 2014). Furthermore, disease-specific areas of vulnerability can be tracked with Positron Emission Tomography (PET) imaging using radioactive ligands, binding specific proteins expressed by cells in distress (Morrison et al., 1998) or binding specific pathologic aggregates (as tau proteins) (Saint-Aubert et al., 2017). Nonetheless, the underlying mechanisms of such network distribution remain poorly understood (Gomez-Ramirez & Wu, 2014). Among other hypotheses, anatomical progression could be explained by spatially-specific patterns of network vulnerability, i.e., neurochemical fragility of neuronal populations (such as those of Von Economo fronto-insular

neurons in bv-FTD, Seeley et al., 2009), sensitive to stressors, and combined with covariates such as genetic background, age or preexisting conditions (e.g. misfolded protein-related disorders) (Saxena & Caroni, 2011). Recent reports have also supported processes of cell-to-cell transmission of misfolded proteins (Clavaguera et al., 2013; Herva & Spillantini, 2015), by aggregates transported across neurons reaching specific sites, able to transfer across synapses.

These biological mechanisms will be ultimately responsible for the disease-specific breakdown of functional connectivity that can be revealed by alterations in the normal patterns of resting state functional Magnetic Resonance Imaging (fMRI) in patient populations, opening new avenues for the development of biomarkers and predictors of clinical and anatomical prognosis. To the latter regard, for example, patients with Alzheimer's disease show impaired functional connectivity between the anterior and posterior components of the so-called default mode network, co-varying positively with the degree of cognitive impairment (Liu et al., 2014). These results support that disruption affects long-distance connections to hub nodes, causing a breakdown in network efficiency (Liu et al., 2014). In sv-PPA patients, Guo et al. (2013) reported functional connectivity alterations between the ATL and a broad range of brain regions in primary and associative cortices. However, the relation between functional connectivity alterations and semantic deficits remains uncertain (Yang et al., 2015). Disrupted fronto-limbic connectivity and increased local functional prefrontal connectivity has been shown in patients with both sv-PPA and bv-FTD (Farb et al., 2013). Moreover, whereas fronto-limbic disconnection has been associated with lower disinhibition scores, prefrontal hyperconnectivity correlated with apathy scores (Farb et al., 2013). Finally, a recent study in patients with Posterior Cortical Atrophy (Migliaccio et al., 2016) has shown reduced functional connectivity in the ventral cortical visual network, whereas in contrast, functional connectivity was found increased in the inferior component of the dorsal visual network. Moreover, greater grey matter atrophy in occipital regions, which are typically impacted in these patients, correlated with increased functional connectivity (Migliaccio et al., 2016).

This novel hodological perspective on neurodegenerative diseases sets a stage in which NIBS effects distributed throughout neural networks might prove particularly fitted to slow down cognitive decline and/or maximize cognitive abilities at each clinical stage of the disease. Most importantly, it provides a rational to tailor NIBS interventions focusing on critical cortical regions crucial for the subsequent progression of neurodegeneration. Explicitly supporting this promise,

tDCS in healthy participants and neurodegenerative patients was shown to increase MRI-resting state functional connectivity between the targeted region and distant interconnected cerebral sites (Keeser et al., 2011; Pereira et al., 2013; Polanía et al., 2011), driving improvements of cognitive performance (Pereira et al., 2013).

Studies carried out during the last decade have demonstrated the potential of repetitive TMS (rTMS) or tDCS to enhance cognitive performance in healthy adults. The use of NIBS in healthy adult human research has significantly contributed to neuroscience knowledge by allowing a causal exploration of brain connectivity and previously hypothesized brain-behavior relations. Encouraging TMS/tDCS results in healthy participants and the recent explosion of tDCS studies in patients with widespread brain damage have led researchers to evaluate the cognitive impact of NIBS in several neurodegenerative diseases (particularly in Alzheimer's disease and PPA using tDCS). Below are presented the studies that explored the effects of NIBS in the pathologies concerned by this thesis.

I.4.1. Progressive Supranuclear Palsy

To date only one study has been carried out to rehabilitate cognitive dysfunction via NIBS in PSP patients. Nonetheless, it is worth-mentioning the use of rTMS for disease characterization purposes and for the treatment of some motor symptoms in PSP. TMS has also been applied successfully in differential diagnostics of PSP patients with parkinsonian symptoms (Kuhn et al., 2004; Morita et al., 2008; Wolters et al., 2004). A pilot study with PSP patients showed only modest and transient improvements impacting the axial muscles after 5 consecutive daily sessions of rapid-rate rTMS over the primary motor cortex (Santens et al., 2009). A recent study (Madden et al., 2019) reported the effects of anodal tDCS over the left DLPFC on language impairments of one PSP patient. This patient received stimulation concomitantly with language tasks and, during stimulation, performances improved in phonemic fluency and action naming tasks.

In view of rTMS or tDCS preliminary evidence coming from other neurodegenerative diseases and from the only tDCS study performed to date, these techniques may have the potential to improve motor symptoms and also language impairments in PSP patients. However, studies using periodical stimulation regimes combined with behavioral and physiological measures are now necessary to confirm such promise.

I.4.2. Behavioral variant of Frontotemporal Dementia

Only three studies have thus far addressed the impact of NIBS on cognitive symptoms in bv-FTD. A decade old pilot study failed to find effects on a verbal fluency task of active vs sham anodal tDCS over the left prefrontal area delivered during 20 minutes (Huey et al., 2007). In contrast, a recent case report (Agarwal et al., 2016), reported improved speech production, along with ameliorations of the Fronto-Temporal Dementia Rating Scale logit scores (see Mioshi et al., 2010) and activities of daily living, following a regime of 10 consecutive days of anodal tDCS over the left DLPFC. A recent study (Antczak et al., 2018) explored a cohort of 9 bv-FTD patients and applied high frequency rTMS to the DLPFC bilaterally for 2 weeks. Authors found improvements in the Montreal Cognitive Assessment total score and particularly in the visuospatial abilities subdomain as well as in the Stroop test.

Due to the lack of significant effects in the unique tDCS study in a cohort of bv-FTD patients (Huey et al., 2007), the use of purely qualitative clinical assessment and interviews on an additional single patient report (Agarwal et al., 2016), and the lack of a control group in the only cohort study with strong significant results (Antczak et al., 2018), the potential of NIBS in bv-FTD patients requires further exploration before reliable conclusions on efficacy can be reached.

I.4.3. Primary Progressive Aphasia

TMS studies. Neurostimulation approaches have been probed as potential treatment to contain language deficits in the three main PPA variants. A single rTMS study explored the effects of right and left DLPFC stimulation with high frequency rTMS combined with online naming tasks in patients with nfv-PPA and reported improvements of action verb naming (Cotelli et al., 2012) for both targets. Regarding lv-PPA, Trebbastoni and colleagues (2013) reported an improvement of both oral and written language skills after high frequency rTMS over the left DLPFC in a single patient. Additionally, another single case study explored the effects of high frequency rTMS over the left prefrontal cortex in a patient with an unspecified PPA variant, reporting improvements on verb production, enduring for at least a month and a half (Finocchiaro et al., 2006).

tDCS studies. Tsapkini and colleagues (2014), tested a mixed population of lv-PPA and nfv-PPA patients and reported lasting improvements in spelling for up to two months after anodal stimulation over the left Inferior Frontal Gyrus combined with online spelling tasks. A recent follow-up study by Tsapkini and colleagues (2018) including a larger cohort of nfv-PPA and also

lv-PPA patients and sv-PPA patients addressed the long-term impact of tDCS. Combining anodal stimulation over the left Inferior Frontal Gyrus with spelling and naming tasks, these authors reported improvements in written spelling lasting for up to 2 months for the nfv-PPA and the lv-PPA groups. However, no beneficial effects of stimulation for the sv-PPA group were reported. More recently, 3 additional studies using mixed populations of PPA variants of either lv-PPA, nfv-PPA and sv-PPA patients (Roncero et al., 2017), a combination of lv-PPA and nfv-PPA (McConathey et al., 2017) or a combination of lv-PPA and sv-PPA (Hung et al., 2017) tested, respectively, the impacts of: (1) anodal left inferior parieto-temporal tDCS during an online picture naming task (Roncero et al., 2017); (2) anodal tDCS over left prefrontal regions on different language abilities (McConathey et al., 2017) and (3) anodal tDCS over the left temporo-parietal region combined with a semantic feature training task (Hung et al., 2017). These studies showed an improvement in semantic processing (Hung et al., 2017; McConathey et al., 2017) and also in picture naming (Roncero et al., 2017). Importantly, a study in a subset of this cohorts employed fMRI to analyze the effects of tDCS on functional connectivity, aiming to assess if tDCS language improvements could be explained by changes in functional connectivity. Authors reported significantly lowered functional connectivity between the left Inferior Frontal Gyrus and other language network areas following stimulation, which correlated with tDCS-driven improvements in written spelling scores (Ficek et al., 2019).

Studies performed in nfv-PPA patients have successfully employed anodal tDCS over the right (Manenti et al., 2015) or left DLPFC (Cotelli et al., 2016, 2014; Manenti et al., 2015) combined with offline (not simultaneously with stimulation) (Manenti et al., 2015, single case study) or online (during stimulation) speech therapy (Cotelli et al., 2016, 2014). Two additional studies applied anodal tDCS to the left posterior perisylvian region and Broca's area (Wang et al., 2013) and the left fronto-temporal region (Gervits et al., 2016). Taken together, these nfv-PPA studies showed improvements in speech production (Cotelli et al., 2014; Gervits et al., 2016), naming accuracy (Cotelli et al., 2016; Manenti et al., 2015; Wang et al., 2013), grammar comprehension (Gervits et al., 2016), auditory word comprehension, oral word-reading and word-repetition (Wang et al., 2013). For some studies, post-tDCS improvements lasted for a period of at least 3 months following stimulation sessions (Cotelli et al., 2016, 2014; Gervits et al., 2016; Manenti et al., 2015). Interestingly, the study by Wang and colleagues (2013) used electroencephalogram (EEG) recordings and observed changes in the nonlinear index of

approximate entropy in different stimulated and non-stimulated brain regions, including left Broca's and Wernicke's areas, suggesting that language improvement were associated with such activations. The study from Cotelli and colleagues (2016) associated response outcomes with cortical grey matter density before the regime of periodical tDCS sessions over the left DLPFC and reported a positive correlation between performance improvements and grey matter density at baseline in the left fusiform, left middle temporal gyrus and right inferior temporal gyri. Additionally, the biophysical model applied in Gervits et al. (2016) showed that the current of left fonto-temporal tDCS was distributed throughout left hemisphere regions crucial for language function, hence supporting the choice of stimulation sites and electrode montages.

In sv-PPA, a recent double-blind cross-over pre-therapeutic trial compared the impact of a single session of anodal or cathodal tDCS over the left and right ATL, respectively, with sham tDCS. It showed beneficial effects on a verbal semantic association paradigm after both active (anodal and cathodal) tDCS strategies (Teichmann et al., 2016). Neuronavigated tDCS was used to precisely target coordinates in the anterior third of the temporal lobe subtending semantic processing and guide electrode placement. Biophysical modeling of DC fields pictured the excitatory/inhibitory impact of left anodal and right cathodal tDCS and supported stimulation sites, and montages. Most importantly, internal semantic dissociations emphasized the intra-semantic-specificity of the effects, with higher improvements generating semantic analogies for items belonging to a 'living' category, which appeared as the most impaired in these patients prior to treatment (Teichmann et al., 2016). Another study correlated response outcomes with baseline performance prior to a regime of cumulative tDCS sessions and showed severity-dependent response to tDCS in sv-PPA, with poor baseline performances being associated to better outcomes (McConathey et al., 2017).

Summary. Together with Alzheimer's disease, the three PPA variants are among the neurodegenerative diseases accruing the highest number of reports on the effects of NIBS in cognitive symptoms, with 13 studies (4 single case reports, 3 studies with less than 10 patients and 6 studies in larger cohorts). A majority of studies targeted the DLPFC whereas only 3 (Roncero et al., 2017; Teichmann et al., 2016; Wang et al., 2013) stimulated language-relevant regions specifically impaired in each PPA variant, a strategy that should best optimize recovery of language deficits. Moreover, 7 studies used either very small cohorts (less than 10 patients) and/or worked on non-homogenous cohorts of patients mixing several PPA variants. Surprisingly, only a

single study employed supportive neuroimaging (fMRI) (Ficek et al., 2019) and another used neurophysiological measures (EEG, magnetoencephalography [MEG]) (Wang et al., 2013) to verify stimulation impact or demonstrate short-term/longer-term neuroplasticity effects associated to tDCS. However, 2 studies used biophysical modeling to infer tDCS local effects and focality (Gervits et al., 2016; Teichmann et al., 2016), and confirmed that electrical field spread was well distributed over the regions of interest aimed by the tDCS montage. Even if the use of rTMS and tDCS in PPA populations should be considered promising, we conclude double-blind large-scale clinical trials using therapeutic regimes including several days of stimulation in large and homogeneous PPA cohorts are needed to confirm this clinical indication.

I.5. Specific Aims

This thesis is organized along three main axes: (1) fundamental research on language, (2) clinical research on language breakdown and therapies and (3) impact of individual factors on the variability of the response to such therapies. The studies included in this PhD dissertation respond to three main specific aims, presented briefly on the first part of this introduction, which we outlined and develop here below.

Specific Aim 1. We aim to explore how the fundamental unit of language, the word, and the information it carries is stored and organized in the mental lexicon, how we gain access to it, and how we process it.

We will focus on syntactic, semantic and orthographic/phonologic information carried by words and identify which models may best explain the processes of writing/reading words. We will address these questions working with patients diagnosed with the semantic and logopenic variants of Primary Progressive Aphasia, a neurodegenerative disease that progressively impairs language abilities. We will explore its deficits with rigorously designed experimental tasks based on different linguistic paradigms.

We hypothesized that we are able access a specific type of information about a word in the mental lexicon independently of being able to access other type of information and that the existence of this mental lexicon is essential for the processing of different types of words (i.e. regular vs irregular words).

Two papers addressing these questions are presented in *Chapter II – Fundamental Research on Language.*

Specific Aim 2. We aim to explore language breakdown caused by neurodegenerative diseases and evaluate the pre-clinical value of transcranial direct current stimulation (tDCS) as to improve language deficits in such diseases.

We will approach this question by studying the types and severity of language impairments in Progressive Supranuclear Palsy (n=12), behavioral variant of Frontotemporal Dementia (n=12) and logopenic variant of Primary Progressive Aphasia (n=12) compared to cohorts of healthy participants of similar age and education level. We will then also explore how one single tDCS session (20 minutes, 1.59 mA, 0.06 mA/cm^2) on either left or right hemisphere sites (adapted to each pathology) can impact the language deficits presented by these cohorts of patients.

We hypothesized that language breakdown occurs at different levels on each disease, depending on the specific brain regions affected, and that tDCS can help ameliorate these deficits. We complete this aim by presenting the design of a pre-registered and currently ongoing clinical trial, a 'Protocole Hôpitalier de Recherche Clinique – PHRC-STIM-SD', that evaluates the long-term effects of repetitive sessions of tDCS in a large cohort of patients with the semantic variant of Primary Progressive Aphasia.

Three papers, each exploring one of the three mentioned neurological conditions, are presented in *Chapter III – Transcranial stimulation: a new therapeutic approach for neurodegenerative diseases?* The design of the clinical protocol is presented in *Chapter V.*

Specific Aim 3. We aim to use computational models simulating tDCS current fields to explore why and how individual patients respond differently to identical tDCS interventions and identify biomarkers predictive of clinical response.

To tackle this issue, we will use MRI-based Finite Element Models of tDCS current distribution and produce individual simulations for patients with the semantic variant of Primary Progressive Aphasia (n=17). Data on electric field strength (total strength and electric field normal component values) will be correlated to head and brain anatomical features (cortical thickness, CSF volume and electrode to brain surface distance). We will particularly assess the ability of such variables to predict tDCS modulation outcomes on a *Semantic association* task generated by a

single session of anodal tDCS (20 minutes, 1.59 mA, 0.06 mA/cm^2) over the anterior temporal lobe.

We hypothesized that individual anatomical features influence peak electric field strength in the brain and, consequently, this will influence clinical outcomes.

The preliminary outcomes of this study are presented using a scientific paper format in *Chapter IV – Influence of individual anatomy on current flow during tDCS: models matter.*

Finally, a general and overarching aim pursued in this thesis is to make our knowledge freely available, to present and expose our research, to provide others a chance to learn from it and question what is here exposed. Along all this dissertation we try to clearly state our questions, present the results of our research and review them in the light of the existing knowledge on the field. To this end, we will complete this work by summarizing our results, critically discussing them and providing a set of short-term and long-term perspectives to make future progress in this field based on the gained information and knowledge (*Chapter VI – General Discussion*).

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CHAPTER II

Fundamental Research on Language

II.1. The structure of the mental lexicon: What primary progressive aphasias reveal

II.2. Does surface dyslexia/dysgraphia relate to semantic deficits in the semantic variant of primary progressive aphasia?

The structure of the mental lexicon: What primary progressive aphasias reveal

The following article is published by Neuropsychologia.

Résumé en français

Le lexique mental contient toute l'information - phonologique, morphologique, sémantique et syntaxique qu'un individu a sur un mot. Selon la plupart des modèles, les informations contenues dans le lexique mental comprendraient trois composantes fondamentales: le lexique sémantique, syntaxique et formelle (code phonologique et orthographique). Ces composantes constitueraient des niveaux indépendants et probablement interactifs. Les données expérimentales actuelles semblent étayer ces modèles mais il reste débattu si les trois composantes lexicales sont liées à des représentations cognitives distinctes, si elles sont séparées d'un point de vue anatomique et par quelle(s) région(s) cérébrales elles sont implémentées. En effet, la plupart des études en neuropsychologie lésionnelle ont porté sur des cas individuels, et les quelques études sur des cohortes de patients ont utilisé des tâches lexicales multiples ne permettant pas de comparaisons directes entre les trois composantes lexicales. Aussi, la grande majorité de ces études de groupe a porté sur des patients ayant des lésions vasculaires sans fournir des détails sur la localisation lésionnelle ne permettant pas d'inférer la séparation et la localisation anatomique des composantes lexicales. Enfin, les investigations en imagerie fonctionnelle n'ont pas comparé les différentes composantes lexicales entre elles mais ont permis de suggérer que le cortex temporal externe joue un rôle crucial dans le stockage lexical des informations. Les Aphasies Primaires Progressives (APP) sont des maladies neurodégénératives affectant les réseaux anatomiques du langage. Parmi elles, la variante dite sémantique et la variante dite logopénique représentent des modèles lésionnels du cortex temporal externe.

Cette étude vise à étudier de manière contrastive les trois composantes du lexique en appliquant des tests comparables utilisant 3 tâches implicites d'une part, et trois tâches explicites, d'autre part. Nous utiliserons le modèle lésionnel des APP en faisant l'hypothèse de mettre en évidence des doubles dissociations entre les 3 composantes lexicales.

Nous avons exploré une cohorte de 20 patients atteints d'une APP (APP sémantique = 9 ; APP logopénique = 11) et 23 sujets sains. Les composantes du lexique ont été explorés avec 3 tâches implicites, des tâches de priming avec décision lexicale sur la cible, et avec 3 tâches explicites, où les participants doivent explicitement décider du lien correct entre un item cible et deux items tests. Dans les deux modalités, implicite et explicite, une tâche pour chaque composante lexicale (sémantique, syntaxique et formelle) a été utilisée. Touts les patients et les sujets sains avaient aussi une Image par Résonance Magnétique (IRM) pour permettre de faire des analyses d'épaisseur corticale.

Nos résultats indiquent que les trois composantes du lexique sont fonctionnellement séparées, comme en témoignent les multiples dissociations au niveau du groupe et de l'individu, confirmant ainsi l'existence d'une structure à trois volets du lexique mental. Les analyses d'épaisseur corticale ont montré une atrophie du cortex temporal latéral gauche dans l'ensemble de la cohorte de patients APP, suggérant que les composantes du lexique sont ségrégées de manière anatomique dans cette région corticale. Nos résultats affinent également les propositions précédentes sur les déficits lexicaux dans les APP en démontrant des troubles différentiels dans les trois composants du lexique dans les APP sémantiques et logopéniques, qui pourraient avoir un impact sur le diagnostic et les stratégies de réhabilitation linguistique.

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The structure of the mental lexicon: What primary progressive aphasias reveal

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ABSTRACT

Like recursive syntax, a structured mental lexicon is specific to the human species but its internal organization remains unclear. It is thought to contain information about the semantic, syntactic (e.g., gender) and formal (orthographic/phonological) features of a word. Previous studies suggested that these three components might be separated at the behavioral level and that they might be implemented by temporal cortices. However, the available investigations are based on case reports or small-cohort studies with patients demonstrating post-stroke aphasia, and they did not contrast the three lexical components in a directly comparable way. Similarly, functional imaging studies with healthy adults did not compare the lexical components but explored them separately using various tasks. Here we assessed the three components with comparable tasks in a relatively large cohort of 20 patients with primary progressive aphasia (PPA), namely logopenic and semantic PPA, which have been shown to affect the temporal cortex. The same tasks were also applied to 23 healthy adults. We thereby primarily aimed at showing multiple intra-lexical dissociations at the behavioral level to demonstrate the existence of a threefold segregation within the mental lexicon. We also sought to confirm the temporal-cortical involvement in the implementation of the lexical components and to characterize differential lexical breakdown in PPA. Lexical components were explored with three implicit processing tasks (semantic, syntactic-gender, word-form priming) and with three explicit matching tasks (semantic, syntactic-gender, word-form). Our results indicate that the three components are functionally segregated as evidenced by multiple dissociations at the group level, and the individual level, thus substantiating the existence of a threefold structure of the mental lexicon. Cortical thickness analyses showed damage to the left lateral temporal cortex in the entire PPA cohort suggesting that lexical components are anatomically segregated within this cortical region. Our results also refine previous proposals about lexical deficits in PPA by demonstrating differential damage to all three components of the lexicon in semantic and logopenic PPA, which might have an impact on PPA diagnosis and language rehabilitation strategies.

1. Introduction

The concept of the 'mental lexicon' was first introduced by Oldfield (1996) who suggested the existence of a 'mental dictionary' in which information about word meaning is retrieved. It is now suggested that the 'dictionary' should be regarded not only as a repertory of word meanings but as a three-fold lexicon comprising syntactic, semantic and word-form (phonological/orthographical) features (e.g., Jackendoff, 2002). However, there are distinct models regarding the organization of the lexicon. In the influential model of Levelt (1992) lexical access occurs serially along two stages: first, the selection of semantic and syntactic representations (lemma level) and, second, the selection of its phonological/orthographic content (lexeme level). Caramazza and Miozzo (1997) proposed an alternative model according to which semantic, syntactic and word-form features can be accessed independently. One argument for the latter model is provided by the " word-on-the-tip-of-the-tongue " phenomenon demonstrating that access to semantic and syntactic information is independent from phonological or orthographic information (Caramazza and Miozzo, 1997). The authors have explored this phenomenon in individual cases analyzing

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the correlation between the retrieval of lexical-syntactic gender information, and of word-form information such as the first phoneme of words that subjects could not retrieve. The absence of significant correlations indicated that access to word-form information is independent from the access to syntactic, and probably semantic, information. Using lesion models, Kavé and Levy (2003) also provided support for separate lexical components by showing that Alzheimer's disease patients can have intact access to syntactic information like noun gender despite deficits in accessing semantic information. The opposite pattern has been evidenced in a small cohort of post-stroke patients suggesting that lexical-syntactic information, namely gender and predicate argument structure, might be stored separately from lexical-semantics (Biran and Friedmann, 2012). In summary, the available investigations suggest that lexical structure probably has different levels which are independent but connected: semantic, syntactic and word-form representations. However, even if the aforementioned case reports and small-cohort studies have suggested functional dissociations between the lexical components, evidence for an intra-lexical segregation can not be generalized without exploring homogenous and large patient cohorts. Furthermore, none of the previous studies has provided direct comparisons between the three lexical components, thus indicating the need for directly comparable tasks to substantiate the three-component hypothesis of the lexicon.

A related issue is the anatomical segregation of the lexical components. Most imaging studies have suggested that the lateral temporal cortex might be involved in the processing of lexical retrieval, but there is no absolute consensus. Functional magnetic resonance imaging (fMRI) with healthy adults exploring lexical-semantic processing have shown activation in various brain areas including the middle temporal and the superior temporal gyrus, the anterior temporal lobe, the inferior frontal gyrus and/or the inferior parietal lobe (e.g., Kuperberg et al., 2008; Lau et al., 2013; Ruff et al., 2008). Using lesion models, particularly the semantic variant of primary progressive aphasia (sv-PPA), which is characterized by degenerative damage to the anterior temporal lobe and semantic deficits, have reinforced the claim about a potential role of this region in lexical semantics (Mesulam et al., 2013; Wilson et al., 2014). Other researchers, however, attribute pivotal roles for lexical-semantics to left prefrontal and temporal-parietal regions (Binder et al., 2003; Devlin et al., 2000; Garavan et al., 2000; Spitsyna et al., 2006). The anatomical correlate for the processing of word-form information is also still debated. Studies using fMRI in healthy adults showed that posterior and middle regions of the temporal lobe and/or the left supramarginal and the fusiform gyrus might be involved in mapping word-orthography on word-phonology or when accessing whole-word forms (e.g., Graves et al., 2008, 2010). Regarding the rare studies exploring syntactic word information, Snijders et al. (2009) have suggested that left inferior frontal gyrus contributes to syntactic unification whereas the left posterior temporal gyrus subtends the retrieval of lexical-syntactic information. Taken together, previous studies suggest that, among other regions, the lateral temporal cortex might play a central role in lexical processing, but none of them has directly contrasted the three lexical components via comparable tasks. Thus, strong evidence for the anatomical implementation of the potentially distinct lexical components in temporal-cortical regions remains to be provided.

Here we addressed these issues by using PPA variants as a lesion model of the lateral temporal cortex and by applying directly comparable tasks tapping semantic, syntactic and word-form information, with the aim of providing robust evidence for multiple dissociations between the three lexical components. Based on the data-driven hypothesis that the left temporal cortex might play a central role in lexical processing, we explored two PPA variants which have been shown to affect this region: logopenic-variant PPA (lv-PPA) which usually damages posterior and middle portions of temporal cortices (besides the posterior-inferior parietal cortex), and sv-PPA demonstrating atrophy of anterior and middle portions of lateral temporal cortices (Gorno-Tempini et al., 2004). PPA is a neurodegenerative condition subdivided into three main variants: sv-PPA characterized by multi-modal semantic deficits, lv-PPA characterized by word-finding problems and verbal short-term memory failure, and agrammatic/nonfluent PPA which does not directly affect lexical processing but rather combinatorial language aspects such as word sequencing through syntax (Gorno-Tempini et al., 2011; Mesulam et al., 2014). As the aim of the present study was to explore lexicalized aspects of syntax we did not include this latter PPA variant in the investigation. This non-inclusion of agrammatic/nonfluent PPA is also in line with evidence that lexical aspects of syntax appear to be implemented by posterior temporal regions (Snijders et al., 2009) and not by Broca's area which subtends combinatorial syntax (e.g., Friederici et al., 2003; Pallier et al., 2011), and which is damaged in the agrammatic/nonfluent variant (Gorno-Tempini et al., 2004). Using sv-PPA and lv-PPA as a combined lesion model of temporal cortices also has an advantage over investigations of post-stroke cohorts because regions that are normally spared by stroke such as the anterior temporal cortex (Caviness et al., 2002; Wise, 2003) are affected in PPA. The use of PPA in this study also allows for addressing a related issue in that it enables a fine-grained characterization of lexical deficits in lv-PPA and sv-PPA.

2. Methods

2.1. Participants

Twenty PPA patients were recruited at the National Reference Center for “PPA and Rare Dementias” of the Pitié Salpêtrière Hospital (Paris): nine patients with sv-PPA and eleven with lv-PPA. The diagnosis was established by expert neurologists following the international diagnostic criteria of Gorno-Tempini et al. (2011). Patients did not present neurological or psychiatric diseases other than PPA. Twenty-three healthy controls, matched with the patients for age ($t(41) = -1.332$, $p = 0.19$), level of education ($t(41) = -1.36$, $p = 0.18$) and gender ($p = 0.76$; Fisher's exact test) were also included. Healthy controls were tested with the Mini Mental State Examination (MMSE; Folstein et al., 1975) to ensure the preservation of their global cognitive abilities (mean score 29.1/30 ± 1.2; Normal > 26/30). They did not have any neurological disease or physical problem that could interfere with cognitive functioning. All participants were native French speakers. Written consent was obtained from all participants and the study has been approved by the local ethical committee. Demographic

Table 1
Demographic data of healthy controls, sv-PPA and lv-PPA patients.

	Controls (means ± SD)	sv-PPA (means ± SD)	lv-PPA (means ± SD)
Number of subjects	23	9	11
Sex (women, men)	10W/13M	6W/3M	4W/7M
Age (years)	66.91 ± 9.08	70.44 ± 6.06	70.64 ± 7.51
Handedness	21R/2L	8R/1L	11R
Years of education	14.8 ± 3.4	14.9 ± 4.3	15.3 ± 2.7
Symptom duration (years)	///////	3.2 ± 1.1	3.1 ± 1.5

SD = standard deviation.

Table 2
Cognitive/language scores of sv-PPA and lv-PPA patients.

	sv-PPA (means ± SD)	lv-PPA (means ± SD)	Normal threshold
MMSE	24.8 ± 3.1	21.6 ± 3.1	≥ 27
FAB	14.6 ± 2.6	13.9 ± 3.1	≥ 16
BDAE – aphasia severity scale	3.8 ± 1.0	3.4 ± 1.1	> 4
BDAE – single-word comprehension	59.5 ± 4.4	69.5 ± 3.6 *	≥ 68
BDAE – sentence repetition	14.9 ± 3.2	10.5 ± 3.1 *	≥ 14
Category fluency	10.0 ± 6.1	15.6 ± 4.7 *	≥ 15
Phonemic fluency	13.1 ± 8.4	12.9 ± 7.5	≥ 15
DO80	39.7 ± 16.7	59.2 ± 15.4 *	≥ 75

SD = standard deviation. MMSE = Mini Mental State Examination. FAB = Frontal Assessment Battery. BDAE = Boston Diagnostic Aphasia Examination. DO80 = Picture naming task. Asterisks indicate significant differences between sv-PPA and lv-PPA.

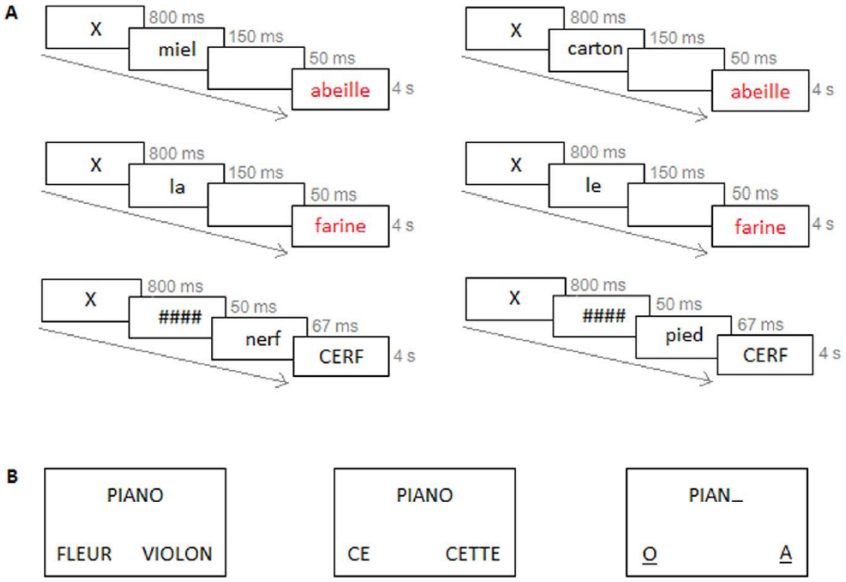

Fig. 1. Illustration of the stimuli and time course of the three implicit processing tasks (A). First line: semantic priming (*honey-bee*; *cardboard-bee*); second line: syntactic priming (concordant gender determinant-flour; non concordant gender determinant-flour); third line: word-form priming (e.g., *beer-DEER*; e.g., *foot-DEER*). Illustration of the stimuli for the three explicit processing tasks (B). First column: semantic task (*piano*; *flower* vs. *violin*); second column: syntactic gender task (*piano*; concordant determiner vs. non-concordant determiner); third column: word-form task (*pian_*; 'a' vs. 'o').

data are illustrated in Table 1.

2.2. General cognitive/language assessment

The general cognitive assessment included the MMSE and the Frontal Assessment Battery (FAB; Dubois et al., 2000). The language assessment was composed of a picture naming test (D080; Deloche and Hannequin, 1997) and the Boston Diagnostic Aphasia Evaluation (BDAE; Mazaux and Orgogozo, 1982). The BDAE included an evaluation of aphasia severity taking into account spontaneous speech and the description of the 'cookies theft picture', a sentence repetition task, a single-word comprehension task requiring pointing to pictures upon auditory word presentation, and a verbal fluency test comprising phonemic and category fluency (Cardebat et al., 1990). According to the international diagnostic criteria of Gorno-Tempini et al. (2011) all sv-PPA patients had single-word comprehension deficits and anomia (without sentence repetition disorders, agrammatism or motor speech disorders), and lv-PPA patients were characterized by word finding difficulties and sentence repetition impairment (without agrammatism, single-word comprehension or motor speech disorders). Cognitive/language scores are summarized in Table 2.

2.3. Experimental tasks

2.3.1. Implicit processing tasks

The three implicit processing tasks used priming paradigms tapping semantic, syntactic and word-form information. Priming reflects shorter reaction times making judgments about target words that are preceded by related prime words as compared to target words preceded by unrelated primes (Neely, 1976; Kuperberg et al., 2008). A task frequently used in priming studies is 'lexical decision' where real words and non-words are used as targets and subjects have to decide whether the item exists or not in their mother tongue (e.g., Kuperberg et al., 2008).

In the semantic task, we used 45 pairs with 2/3 of real words as targets and 1/3 of non-words. The primes were either semantically associated with the target or without any semantic relationship (e.g. honey-bee vs. cardboard-bee). In the word-form task we used 45 pairs with 2/3 of real words as targets and 1/3 of non-words. The primes were words with a similar spelling code or with no similarity (e.g. deer-beer vs. foot-beer). In the syntactic task, we focused in noun gender information using 52 pairs with 2/3 of real words as targets (inanimate items for which no natural gender could be inferred) and 1/3 of non-words. The primes were determiners that either agreed in gender with the target or not. French language was used across all tasks given that French, unlike English, provides the opportunity to test syntactic gender. Each priming task contained two lists of prime-target pairs. In each list half of the targets were paired with related primes and the other half with unrelated primes. This was done to avoid a target appearing twice in a list, which could lead to biasing repetition priming effects. Related and unrelated primes were matched for frequency and number of letters (all Fs < 1) using the LEXIQUE 2 database (New et al., 2004). All non-word targets were orthographically and phonotactically legal and had the same number of letters as target words (all Fs < 1). Fig. 1A illustrates the three tasks.

They were presented on a computer using the *E-prime* software and were applied at two different moments of the day (morning/afternoon,

list 1/list 2) in order to minimize eventual repetition priming effects for a given target. Half of the participants saw one of the two lists in the morning and the other in the afternoon, and the other half of the participants saw them in the reverse order. For the semantic and syntactic tasks, each trial began with a fixation cross (800 ms), followed by the prime word written in black (150 ms), then a blank screen (50 ms), followed by the target written in red (4 s; SOA = 200 ms). For the word-form task we used a masked priming paradigm. Each trial began with a fixation cross (800 ms) followed by a series of pound signs (500 ms). The prime was then presented in lowercase characters (67 ms), immediately followed by the target presented in capital letters to avoid purely visual effects (4 s; SOA = 67 ms). This masked priming procedure was used because previous studies have shown that with unmasked conditions word-form priming effects generally do not arise (e.g. Velan and Frost, 2011). Between each trial there was a blank screen during 700 ms.

The instructions given to the participants were to “be focused on the screen during the whole task without speaking”, to “answer as fast and accurately as possible” and “to press the 'yes' button on the computer keyboard if the word target exists in French and the "no" button if the word doesn’t exist”. Participants answered by pressing "yes" and “no” with the index finger and with the middle finger of their dominant hand, respectively. Before each task participants were familiarized with the procedure by five training trials. The order of the three tasks was randomized.

2.3.2. Explicit processing tasks

Three additional explicit processing tasks were applied to screen for ‘good’ and ‘poor’ performers in the semantic, syntactic and word-form domains of the lexicon. They explicitly directed the participants’ attention to associations between stimuli by asking them to make a judgment of links between the stimuli presented, thus involving conscious control processes (Kuperberg et al., 2008).

Thirty target words were selected using the Lexique 2 database (New et al., 2004). All targets were concrete French nouns. Half had feminine gender and half masculine gender, with word frequencies ranging from 570.3 to 0.67 per million. In the semantic task, each target was paired with two items, one being semantically related, either at a categorical level (50% of stimuli) or at an associative level (50% of stimuli), and a distractor without any semantic relation to the target. The targets, the related items and the distractors were matched for frequency (all Fs < 1) and for the number of letters (all Fs < 1). In the word-form task a letter was removed from each target, either the first or the last. Two letters were presented along with the target, one that completed the word and a distractor letter that did not allow for providing a real French word although it allowed for an orthographically legal word. In the syntactic task two determiners were presented along with the target. One determiner agreed in gender with the target whereas the distractor did not. All targets were presented at the top of the computer screen and were accompanied by the related item and the distractor at the left or right bottom of the screen. In half of the trials the distractor was on the left side, in the other half it was on the right. The noun stimuli used in the explicit processing tasks were all distinct from the words of the priming tasks. Fig. 1B illustrates the three explicit tasks.

They were conducted after the application of the first three lists of the priming tasks. Stimuli were presented on a computer screen. The word-form task was always presented first so that subjects did not see the full word before this word completion task. The order of the two other tasks was randomized. In the semantic task the participants were instructed to point with the index finger of the dominant hand to the word that was associated with the target word. In the word-form task the instruction was to point to the letter that completed the word, and in the syntactic task participants were required to point to the determiner that was in gender agreement with the target. Each task was preceded by five training trials to familiarize the participants with the tasks.

2.4. Data analyses, MRI acquisition and image processing

For the priming tasks, analyses (ANOVAs) compared reaction times (RT) for related and unrelated targets. Priming effects were defined by the RT contrast between unrelated minus related prime-target pairs. For the explicit tasks the analyses were based on performance accuracy. To check for dissociations between the three lexical components, the whole PPA group was subdivided into two subgroups according to the performance on the explicit tasks. This subdivision resulted in subgroups of “good performers” (SEM+ [N = 10], SYNT+ [N = 10], FORM+ [N = 10]), and of “poor performers (SEM- [N = 10], SYNT- [N = 10], FORM- [N = 10]). Priming effects were then reanalyzed for these subgroups using ANOVAs.

High resolution T1-weighted MRIs were acquired at the Pitié-Salpêtrière Hospital for 17 out of 20 PPA patients and for 12 healthy controls using a magnetization-prepared rapid gradient echo sequence (MPRAGE). Cortical thickness measurements were performed from T1-weighted images using FreeSurfer 5.3 software (http://surfer.nmr.mgh.harvard.edu/). Briefly, image processing included removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, intensity normalization, tessellation of the grey matter–white matter boundary, automated topology correction and surface deformation following intensity gradients to optimally place the grey matter–white matter and grey matter–cerebrospinal fluid borders at the location where the greatest shift in intensity defined the transition to the other tissue class. Cortical thickness was calculated by measuring the distance between representations of the grey matter–-white matter and grey matter–cerebrospinal fluid boundaries across each vertex of the tessellated surface (Fischl and Dale, 2000). All cortical thickness maps were registered onto the common template provided with FreeSurfer (FSAverage template).

Surface-based analyses of cortical thickness were performed using SurfStat software (http://www.math.mcgill.ca/keith/surfstat/). Cortical thickness maps were smoothed using a 20 mm surface-based kernel. The comparison of cortical thickness between groups was carried out with a two-sample *t*-test at each vertex (sv-PPA *vs*. controls; lv-PPA *vs*. controls; all PPA patients *vs*. controls). In all analyses, statistics were corrected for multiple comparisons using the random field theory for non-isotropic images (Worsley et al., 1999). A statistical threshold of $p < 0.001$ was first applied. An extent threshold of $p < 0.05$ corrected for multiple comparisons was then applied at the cluster level.

3. Results

3.1. Implicit processing tasks

Regarding performance accuracy, PPA patients had slightly lower performance (94.2% correct ± 6.1; lv-PPA 90.6% correct ± 9.4, sv-PPA 97.8% correct ± 2.8) than controls (99.5% correct ± 0.9), but the overall high accuracy percentage in PPA patients showed that they reliably and accurately performed the lexical decision task.

ANOVAs were conducted by participants (F1) and by items (F2) with reaction times (RT) as the dependent variable. For each participant, incorrect responses and missing data were excluded from the analyses. The independent variables were “group” (PPA, controls) and “target type” (related, unrelated). Analyses were conducted separately on the three priming tasks given that they slightly differed in the experimental design (masked word-form priming, unmasked semantic and syntactic priming). Fig. 2 summarises the RT with the tasks for controls and PPA patients.

In the semantic priming task RT were slower in PPA (1144 ms ± 386) than in controls (791 ms ± 228; $F1(1,41) = 14.04$, $p = 0.001$; $F2(1,58) = 396.14$, $p < 0.001$). There was a target type effect (related 921 ms ± 365, unrelated 989 ms ± 349; $F1(1,41) = 17.53$,

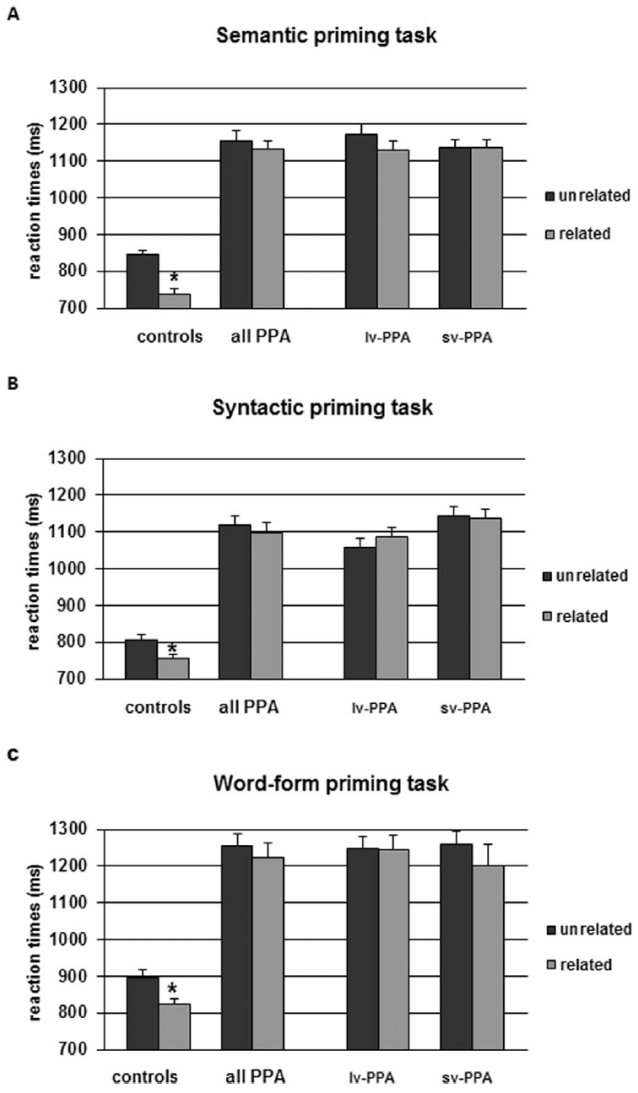

Fig. 2. Priming effects as reflected by the comparison between unrelated and related targets in the semantic (A), syntactic (B) and word-form (C) priming tasks for healthy controls, the whole PPA group, lv-PPA and sv-PPA (* = $p < 0.05$).

$p < 0.001$; F2(1,58) = 8.00, p = 0.006) and a target type × group interaction (F1(1,41) = 6.33, p = 0.016; F2(1,58) = 6.93, p = 0.011). The interaction was linked to the fact that controls had faster RT with related targets (738 ms ± 203) than with unrelated targets (844 ms ± 244; F1(1,22) = 25.40, $p < 0.001$; F2(1,58) = 34.23, $p < 0.001$) whereas there was no difference in PPA (related 1132 ms ± 400, unrelated 1156 ms ± 382; both Fs < 1). The magnitude of the significant priming effect in controls was 106 ms whereas in PPA patients the non significant effect was 24 ms. Restricted analyses compared RT in lv-PPA and sv-PPA for related vs. unrelated targets. Both PPA groups had similar RT (lv-PPA 1151 ms ± 447; sv-PPA 1136 ms ± 307; both Fs < 1). There was no effect of target type (related lv-PPA 1128 ms ± 465, related sv-PPA 1137 ms ± 331; unrelated lv-PPA 1173 ms ± 451, unrelated sv-PPA 1135 ms ± 301; both Fs < 1), and no group x target type interaction (both Fs < 1).

In the syntactic priming task RT were slower in PPA (1103 ms ± 391) than in controls (781 ms ± 207) (F1(1,41) = 11.85, p = 0.001; F2(1,58) = 112.24, $p < 0.001$). There was a target type effect (related 919 ms ± 349, unrelated 942 ms ± 345; F1(1,41) = 6.44, p = 0.011; F2(1,58) = 6.11, p = 0.019) and a target type × group interaction (F1(1,41) = 5.24, p = 0.027; F2(1,58) = 6.00, p = 0.023). The interaction was linked to the fact that controls had faster RT with related targets (754 ms ± 189) than with unrelated targets (807 ms ± 225; F1(1,22) = 9.38, p = 0.006; F2(1,58) = 17.99 $p < 0.001$) whereas there was no difference in PPA (related 1097 ms ± 396, unrelated 1117 ± 396; both Fs < 1). The magnitude of the significant priming effect in controls was 53 ms whereas in PPA patients the non significant effect was only 20 ms. Restricted analyses compared RT in lv-PPA and sv-PPA for related vs. unrelated targets. Both PPA groups had similar RT (lv-PPA 1072 ms ± 422; sv-PPA 1141 ms ± 358; both Fs < 1). There was no effect of target type (related lv-PPA 1087 ms ± 443, related sv-PPA 1137 ms ± 355; unrelated lv-PPA 1057 ms ± 421, unrelated sv-PPA 1145 ms ± 382; both Fs < 1), and no group x target type interaction (both Fs < 1).

In the word-form priming task RT were slower in PPA (1239 ms ± 333) than in controls (859 ms ± 185) (F1(1,41) = 22.71, $p < 0.001$; F2(1,58) = 265.28, $p < 0.001$). There was a target type effect (related 1009 ms ± 312, unrelated 1061 ms ± 338; F1(1,41) = 10.50, p = 0.002; F2(1,58) = 6.23, p = 0.015) and a target type × group interaction (F1(1,41) = 6.33, p = 0.021; F2(1,58) = 5.93, p = 0.031). The interaction was linked to the fact that controls had faster RT with related targets (823 ms ± 154) than with unrelated targets (894 ms ± 209; F1(1,22) = 16.04, p = 0.001; F2(1,58) = 20.70, $p < 0.001$) whereas there was no difference in PPA (related 1224 ms ± 312, unrelated 1254 ms ± 360; F1(1,19) = 1.15, p = 0.296; F2(1,58) = 1.51, p = 0.225). The magnitude of the significant priming effect in controls was 71 ms whereas in PPA patients the non significant effect was only 30 ms. Restricted analyses compared RT in lv-PPA and sv-PPA for related vs. unrelated targets. Both PPA groups had similar RT (lv-PPA 1246 ms ± 351; sv-PPA 1230 ms ± 319; both Fs < 1). There was no effect of target type (related lv-PPA 1244 ms ± 335, related sv-PPA 1200 ms ± 299; unrelated lv-PPA 1249 ms ± 382, unrelated sv-PPA 1259 ms ± 354; F1 < 1; F2(1,58) = 1.65, p = 0.205), and no group x target type interaction (both Fs < 1).

In summary, controls demonstrated significant priming effects in the three priming tasks whereas PPA as a whole group, as well as lv-PPA and sv-PPA separately, did not display priming effects in the three tasks.

3.2. Explicit processing tasks

ANOVAs were conducted by participants but not by items given that the stimulus-items used in the three tasks were distinct. Performance accuracy was the dependent variable. The independent variables were "group" (PPA, controls) and "task" (semantic, syntactic, word-form). Fig. 3 summarises the results.

Performance was poorer in PPA patients (91.6% correct ± 10.7) than in controls (99.4% correct ± 1.3; F(1,41) = 21.75, $p < 0.001$). There was a task effect (semantic task 95.0% correct ± 9.2, syntactic task 98.7% correct ± 3.9, word-form task 93.6% correct ± 9.9; F(2,82) = 11.74, $p < 0.001$) and a group x task interaction (F(2,82) = 9.64,

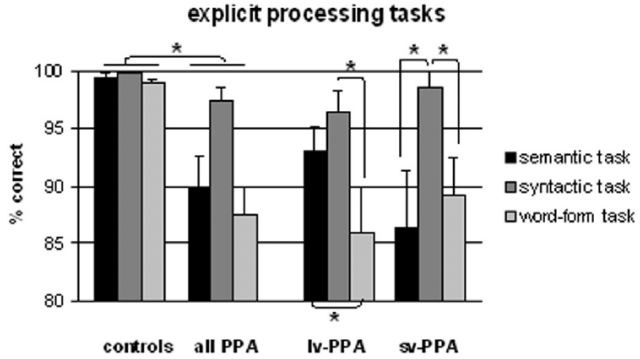

Fig. 3. Performance on the three explicit processing tasks for healthy controls, lv-PPA and sv-PPA (* = $p < 0.05$).

$p < 0.001$). The interaction was linked to the fact that PPA patients had distinct performance for the three tasks (semantic task 90.0% correct ± 11.7, syntactic task 97.3% correct ± 5.4, word-form task 87.4% correct ± 11.6; $F(2,38) = 10.21$, $p < 0.001$) whereas controls had similar performance (semantic task 99.4% correct ± 1.3, syntactic task 99.9% correct ± 0.7, word-form task 99.0% correct ± 1.6; $F(2,44) = 2.32$, $p = 0.110$). Restricted analyses showed that PPA patients had lower performance for the three tasks (semantic task $F(1,41) = 14.89$, $p < 0.001$, syntactic task $F(1,41) = 5.01$, $p = 0.031$, word-form task $F(1,41) = 22.64$, $p < 0.001$).

A second series of analyses compared performance between each of the three tasks in lv-PPA and sv-PPA to provide the performance pattern of the two PPA variants with respect to the three lexical components. Lv-PPA patients had lower performance in the word-form task (85.9% correct ± 13.2) than in the semantic task (93.0% correct ± 7.4; $F(1,10) = 8.08$, $p = 0.017$), and lower performance in the word-form task than in the syntactic task (96.4% correct ± 6.1; $F(1,10) = 9.40$, $p = 0.012$). Performance was similar in the semantic and the syntactic task ($F(1,10) = 3.67$, $p = 0.085$). Sv-PPA patients had similar performance in the word-form task (89.2% correct ± 9.8) and the semantic task (86.3% correct ± 15.0; $F < 1$. They had lower performance in the semantic than in the syntactic task (98.5% correct ± 4.14; $F(1,8) = 8.49$, $p = 0.019$), and in the word-form task than in the syntactic task ($F(1,8) = 10.33$, $p = 0.012$). Comparisons of performance between lv-PPA and sv-PPA versus controls showed that patients were less accurate on all tasks with one exception: sv-PPA and controls had similar scores for the syntactic task (semantic task: lv-PPA vs. controls $F(1,32) = 16.76$, $p < 0.001$, sv-PPA vs. controls $F(1,30) = 18.10$, $p < 0.001$; syntactic task: lv-PPA vs. controls $F(1,32) = 7.71$, $p = 0.009$, sv-PPA vs. controls $F(1,30) = 2.06$, $p = 0.162$; word-form task: lv-PPA vs. controls $F(1,32) = 22.59$, $p < 0.001$, sv-PPA vs. controls $F(1,30) = 22.94$, $p < 0.001$). Finally, we compared lv-PPA and sv-PPA. Sv-PPA patients had poorer performance than lv-PPA patients in the semantic task ($F(1,18) = 8.69$, $p = 0.046$) whereas performance was similar in the word-form and in the syntactic task (both $Fs < 1$).

3.3. Refined analyses and dissociations in the implicit processing tasks

The results of the three explicit tasks allowed for subdividing the whole PPA group into six subgroups yielding for each lexical aspect a subgroup of 'good performers' (SEM+, SYNT+, FORM+) and of 'poor performers' (SEM-, SYNT-, FORM-). This approach aimed at refining the analyses on the three priming tasks to provide evidence for i) the existence of genuine priming effects in PPA, and ii) for multiple dissociations with respect to the semantic, syntactic and word-form components of the lexicon. We used accuracy scores in the different explicit tasks to disentangle good and poor performers in the three lexical domains. The SEM+, the SYNT+ and the FORM+ subgroups each contained the 10 best performers in the semantic, syntactic and word-form tasks, respectively. Conversely, the SEM-, the SYNT- and the FORM- subgroups contained the 10 poorest performers in the semantic, syntactic and word-form tasks, respectively.

ANOVAs were conducted by participants (F1) and by items (F2) for each of the six subgroups. The dependent variable was RT and the independent variable was "target type" (related, unrelated). For each participant, incorrect responses and missing data were excluded from the analyses.

In the semantic priming task the SEM+ subgroup had faster RT for related targets (955 ms ± 253) than for unrelated targets (1046 ms ± 254; ($F1(1,9) = 8,57$, $p = 0017$; $F2(1,58) = 6,79$, $p = 0012$) corresponding to a significant priming effect of 91 ms. In contrast, the SEM- subgroup had similar RT for related targets (1309 ms ± 451) and for unrelated targets (1266 ms ± 465; ($F1(1,9) = 2,75$, $p = 0131$; $F2(1,58) = 1,08$, $p = 0304$). The comparison of overall RT in the SEM+ and SEM- subgroups showed that they were comparable in that they had similar RT ($F1(1,18) = 2.99$, $p = 0.11$; $F2 < 1$). In the syntactic priming task the SYNT+ subgroup had faster RT for related targets (968 ms ± 336) than for unrelated targets (1032 ms ± 387; ($F1(1,9) = 6,82$, $p = 0028$; $F2(1,58) = 6,66$, $p = 0029$), corresponding to a significant priming effect of 64 ms. In contrast, the SYNT- subgroup had similar RT for related targets (1261 ms ± 415) and for unrelated targets (1237 ms ± 418; both $Fs < 1$). The comparison of overall RT in the SYNT+ and SYNT- subgroups showed that they were comparable in that they had similar RT ($F1(1,18) = 1.41$, $p = 0.25$; $F2 < 1$). In the word-form priming task the FORM+ subgroup had faster RT for related targets (1228 ms ± 294) than for unrelated targets (1323 ms ± 336; $F1(1,9) = 36,64$, $p < 0001$; $F2(1,58) = 5,09$, $p = 0028$), corresponding to a significant priming effect of 95 ms. In contrast, the FORM- subgroup had similar RT for related targets (1219 ms ± 344) and for unrelated targets (1184 ms ± 387; both $Fs < 1$). The comparison of overall RT in the FORM+ and FORM- subgroups showed that they were comparable in that they had similar RT (both $Fs < 1$).

In addition, the following dissociations were found: 1) the SEM+ subgroup which had significant priming effects in the semantic task did not have any significant priming effects in the syntactic or the word-form task (syntactic task: related targets 1014 ms ± 287, unrelated targets 987 ms ± 274; both $Fs < 1$. Word-form task: related targets 1120 ms ± 268, unrelated targets 1157 ms ± 315; $F1(1,9) = 1.36$, $p = 0.273$, $F2(1,58) = 1.44$, $p = 0.235$). 2) The SYNT+ subgroup which had significant priming effects in the syntactic task did not have any significant priming effects in the semantic or the word-form task (semantic task: related targets 1048 ms ± 358, unrelated targets 1087 ms ± 324; $F1(1,9) = 1.83$, $p = 0.209$, $F2 < 1$. Word-form task: related targets 1124 ms ± 310, unrelated targets 1142 ms ± 358; $F1 < 1$, $F2(1,58) = 1.02$, $p = 0.317$). 3) The FORM+ subgroup which had significant priming effects in the word-form task did not have any significant priming effects in the semantic or the syntactic task (semantic task: related targets 1189 ms ± 427, unrelated targets 1239 ms ± 429; $F1(1,9) = 1.27$, $p = 0.289$, $F2 < 1$. Syntactic task: related targets 1203 ms ± 437, unrelated targets 1185 ms ± 413; both $Fs < 1$).

In summary, we found multiple dissociations between the three lexical components: 1) Priming for lexical semantics but not for lexical syntax (SEM+ subgroup), 2) Priming for lexical syntax but not for lexical semantics (SYNT+ subgroup), 3) Priming for word-form representations but not for lexical semantics (FORM+ subgroup), 4) Priming for lexical semantics but not for word-form representations (SEM+ subgroup), 5) Priming for lexical syntax but not for word-form representations (SYNT+ subgroup), 6) Priming for word-form representations but not for lexical syntax (FORM+ subgroup). The priming dissociations revealed by the different PPA subgroups are illustrated in Table 3.

Moreover, such dissociations were also present at the individual level in several patients. We identified three patients demonstrating normal and significant priming effects as compared to priming in controls in the semantic task ($p > 0.1$) but not any priming effect in the syntactic or the word-form task ($p < 0.05$). Three other patients demonstrated normal and significant priming as compared to controls in the word-form task ($p > 0.1$) but not in the syntactic or the semantic

Table 3
Multiple dissociations of priming effects in the SEM+, SYNT+ and FORM+ subgroups of PPA.

	Semantic priming	Syntactic priming	Word-form priming
SEM+ subgroup	91 ms*	−27 ms (ns)	37 ms (ns)
SYNT+ subgroup	39 ms (ns)	64 ms*	18 ms (ns)
FORM+ subgroup	50 ms (ns)	−18 ms (ns)	95 ms*

ns = not significant.
* = significant at $p < 0.05$.

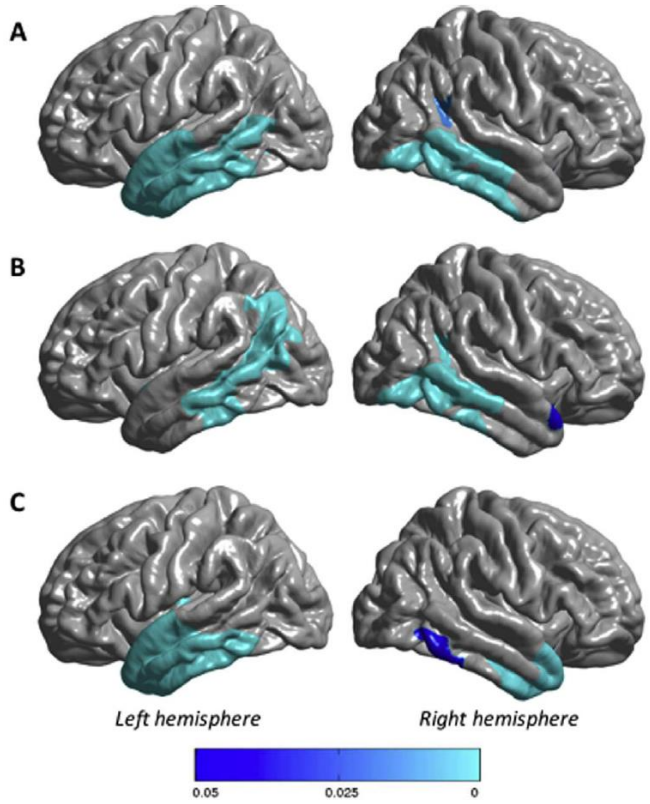

Fig. 4. Regions of significantly reduced cortical thickness in PPA patients versus healthy controls. Correction for multiple comparisons using the Random Field Theory, with corrected p-values: $p < 0.05$ for clusters. A) whole PPA group, B) lv-PPA, C) sv-PPA. The color bar represents p-values varying between "0.05" and "0". Note that the zero p-values are not strictly "0" but that they are close to "0".

task ($p < 0.05$). Finally, one patient had normal and significant priming effects as compared to controls in the syntactic task ($p > 0.1$) but not in the semantic or the word-form task (both $p < 0.05$).

3.4. Cortical thickness analyses

The whole-brain between-group analysis showed lower cortical thickness in PPA patients as compared to controls in the left lateral temporal cortex. In sv-PPA, cortical thickness was diminished primarily in the left anterior and middle lateral temporal cortex, and in lv-PPA thickness was diminished essentially in the left middle temporal cortex and in posterior regions of the middle and inferior temporal gyrus. In lv-PPA and sv-PPA regions of reduced cortical thickness had a non negligible overlap and the whole PPA group demonstrated reduced cortical thickness of almost all regions of lateral temporal cortices. Results are illustrated in Fig. 4.

4. Discussion

We explored the internal organization of the lexicon assessing lexical-semantic, syntactic-gender and word-form aspects in a relatively large cohort of PPA patients to show multiple behavioral dissociations using comparable experimental paradigms. We also sought to confirm the central role of temporal cortices in the implementation of the three lexical components and to characterize their potential differential breakdown in lv-PPA and sv-PPA. Our main findings provide clear evidence for the existence of distinct syntactic, semantic and word-form components, thus demonstrating a threefold segregation of the mental lexicon. The use of a combined lv/sv-PPA model furthermore suggests the anatomical implementation of these components by lateral temporal cortices.

Results with healthy adults showed significant semantic, syntactic and word-form priming effects indicating that the three different types of word information are stored in the lexicon and that the corresponding lexical representations are sensitive to spreading pre-activation. Patient data from the priming tasks suggested that the different lexical representations are degraded in both PPA variants, but the explicit processing tasks demonstrated that this impairment is distinct in sv-PPA and lv-PPA. Furthermore, the sub-division of patients according to semantic, syntactic and word-form performance on the three explicit tasks showed that good performers in a given lexical domain demonstrated significant effects in the corresponding priming task whereas poor performers did not. Moreover, the subgroups having significant priming in a given domain did not display significant priming in the two other lexical domains. These results suggest that priming effects exist in subgroups of PPA patients, that their absence reflects damage to the tested lexical component and that the three components are functionally segregated as shown by multiple dissociations at the group level. The functional segregation of lexical components was also corroborated by priming data of several patients providing evidence for dissociations at the individual level. Finally, cortical thickness analyses revealed predominantly left-lateralized atrophy of the lateral temporal cortex, with lv-PPA patients demonstrating diminished thickness mainly in posterior-middle temporal cortices and sv-PPA having diminished thickness primarily in anterior and middle temporal regions, thus presenting non negligible overlap. The combined lv/sv-PPA cohort therefore provided a valuable model of damage to almost all regions of left lateral temporal cortices. This result indicates that the semantic, syntactic-gender and word-form components of the lexicon involve the lateral temporal cortex and that the functional segregation might be linked to an anatomical segregation within this brain region.

4.1. Functional segregation of the lexicon

Several studies have suggested that the three lexical components can be dissociated at the behavioral level. However, they were mostly based on case reports (Badecker et al., 1995) or small-cohort studies (e.g., Biran and Friedmann, 2012; Caramazza and Miozzo, 1997; Kavé and Levy, 2003), and they did not compare the three components in a direct way, thus limiting the generalization of their results towards a comprehensive data-driven model of the lexicon. In the current study we provided evidence for multiple dissociations at the group level using a relatively large cohort of PPA patients and implementing directly comparable tasks. One might ask whether non-lexical factors, such as attention disorders in PPA, could have abolished priming effects in the whole group given that reaction times were significantly slower in PPA than in controls. However, refined analyses after splitting the whole group in good and poor lexical performers on the basis of an independent explicit task show that this is not the case. Significant priming dissociations at both the group and the individual patient level demonstrate that PPA patients are sensitive to priming, and that the differential sensitivity resulting in dissociations is not due to task-related effects but to genuine lexical deficits. Thus, the segregation of the lexicon into three components is supported by our cohort data which substantiates previous single-case and small-cohort studies which only revealed "one vs. one component" dissociations such as lexical syntax vs. word-form representations (Caramazza and Miozzo, 1997), or lexical-syntax vs. lexical-semantic representations (Biran and Friedmann, 2012; Kavé and Levy, 2003).

The existence of distinct lexical representations is also supported by our results with healthy adults demonstrating significant priming effects in the three distinct lexical domains. These findings replicate some results from previous studies using semantic and word-form priming paradigms (e.g., Pastizzo and Feldman, 2009; Velan and Frost, 2011), and they add new evidence with respect to syntactic priming in healthy adults, which is still debated. Gender priming effects have been

demonstrated by Akhutina et al. (2001), whereas other authors did not find syntactic priming (e.g., Finocchiaro and Caramazza, 2006). Such diverging results might be linked to differences in task demands. Our data deriving from methodologically comparative assessments in healthy adults in the three lexical domains corroborate the existence of priming-sensitive semantic and word-form representations, and provide novel evidence for lexical-syntactic gender representations.

4.2. Anatomical implementation of lexical components

We also provide some hints with respect to the neural substrate of the lexical components. Previous imaging studies with healthy adults (Graves et al., 2008; Lau et al., 2013; Snijders et al., 2009) could not provide the anatomical implementation of the three components, mainly because they have not been compared in a direct way. The variability of hardly comparable tasks has generated some controversy with respect to a potential core region for lexical processing, suggesting that temporal, parietal and/or frontal regions might be involved. However, most studies appear to converge towards a crucial implication of lateral temporal cortices in the processing or storage of lexical information (Lau et al., 2013; Pillay et al., 2014; Schwartz et al., 2009; Tyler et al., 2011). We therefore used a lesion model of lateral temporal cortices, a merged lv/sv-PPA cohort, to check whether this region genuinely plays a central role in the implementation of lexical information and whether differential damage to this region results in functional dissociations of semantic, syntactic and word-form components. Our findings show that the PPA cohort demonstrates largely selective thinning of nearly the entire lateral temporal cortex, predominating on the left hemisphere. The priming data showing multiple intra-lexical dissociations and differential breakdown of the three lexical components in patients with differential damage to lateral temporal cortices therefore indicate that this cortical region plays a necessary core role in the processing of the different lexical aspects. In line with these findings, we propose that the lexicon is primarily implemented by the lateral temporal cortex and that the functional segregation of the three lexical components might correspond to an anatomical segregation within lateral temporal cortices. It should be noted that the evidenced behavioral-lexical dissociations were found in the combined lv/sv-PPA cohort-model and that they were not linked to the PPA variants as such. Lv-PPA and sv-PPA had different cortical thickness distributions but there was overlap of thickness reduction and large portions of lateral temporal cortices might be dysfunctional in both PPA variants. Thus the observed dissociations of the three lexical components are not linked to the two PPA variants per se but rather to subgroups of patients within the merged lv/sv-model. One crucial issue is now to identify the exact temporal-cortical correlates of the three lexical components. We conducted anatomo-functional correlation analyses but the merged PPA group (17 MRI scans), and even the combined PPA plus control group, did not provide sufficient statistical power to robustly identify the lexical correlates. Further studies with larger patient cohorts demonstrating damage to the temporal cortex are therefore required to carry out informative correlation analyses and to identify the cortical regions hosting each lexical component.

4.3. Implications for PPA

Our data also refine the understanding of lexical deficits in PPA. Previous studies have suggested that PPA patients have lexical disorders such as impaired lexical/verbal semantics in sv-PPA (Mesulam et al., 2013, 2014; Wilson et al., 2014) or lexical word-form deficits in lv-PPA (e.g., Leyton et al., 2012; Migliaccio et al., 2016; Teichmann et al., 2013). One should note that these studies did not use lexicon-specific tasks like verbal semantic priming or masked word-form priming as in the present investigation. In contrast to these two PPA variants, previous studies also suggest that agrammatic/nonfluent PPA demonstrates no or only slight lexical dysfunction as shown for example in naming tasks (Gorno-Tempini et al., 2004; Leyton et al., 2011; Migliaccio et al., 2016; Race et al., 2013). However, little is known about the exact damage to the different components of the lexicon in PPA. Our data from the explicit processing tasks indicate that sv-PPA patients have significant damage predominantly within both the semantic and the word-form component of the lexicon. In contrast, syntactic representations are relatively spared in both PPA variants. They also show that the lexical deficit in lv-PPA predominates on the word-form component of the lexicon with relatively spared lexical-semantic and syntactic representations. However, our priming data are more sensitive showing impairment of all three lexical components in lv-PPA and sv-PPA. Priming tasks thus might allow for identifying even slight lexical damage in PPA which could be important to guide specific rehabilitation strategies.

Our data also reinforce some findings suggesting that the linguistic deficit in the different PPA variants is more wide-spread than proposed in the international diagnostic criteria of Gorno-Tempini et al. (2011). Several studies have shown that word-finding deficits in lv-PPA are not only related to “lexical” access but that they are also caused by genuine semantic impairments, especially after some years of disease evolution (Leyton et al., 2013; Teichmann et al., 2013; Wicklund et al., 2014). Similarly, studies using lexical decision tasks on written words in sv-PPA seem to suggest that the orthographical word-form component of the lexicon could be impaired (Coltheart et al., 2010; Pulvermüller et al., 2010; Rogers et al., 2004). Our data appear to confirm this latter assumption via the use of a masked priming task tapping orthographical word-forms while minimizing potential semantic biases due to the masked procedure. Generally speaking, our results strengthen previous results through the use of well-controlled priming tasks, and indicate that lv-PPA and sv-PPA progressively erode the entire range of lexical representations by damaging their respective cortical underpinnings. Such erosion might evolve along a gradient related to disease evolution and to progressive damage-spreading within the lateral temporal cortex.

5. Conclusion

Our data strongly support language models of three separate lexical components (e.g., Carramaza and Miozzo, 1997) and suggest that the semantic/syntactic/word-form segregation is implemented by lateral temporal cortices. They also provide the basis for larger patient cohort or functional imaging studies to specify the temporal-cortical underpinnings of each component. With respect to PPA, our results generate detailed insight into lexical dysfunction, which could have an impact on diagnosis and rehabilitation strategies.

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Does surface dyslexia/dysgraphia relate to semantic deficits in the semantic variant of primary progressive aphasia?

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Résumé en français

La variante sémantique de l'aphasie primaire progressive (APP-vs) est une maladie neurodégénérative qui provoque une dyslexie/dysgraphie de surface, entraînant des erreurs de lecture/écriture de mots irréguliers - avec des correspondances non transparentes graphème-phonème (par exemple, 'lichen') - opposé aux mots normaux, dis réguliers (par exemple, 'lion'). Selon les modèles connexionnistes de lecture, la plupart des auteurs attribuent ce déficit à des troubles sémantiques, mais cette hypothèse est en contradiction avec des modèles symboliques, affirmant que la lecture/écriture des mots irréguliers repose sur le lexique mental. D'ailleurs, plusieurs études ont mis en cause cette 'vision sémantique' en rapportant des patients présentant un déficit sémantique massif sans dyslexie de surface. En effet, conformément à cette controverse, les deux modèles de lecture les plus influents, les connexionnistes et symboliques, postulent deux mécanismes complètement différents pour la dyslexie/dysgraphie. Le prototype des connexionnistes est le modèle triangulaire de traitement parallèle, dans lequel des représentations sémantiques, phonologiques et orthographiques sont interconnectés via un réseau associatif. Le modèle affirme que le traitement de mots irréguliers dépend nécessairement d'une voie de lecture/écriture impliquant la sémantique, tandis que les mots ordinaires peuvent également être traités par une voie directe allant des représentations orthographiques aux phonologiques. Inversement, les modèles de lecture symboliques et plus particulièrement le modèle DRC (*Dual Route Cascaded*) indiquent qu'en plus des représentations sémantiques, phonologiques et orthographiques, il existe un niveau intermédiaire appelé le lexique mental qui contient formes de mots entiers. Selon les modèles de la DRC, ce niveau lexical est essentiel au traitement des mots irréguliers mappant les entrées de mots du lexique orthographique directement sur les entrées de mots du lexique phonologique pendant la lecture.

Notre étude a cherché à déterminer si l'APP-vs affecte le lexique en plus du système sémantique, et si les déficits sémantiques ou lexicaux sont à l'origine de la dyslexie/dysgraphie de surface, tout en contestant les deux modèles majeurs du langage écrit.

Nous avons exploré une cohorte de 12 patients atteints d'une APP-vs et 25 témoins sains en utilisant une tâche de lecture et d'écriture, une tâche sémantique (décision catégorielle: vivant ou non vivant) et une tâche lexicale (décision lexicale: mot vs non-mot non-voisin). Des analyses de corrélation ont été menées pour évaluer la relation entre les scores de lecture/écriture de mots irréguliers et la performance sémantique par rapport au lexique. En outre, des analyses item-par-item ont exploré la cohérence des erreurs de lecture/écriture avec les erreurs sémantiques et lexicales spécifiques à chaque item.

Nos résultats ont montré que les patients atteints d'une APP-vs ont des difficultés à lire et à écrire des mots irréguliers et qu'ils ont des performances altérées dans les tâches sémantiques et lexicales. Les scores de lecture/écriture avec des mots irréguliers étaient significativement corrélés aux performances dans la tâche lexicale mais pas dans la tâche sémantique. Les analyses item-par-item ont révélé que l'échec dans la tâche lexicale sur un mot irrégulier donné était un excellent prédicteur des erreurs de lecture/écriture avec ce même item (valeur prédictive positive: 77,5%), ce qui n'était pas le cas pour la tâche sémantique (valeur prédictive positive: 42,5%). Nos résultats montrent que les atteintes des patients avec une APP-vs ne se limitent pas aux troubles sémantiques, mais qu'ils présentent également des atteintes du lexique mental, ce qui semble être le principal facteur de dyslexie/dysgraphie de surface. Nos données supportent des modèles symboliques alors qu'elles défient les connexionnistes.

Does surface dyslexia/dysgraphia relate to semantic deficits in the semantic variant of primary progressive aphasia?

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Abstract

The semantic variant of primary progressive aphasia (sv-PPA) is a degenerative condition which causes surface dyslexia/dysgraphia, resulting in reading/writing errors of irregular words with non-transparent grapheme-to-phoneme correspondences (e.g., ‘plaid’) as opposed to regular words (e.g., ‘cat’). According to connectionist models, most authors have attributed this deficit to semantic impairments, but this assumption is at odds with symbolic models, such as the DRC account, stating that the reading/writing of irregulars relies on the mental lexicon. Our study investigated whether sv-PPA affects the lexicon in addition to the semantic system, and whether semantic or lexical deficits cause surface dyslexia/dysgraphia, while challenging the two major models of written language.

We explored a cohort of 12 sv-PPA patients and 25 matched healthy controls using a reading and writing task, a semantic task (category decision: living vs. non-living), and a lexical task (lexical decision: word vs. no-neighbor non-word). Correlation analyses were conducted to assess the relationship between reading/writing scores of irregulars and semantic vs. lexical performance. Furthermore, item-by-item analyses explored the consistency of reading/writing errors with item-specific semantic and lexical errors.

Results showed that sv-PPA patients are impaired at reading and writing irregular words, and that they have impaired performance in both the semantic and the lexical task. Reading/writing scores

with irregulars correlated significantly with performance in the lexical but not the semantic task. Item-by-item analyses revealed that failure in the lexical task on a given irregular word is a good predictor of reading/writing errors with that item (positive predictive value: 77.5%), which was not the case for the semantic task (positive predictive value: 42.5%).

Our findings show that sv-PPA is not restricted to semantic damage but that it also comprises damage to the mental lexicon, which appears to be the major factor for surface dyslexia/dysgraphia. Our data support symbolic models whereas they challenge connectionist accounts.

Keywords: semantic variant of primary progressive aphasia; surface dyslexia and dysgraphia; semantics; lexicon

1. Introduction

The semantic variant of primary progressive aphasia (sv-PPA) is a degenerative condition affecting the anterior temporal lobes and causing relatively selective damage to semantic representations (Gorno-Tempini et al., 2004; 2011). In the language domain, this condition leads to anomia, deficits in single-word comprehension, and, frequently, to surface dyslexia/dysgraphia. The latter impairment is reflected by reading/writing errors with irregular words (also called exception words) for which the phoneme-grapheme correspondence is non-transparent (e.g., 'plaid' incorrectly read as "/pleɪd/" and written as "plad"), as opposed to regulars for which this correspondence is transparent (e.g., 'cat'). Written language has been much less explored in sv-PPA than oral language but surface dyslexia and dysgraphia have already been integrated in the most recent diagnosis criteria (Gorno-Tempini et al., 2011), and they have causatively been attributed to impaired semantics (Patterson and Hodges, 1992; Graham et al., 2000; Woollams et al., 2007; Caine et al., 2009; Brambati et al., 2009; S.M. Wilson et al., 2009; M.A. Wilson et al., 2012; Binney et al., 2016). More specifically, it has been shown that reading errors with irregulars in sv-PPA patients correlate with their scores in the Pyramid and Palm Trees Test requiring semantic associations (Binney et al., 2016), and with their scores on picture naming tasks requiring lexical-semantic aptitudes (Brambati et al., 2009). Likewise, some authors have shown that reading errors with irregulars are correlated with cortical thickness measures of the anterior temporal lobe implementing semantics (Brambati et al., 2009; Binney et al., 2016), and functional MRI in healthy adults has revealed that this region is activated during the reading of irregular words (M.A. Wilson et al., 2012; Hoffman et al., 2015; Provost et al., 2016). However, several studies have shed substantial doubt on this semantic-centered view by reporting patients who had massive semantic deficits without any surface dyslexia (Schwartz et al., 1979; Cipolotti and Warrington, 1995;

Lambon Ralph et al., 1995; Blazely et al., 2005; M.A. Wilson and Martínez-Cuitiño, 2012). Recently, Playfoot et al. (2018) assessed two sv-PPA patients with different language tasks and did not find correlations between semantic impairment and difficulties in reading of irregular words. Moreover, an investigation of sv-PPA cases has suggested that surface dyslexia in sv-PPA might not be related to semantic deficits but to lexical impairment (Boukadi et al., 2016).

In line with this controversy, the two most influential models of reading, namely connectionist and symbolic accounts, postulate two completely different mechanisms for dyslexia/dysgraphia. The prototype of connectionist accounts is the triangular Parallel Distributed Processing (PDP) model (Plaut et al. 1996), in which semantic, phonological/sound and orthographical patterns are directly interconnected via 'hidden layers/units', without any explicit implementation of lexical representations. The model claims that the processing of irregular words, especially of low-frequency irregulars, necessarily depends on a reading/writing route involving semantics, while regular words can also be processed via a direct route from orthographical to sound patterns. This route is also crucial for novel or non-words which are exclusively processed via this direct pathway. Conversely, symbolic reading models and more particularly the Dual Route Cascaded (DRC) model (Coltheart et al., 2001) state that, in addition to semantic, phonological/sound and orthographical patterns, there is an intermediate and explicit mental lexicon, which contains whole word forms. According to DRC models, this lexical level is critical to the processing of irregular words independently from semantics, mapping word entries in the orthographic lexicon directly onto word entries in the phonological lexicon, during reading, and vice versa during writing.

In sv-PPA the supposedly causative association of semantic failure and surface dyslexia/dysgraphia is in line with PDP models. However, this causality is at odds with the DRC account predicting that sv-PPA patients also demonstrate critical damage to the orthographic or

phonological component of the mental lexicon, which would be the causative factor for reading/writing errors with irregulars (Coltheart et al., 2010). In this controversial context, testing the reading/writing of irregular words in a cohort of sv-PPA patients along with contrastive tasks tapping item-specific semantic and lexical representations would allow for challenging the two models. Likewise, it would provide answers regarding the language components related to surface dyslexia/dysgraphia in sv-PPA by exploring the relationship between reading/writing of irregular words and lexical vs. semantic performances, on both a global correlative and an item-by-item basis.

Regarding tasks specifically tapping lexical representations, lexical decision paradigms (word vs. non-word) are claimed to be a reliable method as attested by computational simulations including computational models with sv-PPA-like lesions (Coltheart et al., 2010). Some connectionist network modellers, however, have suggested that lexical decision relies on the activation of semantic word knowledge (e.g., Woollams et al., 2007; Dilkina et al., 2010). It appears that the critical parameter which makes lexical decision about a real word a genuine lexical task is the nature of the non-words used in the task, namely their word-unlike characteristics (see e.g., Binder et al., 2003). More specifically, some models assuming both lexical and semantic word codes suggest that, in lexical decision tasks, lexical representations are activated by words and by word-like non-words (e.g., McClelland and Rumelhart, 1981). Such quasi-equal lexical activation levels would force the intervention of the semantic system allowing for deciding that a meaningful item is a word (YES answer in lexical decision) and that an item having no meaning is a non-word (NO answer in lexical decision). The parameter of 'word-likeness' is reflected by the orthographical/phonological neighborhood size: no-neighbor non-words are 'word-unlike' whereas multi-neighbor non-words are 'word-like' (Andrews, 1992; Coltheart et al., 2010). Thus,

only lexical decision tasks mixing real words and no-neighbor non-words would allow for specifically tapping the lexical level. This claim is also corroborated by a seminal work of James (1975) who found faster lexical decision responses with semantically concrete than abstract words when mixing words with word-like (multi-neighbor) non-words. Such semantic effects totally disappeared when the non-words were unfamiliar letter strings (no-neighbor non-words). Similarly, Evans et al. (2012) found that semantic priming effects in lexical decision tasks increase in magnitude when the added non-words become progressively more word-like, as measured by their orthographical and phonological neighbor size.

In the present study, we therefore explored a cohort of sv-PPA patients using, in addition to reading and writing tasks, a lexical decision paradigm with stimuli comprising non-words without any orthographical or phonological neighbor to provide a reliable lexical marker. Conversely, to directly assess semantic representations, and to diversify the tasks for the patients, we used category decision (living vs. non-living) to provide a semantic marker. Importantly, the tasks included the same irregular word stimuli to allow for direct comparisons/correlations, and for item-by-item analyses of the consistency of reading/writing errors with item-specific category and lexical decision errors. This approach contrasts with previous studies on sv-PPA, which rarely assessed both reading and writing and/or did not use both lexical and semantic markers comprising the same stimuli for item-specific analyses with the exception of some rare studies exploring mainly single cases. With such a stringent approach, we aimed to determine whether sv-PPA patients demonstrate both semantic and lexical damage as predicted by DRC models, whether lexical or/and semantic deficits are related to surface dyslexia/dysgraphia, and whether sv-PPA cohort-based data can provide novel support for either connectionist or symbolic models.

2. Methods

2.1. Participants

Twelve sv-PPA patients were included in the study at the National Reference Center for "PPA and rare dementias" of the Pitié Salpêtrière Hospital, Paris, France. Clinical diagnosis was based on a multi-disciplinary evaluation including neurological examination, standard neuropsychological tests and a detailed language evaluation. All patients satisfied the current consensus criteria for sv-PPA (Gorno-Tempini et al., 2011): they demonstrated isolated or highly predominant language disorders and had progressive single-word comprehension deficits and anomia. They did not have sentence repetition deficits, agrammatism or motor speech disorders. The diagnosis of sv-PPA was also imaging-supported given that all patients had atrophy on MRI affecting the anterior temporal lobes, with left hemispheric lateralization. Patients did not present any neurological/psychiatric disease other than sv-PPA and they did not have non-degenerative lesions on routine MRI such as cerebrovascular disorders. Twenty-five healthy controls, matched with the patients for age and number of years of education were also included in the study (both $Fs < 1$). Healthy controls were tested with the Mini Mental State Examination (MMSE; Folstein et al., 1975) to ensure the normality of their cognitive abilities (mean score $28.9/30 \pm 1.1$; normal ≥ 27). They did not have any neurological disease or medical problem that could interfere with cognitive functioning. All participants were native French speakers. Demographic data are summarized in Table 1.

All data were generated during a routine clinical work-up and were retrospectively extracted for the purpose of this study. Therefore, according to French legislation, explicit consent was waived. However, regulations concerning electronic filing were followed, and patients and their relatives were informed that anonymized data might be used in research investigations. The study received approval from the Ethics Committee of the Pitié Salpêtrière Hospital.

Table 1 Demographic data of healthy controls and sv-PPA patients

	controls (mean ± SD)	**sv-PPA** (mean ± SD)
Number of subjects	25	12
Sex (women, men)	13W/12M	8W/4M
Age (years)	65.8 ± 8.6	66.4 ± 7.2
Handedness (R/L)	25R/0L	12R/0L
Years of education	13.4 ± 3.4	12.9 ± 4.3
Symptom duration (years)	///////	3.5 ± 2.1

SD = standard deviation

2.2. General cognitive/language assessment

The general cognitive assessment included among various standard tests the MMSE and the Frontal Assessment Battery (FAB; Dubois et al., 2000). The language assessment consisted of a picture naming test (D080; Deloche and Hannequin, 1997) and the Boston Diagnostic Aphasia Evaluation (BDAE; Mazaux & Orgogozo, 1982). The BDAE included an evaluation of aphasia severity taking into account spontaneous speech and the description of the 'cookie theft picture', a sentence repetition task, and a single-word comprehension task requiring pointing to pictures upon auditory word presentation. We also applied a verbal fluency test comprising letter and category fluency (Cardebat et al., 1990) and a semantic matching test in its verbal and picture version (Pyramids and Palm Trees Test; Howard and Patterson, 1992). Cognitive/language scores are summarized in Table 2.

Table 2 Cognitive/language scores of sv-PPA patients

	sv-PPA (mean ± SD)	**Normal threshold**
MMSE (/30)	23.7 ± 3.5	≥ 27
FAB (/18)	14.7 ± 2.9	≥ 16
BDAE – aphasia severity scale	3.1 ± 0.8	> 4
BDAE – single-word comprehension	59.3 ± 4.1	≥ 68
BDAE – sentence repetition	15.1 ± 3.4	≥ 14
Category fluency ('fruits' / 2 minutes)	9.9 ± 5.0	≥ 15
Letter fluency ('P' / 2 minutes)	13.8 ± 8.5	≥ 15
DO80 (/80)	39.5 ± 15.8	≥ 75
PPTT verbal (/50)	33.9 ± 9.7	≥ 45
PPTT pictures (/50)	34.7 ± 9.3	≥ 45

SD = standard deviation. MMSE = Mini Mental State Examination. FAB = Frontal Assessment Battery. BDAE = Boston Diagnostic Aphasia Examination. DO80 = Picture naming task. PPTT = Pyramids and Palm Trees Test. Normal thresholds are calculated as a function of normative values according to the age, sex and educational level of our patient population.

2.3. Experimental Tasks

2.3.1. Reading and Writing tasks

The materials of the reading task included 30 irregular words for both reading and writing according to the irregularity criteria of Beauvois and Derouesné (Brain, 1981) (nouns corresponding to living and non-living entities). There were no homophones among the stimuli.

They were contrasted with 30 regular words (nouns corresponding to living and non-living entities), which can also be processed via a direct route from orthographical to phonological patterns, and with 30 non-words the processing of which necessarily depends on this direct sublexical route. Participants were asked to read aloud the stimuli printed in black on white paper sheets (*Times New Roman* font, size 48).

For the writing task, the materials consisted of 15 irregular and 15 regular words (nouns corresponding to living and non-living entities), and of 15 non-words. The participants were asked to write-to-dictation the stimuli, which were auditorily presented by a native French speaker.

Within and between both tasks irregular and regular words were matched for frequency, number of letters and bigram and trigram frequencies (all Fs < 1), and non-words were matched for number of letters with the irregular and regular words (both Fs < 1) (LEXIQUE 2 database, New et al., 2004).

Non-words did not have any orthographical or phonological neighbor and they were orthographically and phonotactically legal.

2.3.2. Lexical decision task

This task was designed as a marker for lexical representations. It contained a written/visual and an auditory version to assess two distinct access routes to abstract representations within the mental lexicon (orthographical and phonological codes), which were predicted to be correlated. The two versions of the task were used to explore access to the distinct components of the mental lexicon given that reading involves the orthographic input component followed by the phonological output component, whereas writing involves the phonological input component followed by the

orthographic output component. In this vein, our two versions of the lexical decision task probed for the integrity/breakdown of these four different lexical components.

Both versions contained 45 irregular words, 45 regular words and 100 non-words. The stimulus materials were the same for both versions and the irregular and regular items were identical to those used in the reading task, on the one hand, and in the writing task, on the other hand. Irregular and regular words were matched for frequency, number of letters and bigram and trigram frequencies (all $Fs < 1$). Non-words were matched with regular and irregular words for the number of letters (all $Fs < 1$). Importantly, non-words were matched for bigram frequencies with both regular words ($t = 1.15$, $p = 0.254$) and irregular words ($t = -1.307$, $p = 0.194$). Likewise, non-words were matched for trigram frequencies with both regular words ($t = 1.3567$, $p = 0.179$) and irregular words ($t = -1.75$, $p = 0.083$). Non-words did not have any orthographical or phonological neighbor. They were orthographically and phonotactically legal.

The stimuli were presented on a computer using *E-prime* software. In the written/visual version each trial began with a fixation cross (800 ms), followed by the stimulus word written in black (5000 ms). Between each trial there was a blank screen during 700 ms. In the auditory version each stimulus trial consisted in the presentation of a fixation cross (800 ms) followed by an auditory target stimulus delivered through headphones. All words had been recorded by a female native French speaker and digitized for binaural headphone presentation using *COOL EDIT* software. In both versions, the participants were asked to decide as accurately and as fast as possible whether the word target exists in French or not, by pressing the “YES” or the “NO” button on a computer keyboard. Participants answered by pressing “YES” or “NO” with the index finger and the middle finger of their dominant hand, respectively. Before being tested on each version of the task participants were familiarized with the procedure by five training trials.

2.3.3. Category decision task

The task assessed whether a given written word refers, or not, to a living entity, and was conceived as a marker for semantic representations. In contrast to the lexical decision task we only used a written version because it is usually assumed that there are no distinct phonological or orthographical codes of semantic representations. This binary task of semantic capacities was used because the procedure, and the involved response mechanisms, are similar to the lexical decision task (word vs. non-word) given that YES/NO answers are also required for (living vs. non-living) decisions. The task takes also into account aspects of interactive models positing that the access to semantic features can be activated by orthographical/phonological features (e.g., Joanisse & Seidenberg, 1999), even if hidden layers, which might reflect an equivalent of lexical representations, are degraded. More specifically, we included 32 words reflecting 'living' categories (e.g., "cat") and 64 words reflecting 'non-living' categories (e.g., "mat"), using 45 irregular words and 51 regular words. The 45 irregular items, and the 45 regular items out of the 51, were exactly the same as those used in the lexical decision task, and as those used in the reading and writing tasks. Among the irregular words 20 corresponded to 'living' items and 25 corresponded to 'non-living' items. 'Living' and 'non-living' items were matched for frequency and number of letters (both Fs < 1). To ensure that our stimuli do not contain semantically ambiguous items regarding the living/non-living contrast we previously conducted a pilot study with 20 young healthy adults who classified with high accuracy the living and non-living items (allover 98% of correct responses).

The stimuli were presented on a computer using *E-prime* software. Each trial began with a fixation cross (800 ms), followed by the stimulus word written in black (5000 ms). Between each trial there was a blank screen during 700 ms. Participants were asked to decide as accurately and as fast as

possible whether the word target represents a 'living' entity or not, by pressing the "YES" or the "NO" button on a computer keyboard. Participants answered by pressing "YES" or "NO" with the index finger and the middle finger of their dominant hand, respectively. Before being tested on the task participants were familiarized with the procedure by five training trials.

The order of the experimental tasks was randomized. They were administered at 60-90 minute intervals to minimize potential cross-task biases given that they included the same irregular and regular word stimuli. To further minimize such biases the tests of the general cognitive and language assessment were administered during these intervals.

2.4. Statistical analyses

We first computed *d'* and c-values for the auditory and visual versions of the lexical decision task and for the category decision task in patients to assess the sensitivity of these tasks and possible response biases. Then, we used a *mixed-effects model* to look for differences between performances of sv-PPA patients and healthy controls, and to compare the different stimulus conditions within the experimental tasks. *Linear mixed models* were used to identify differences between reaction times (RT) on correct answers for sv-PPA patients and healthy controls in the auditory and visual versions of the lexical decision task and in the category decision task. We then conducted Pearson's correlations assessing the relationship between performance in the lexical decision and the category decision task, to strengthen the claim that the two tasks tap distinct representations, namely lexical and semantic information. We also assessed the relationship between word frequency and RT in the lexical decision task to support that lexical access was occurring in this task. Correlation analyses were also used to explore the relationship between the

reading/writing performances on irregular words and performance on these irregulars in the lexical decision task (lexical marker) and the category decision task (semantic marker). All these correlation analyses were conducted in patients and in healthy controls. Bonferroni correction for multiple comparisons was applied. In a second step we analyzed, on an item-by-item basis (consistency analyses), whether lexical decision errors and/or category decision errors on a given irregular word reliably predict errors on that item in the writing and the reading task. Finally, we conducted a multiple regression assessing the prediction of reading/writing errors with irregular words based on category decision and visual lexical decision measures with the aim to identify which of those two latter measures has the best power to explain reading/writing errors on irregulars.

3. Results

3.1. Sensitivity and response bias

Mean *d'* for the auditory and visual lexical decision tasks and for the category decision task were, respectively, 2.72, 2.55 and 1.13. All *d'* values were significantly different from '0' (all $p < 0.001$) indicating that patients were answering above the chance level. Mean *c-values* were 0.23 and 0.02 for the auditory and visual lexical decision tasks, respectively, showing a small bias towards 'YES' answers ('word exists') which was not significant. For the category decision task patients also showed a non-significant bias towards 'YES' answers (mean *c-value* = 0.07).

3.2. Analyses of the experimental tasks

All analyses were conducted with 'group' (sv-PPA, controls) and 'stimulus type' as fixed effects and 'subjects' and 'items' as random effects. Results of the reading and the writing task are

illustrated in Figure 1. Results of the two versions of the lexical decision task and the results of the category decision task are illustrated in Figure 2. Mean values and standard deviations for patients and healthy controls, and for all tasks are illustrated in the Supplementary Tables 1-5.

3.2.1. Reading task: The stimulus types were 'irregular words', 'regular words' and 'non-words'. A significant main effect of 'group' was found, with patients showing poorer performances than controls ($p < 0.001$). There was also a 'stimulus type' effect ($p < 0.001$) and a significant interaction between 'group' and 'stimulus type' ($p < 0.001$). Pairwise comparisons with Sidak adjustment for multiple comparisons showed that this interaction was related to the fact that patients had poorer performance with irregular words than with non-words ($p = 0.001$) and regular words ($p < 0.001$) whereas controls demonstrated the inverse pattern for non-words ($p = 0.029$). Performance with regular words was better than with non-words for controls ($p = 0.001$) whereas there was no difference between regular and irregular words. The comparison between controls and patients showed that irregular words yielded poorer performance in patients than in controls ($p < 0.001$) whereas performance with regular words and non-words was similar in patients and controls. Detailed statistical results are shown in Table 3.

Table 3 Mixed-effects model for the reading task (df = degrees of freedom)

Source	Numerator df	Denominator df	F-value	p-value
Intercept	1	100.210	2566.660	<0.001
Group	1	35.000	30.86	<0.001
Stimulus type	2	88.762	8.723	<0.001
Interaction	2	3202.000	77.548	<0.001

3.2.2. Writing task: We used the same stimulus types as in the reading task. A significant main effect of 'group' was found, with patients showing poorer performances than controls ($p < 0.001$). There was also a 'stimulus type' effect ($p < 0.001$) and a significant interaction between 'group' and 'stimulus type' ($p < 0.001$). Pairwise comparisons with Sidak adjustment for multiple comparisons showed that this interaction was related to the fact that patients had poorer performance with irregular words than with non-words, and performance with regular words was better than with irregular words and non-words (regular vs. irregular words: $p < 0.001$ regular words vs. non-words: $p = 0.016$). There was no difference between stimulus type for controls. The comparison between controls and patients showed that irregular words and non-words yielded poorer performance in patients than in controls (irregular words: $p < 0.001$; non-words: $p = 0.017$) whereas performance with regular words was similar in patients and controls. Detailed statistical results are shown in Table 4.

Table 4 Mixed-effects model for the writing task (df = degrees of freedom)

Source	Numerator df	Denominator df	F-value	p-value
Intercept	1	55.996	2104.967	<0.001
Group	1	35.000	82.972	<0.001
Stimulus type	2	44.648	25.704	<0.001
Interaction	2	1582.000	108.861	<0.001

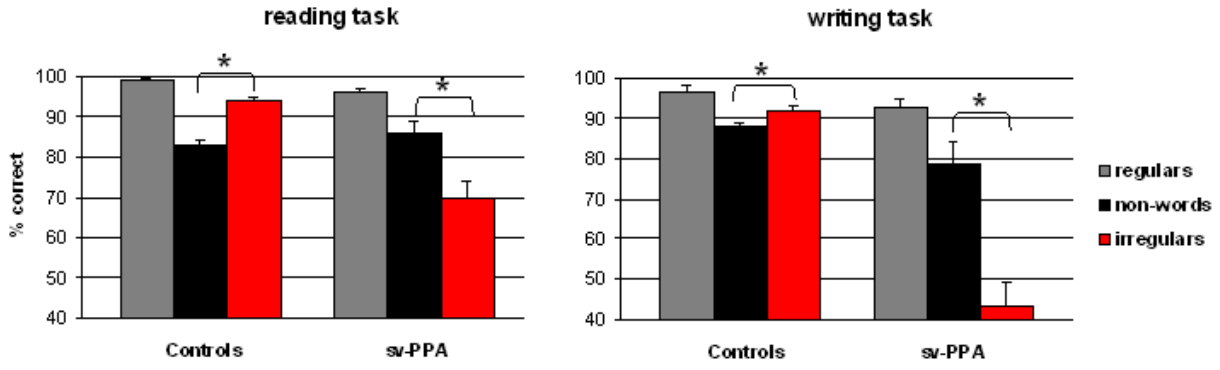

Figure 1. Performance of sv-PPA patients and healthy controls in the reading and writing tasks.

3.2.3. Lexical decision task: The independent variables were "group" and "stimulus type" (regular words, irregular words). For the written/visual version, a significant main effect of 'group' was found, with patients showing poorer performances than controls ($p < 0.001$). There was no stimulus type effect and no group x stimulus type interaction. Using reaction times (RT) as the dependant variable, there was a main effect of 'group', with patients showing slower RT than controls ($p < 0.001$). There was no stimulus type effect and no group x stimulus type interaction. For the auditory version, there was also a main effect of 'group', with patients showing poorer performance than controls ($p < 0.001$). There was no stimulus type effect and no group x stimulus type interaction. Using RT as the dependant variable, there was a main effect of 'group', with patients showing slower RT than controls ($p < 0.001$). There was no stimulus type effect and no group x stimulus type interaction. Detailed statistical results are shown in Table 5a and 5b.

Table 5a Mixed-effects model for performances in the visual version of the lexical decision task (df = degrees of freedom)

Source	Numerator df	Denominator df	F-value	p-value
Intercept	1	47.769	7590.323	<0.001
Group	1	35.800	35.479	<0.001
Stimulus type	2	204.196	1.453	0.236
Interaction	2	6802	0.668	0.513

Table 5b Mixed-effects model for performances on the auditory version of the lexical decision task (df = degrees of freedom)

Source	Numerator df	Denominator df	F-value	p-value
Intercept	1	56.993	10680.742	<0.001
Group	1	35.594	52.413	<0.001
Stimulus type	2	205.820	0.486	0.616
Interaction	2	6802	10.698	<0.001

3.2.4. Category decision task: The independent variables were "group" (sv-PPA, controls), category ('living', 'non-living') and "stimulus type" (regular words, irregular words). A significant main effect of 'group' was found, with patients showing poorer performances than controls ($p < 0.001$). There was no category effect, no stimulus type effect and no interaction between the variables. Using RT as the dependent variable, there was a main effect of 'group', with patients showing slower RT than controls. There was no category effect, no stimulus type effect and no interaction between the variables. Detailed statistical results are shown in Table 6.

Table 6 Mixed-effects model for performances in the category decision task (df = degrees of freedom)

Source	Numerator df	Denominator df	F-value	p-value
Intercept	1	63.699	1438.975	<0.001
Group	1	36.501	42.078	<0.001
Stimulus type	1	97.951	0.112	0.739
Category	1	97.951	0.141	0.708
Group*StimulusType*Category	2	197.480	2.163	0.118
Group*StimulusType	1	3417.000	0.865	0.352
Group*Category	1	3417.000	0.928	0.335

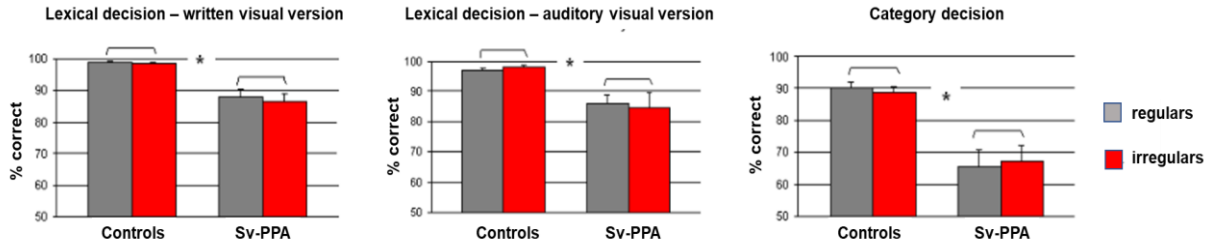

Figure 2. Performance of sv-PPA patients and healthy controls in the lexical decision task (written/visual version, auditory version) and in the category decision task.

3.3. Pearson's correlation analyses

Correlation analyses were performed by extracting the mean performance (all items aggregated) for each participant for each of the tasks. The analyses were first conducted in patients which provide sufficient performance variability i) to explore whether the lexical markers (lexical decision scores) and the semantic markers (category decision scores) tap distinct language

representations, i.e. lexical vs. semantic codes, and ii) to evaluate whether lexical and/or semantic markers are related to reading/writing failures with irregular words. Correlation results are summarized in Table 7. In addition, we also conducted correlation analyses in healthy controls even if their performance variability and near ceiling-effects might make such correlations less informative and meaningful (see Table 8).

Regarding the first issue, performance of patients and of healthy controls in the auditory and written/visual lexical decision task were correlated, indicating that both tasks tap related, yet distinct representations within the mental lexicon containing orthographic and phonological codes. By contrast, performance in the category decision task did not correlate with those in the written/visual or the auditory version of the lexical decision task, with the exception of written/visual lexical decision in controls. In patients and controls there was a negative correlation between word frequency and response reaction times (RT) in the visual and in the auditory version of the lexical decision task i) for all word items, ii) for irregular items, and iii) for regular items (with the exception of auditory lexical decision in controls), supporting that lexical access was occurring in the task.

Regarding the second issue, reading performance of patients with irregular words was significantly correlated with scores in the written/visual and in the auditory version of the lexical decision task. By contrast, there was no correlation between reading scores and scores in the category decision task. Likewise, writing performance with irregulars was correlated with scores in the written/visual version and in the auditory version of the lexical decision task. Conversely, no correlation was found between the scores on irregulars and the scores in the category decision task. In controls there were no significant correlations probably due to ceiling effects, with the exception of writing performance with irregular words and performance in the visual lexical decision task. In addition,

we conducted correlation analyses with two standard test of semantics: the Pyramids and Palm Trees Test and the single-word comprehension test of the BDAE. Scores of the verbal version but not of the picture version of the PPTT were correlated with reading and writing performance on irregular words. Scores of the Pyramids and Palm Trees Test did not correlate with values of the category decision task. Scores on single-word comprehension correlated significantly with the scores of the experimental category decision task indicating that our task genuinely assesses semantic capacities constituting the main criterion for sv-PPA diagnosis (Gorno-Tempini et al., 2011). As for the category decision task, scores of the single-word comprehension test were not correlated with reading and writing performance on irregular words.

Table 7 Pearson's correlation results between the different measures for sv-PPA patients

Correlated measures	R	p-value
Auditory lexical decision / Visual lexical decision	0.86	0.0003
Category decision / Visual lexical decision	0.29	0.35
Category decision / Auditory lexical decision	0.28	0.38
Word frequency (total) / Visual lexical decision RT	-0.31	0.003
Word frequency (regulars) / Visual lexical decision RT	-0.38	0.009
Word frequency (irregulars) / Visual lexical decision RT	-.052	<0.001
Word frequency (total) / Auditory lexical decision RT	-0.3	0.005
Word frequency (regulars) / Auditory lexical decision RT	-0.36	0.015
Word frequency (irregulars) / Auditory lexical decision RT	-0.34	0.0023
Reading (irregulars) / Visual lexical decision	0.82	0.001
Reading (irregulars) / Auditory lexical decision	0.69	0.009
Reading (irregulars) / Category decision	0.38	0.39
Writing (irregulars) / Visual lexical decision	0.74	0.006
Writing (irregulars) / Auditory lexical decision	0.75	0.005
Writing (irregulars) / Category decision	0.27	0.45

Reading (irregulars) / Verbal PPTT	0.59	0.043
Writing (irregulars) / Verbal PPTT	0.58	0.046
Reading (irregulars) / Picture PPTT	0.41	0.18
Writing (irregulars) / Picture PPTT	0.18	0.57
Reading (irregulars) / Single-word comprehension	0.126	0.694
Writing (irregulars) / Single-word comprehension	- 0.007	0.982
Category decision / Verbal PPTT	-0.168	0.602
Category decision / Visual PPTT	-0.532	0.075
Category decision / Single-word comprehension	0.63	0.028

RT = Reaction times. PPTT = Pyramids and Palm Trees Test

Table 8 Pearson's correlation results between the different measures for the healthy controls

Correlated measures	**R**	**p-value**
Auditory lexical decision / Visual lexical decision	0.4033	0.045
Category decision / Visual lexical decision	0.49	0.012
Category decision / Auditory lexical decision	0.261	0.207
Word frequency (total) / Visual lexical decision RT	-0.4	0.0001
Word frequency (regulars) / Visual lexical decision RT	-0.545	0.0001
Word frequency (irregulars) / Visual lexical decision RT	-0.442	0.0024
Word frequency (total) / Auditory lexical decision RT	-0.3622	0.001
Word frequency (regulars) / Auditory lexical decision RT	-0.171	0.262
Word frequency (irregulars) / Auditory lexical decision RT	-0.415	0.005
Reading (irregulars) / Visual lexical decision	0.1	0.634
Reading (irregulars) / Auditory lexical decision	0.279	0.175

Reading (irregulars) / Category decision	0.222	0.285
Writing (irregulars) / Visual lexical decision	0.434	0.03
Writing (irregulars) / Auditory lexical decision	-0.289	0.161
Writing (irregulars) / Category decision	0.037	0.86

3.4. Item-by-item consistency analyses

In the patient group, we analyzed the consistency of errors for each of the irregular words between the reading and writing tasks, and the two versions of the lexical decision task and between the reading and writing tasks and the category decision task. This procedure allowed for determining the predictive value of the lexical task (lexical decision) and the semantic task (category decision) for reading/writing errors on irregular words. More specifically, we calculated 1) the number of item-specific co-occurring reading/writing errors and lexical decision errors (written/visual version) on irregular words divided by the total number of errors on irregulars in the written/visual version of the lexical decision task, 2) the number of item-specific co-occurring reading/writing errors and lexical decision errors (auditory version) on irregular words divided by the total number of errors on irregulars in the auditory version of the lexical decision task, 3) the number of item-specific co-occurring reading/writing errors and category decision errors divided by the total number of errors on irregulars in the category decision task.

The results showed that the item-specific consistency is high between the reading/writing tasks and the two versions of the lexical decision task (Positive Predictive Values written/visual version: 77.6%; auditory version: 77.4%). By contrast, the consistency is lower between the reading/writing tasks and the category decision task (Positive Predictive Value: 42.4%). Thus, lexical errors for a given irregular item are highly predictive of reading/writing errors with that

item whereas semantic errors for a given irregular item are less predictive of reading/writing errors with that item.

3.5. Multiple regression model

A multiple regression was conducted using the number of reading/writing errors with irregulars as the dependent variable and category decision and visual lexical decision performances as explanatory variables. Auditory lexical decision was not included in the model as an explanatory variable since there is a high correlation between this measure and visual lexical decision, which would violate the multicollinearity assumption that requires that no strong correlation exists between explanatory variables in order to perform a multiple regression. Our multiple regression model statistically significantly predicted reading/writing errors with irregulars ($F(2, 9) = 6.974$, $p = 0.01$, adjusted $R^2 = 0.521$). In particular, only the visual lexical decision variable, but not the category decision variable, added statistically significantly to the prediction ($p = 0.005$). Regression coefficients and standard errors are shown in Table 9.

Table 9 Summary of multiple regression analysis

Variables	B	SE_B	β
Intercept	117.661	24.693	
Category decision	-0.170	0.117	-0.315
Visual lexical decision	-0.902	0.243	-0.803*

* $p < 0.005$. B = unstandardized regression coefficient. SE_B = Standard error of the coefficient. β = standardized coefficient

4. Discussion

We explored a cohort of sv-PPA patients to investigate whether surface dyslexia/dysgraphia is related to damage to the semantic system as proposed by authors adhering to connectionist models or whether, in accordance with symbolic accounts, it is linked to impairments of the orthographic or phonological component of the mental lexicon. Concomitantly we investigated two directly related issues: whether sv-PPA patients demonstrate lexical damage in addition to semantic breakdown, and whether cohort-based sv-PPA findings can provide novel evidence supporting either symbolic or connectionist models. Our findings, based on reading/writing scores with irregular words, on lexical and semantic markers, and on the application of correlations, item-by-item consistency analyses, and a multiple regression model show i) that sv-PPA affects the mental lexicon, ii) that the lexical but not the semantic impairment correlates with markers of surface dyslexia/dysgraphia, iii) that lexical failure on a given irregular item reliably predicts reading/writing errors on that item, and iv) that lexical decision markers but not semantic category decision markers predict reading/writing errors with irregulars.

More specifically, our results showed that in sv-PPA reading and writing performance with irregular words was significantly lower than performance with regular words and non-words, thus providing the signature of surface dyslexia/dysgraphia. Results from both the auditory and the written/visual version of the no-neighbor non-word controlled lexical decision task revealed poor performance in sv-PPA, indicating lexical impairment. Importantly, trigram/bigram frequencies were matched between irregular (and regular) words and non-words to avoid that lexical decisions might be made upon orthographical/sound features, as often stipulated by connectionist modelers, and to show that they rather depend on genuine lexical representations. There was also a negative correlation between word frequency and reaction times in both versions of the task for i) all items

(regulars and irregulars combined), ii) for regulars, and iii) for irregulars. These results further corroborate that lexical access was occurring, and they justify the use of no-neighbor non-words which enabled participants to access word-specific knowledge rather than word meaning. Such lexical deficits concomitantly occurred with semantic breakdown as shown by massive impairment in the category decision task. The correlation analyses showed that reading/writing performance with irregulars was significantly related to lexical decision scores whereas there was no correlation with semantic-based category decision results. The link between surface dyslexia/dysgraphia and lexical impairment was substantiated by the item-by-item analyses revealing a high item-specific consistency between reading/writing errors and lexical decision errors. These analyses demonstrated a high positive predictive value (77.5%) indicating that lexical errors on an irregular item co-occur with reading/writing failure on that item. By contrast, semantic errors were poorer item-specific predictors of reading/writing errors (42.5%). Finally, the multiple regression analysis showed that the lexical decision marker, but not the category decision marker, significantly predicts reading/writing errors with irregular words, thus reinforcing and extending our item-by-item analyses. Regarding correlations in our healthy control group with lexical or semantic markers it is probable that the lack of significant results is simply related to the low performance variability in the healthy population yielding near-ceiling effects. However, this lack of correlations in healthy adults does not weaken our data or conclusions. Sv-PPA was explored because it represents a powerful model of semantic/lexical disorders and of reading/writing impairments with irregular words, thus allowing for elucidating the issue whether disorders with irregular words are predicted by semantic or lexical impairment, or both factors. Furthermore, sv-PPA patients demonstrate an exploitable variability of performance levels, thus allowing for meaningful correlation analyses which show that only lexical markers correlate significantly with

performance on irregular words. However, future studies could explore the link between irregulars and semantic vs. lexical capacities in healthy participants by using more continuous markers/measures of reading/writing which might provide the necessary data variability as for example millisecond-measures of reading times for irregulars.

Our findings are in line with previous studies showing the existence of surface dyslexia in sv-PPA (e.g., Patterson and Hodges, 1992; Caine et al., 2009, Brambati et al., 2009; M.A. Wilson et al., 2012), demonstrating poor performance on lexical decision in sv-PPA (Graham et al., 2000; Rogers et al., 2004; Benedet et al., 2006; Patterson et al., 2006; Jeffries et al., 2010), and suggesting lexical disorders in this PPA variant (Mesulam et al., 2013; 2014; Wilson et al., 2014; 2017; Boukadi et al., 2016). Our data extend and enrich previous evidence and challenge several findings suggesting that surface dyslexia is specifically related to semantic breakdown (e.g., Macoir and Bernier, 2002; Brambati et al., 2009; Wilson et al., 2012). First, unlike most investigations focusing primarily on surface dyslexia in sv-PPA, our study extends the processing failure on irregular words to the writing modality. Although some rare studies did find surface dysgraphia in sv-PPA (Graham et al., 2000; Macoir and Bernier., 2002; Caine et al., 2009; Shim et al., 2012), they did not provide direct comparisons between reading and writing with experimental materials using the same word stimuli. The only exception for such a direct comparison is the study of Henry et al. (2012) who included 6 sv-PPA patients within a cohort of 15 PPA patients, yet without providing statistical analyses of reading/writing data for the sv-PPA subgroup. Second, our results enrich and specify findings from previous lexical decision tasks, and proposals that sv-PPA entails lexical impairment, given that investigations applying lexical decision paradigms in sv-PPA used word and non-word stimuli which could hardly demonstrate that low performance was related to lexical rather than semantic failure. In this context, the exclusive use of no-neighbor non-words in

the present lexical decision design allowed for specifically assessing lexical representations (Binder et al., 2003; Coltheart, 2010), thus confirming the existence of genuine lexical impairment in sv-PPA. Furthermore, negative correlation between word frequency and reaction times in both versions of the lexical decision task for regulars and irregulars corroborate that lexical access occurs. The claim about lexical impairment is also consistent with our correlation analyses indicating that the lexical decision task and the category decision task tap distinct representations, i.e. lexical (orthographic or phonological) vs. semantic information. More specifically, they showed significant correlation values between the auditory and the written/visual version of the lexical decision task whereas no correlation was found between lexical decision and category decision scores. This lexical/semantic distinction also holds for the item-by-item analyses showing that the co-occurrence of errors in the written/visual and auditory version of the lexical decision task was high (85%) whereas it was low for the lexical decision and the semantic-based category decision task (35%). Third, our main finding challenges previous accounts assuming the causal role of exclusively semantic deficits in surface dyslexia, as our results have revealed a direct relationship between reading/writing errors on irregular words and lexical markers, via both correlation and item-by-item consistency analyses.

These outcomes, however, do not allow for inferring that semantics does not play a role in surface dyslexia/dysgraphia given that scores on the verbal version of the Pyramids and Palm Trees Test slightly correlated with performance on irregular words in the reading and writing task. This is consistent with findings of Binney et al., (2016) who also showed correlations between reading of irregulars and the verbal but not the picture version of the Pyramids and Palm Trees Test. Furthermore, in our study the item-specific consistency of reading/writing errors with semantic failure is not negligible, reflecting about 40% of concomitant semantic and reading/writing errors

with irregulars. Nevertheless, this percentage is substantially lower than the item-by-item consistency between surface dyslexia/dysgraphia and lexical breakdown. Our results regarding item-by-item consistency are also in line with previous studies exploring such consistency in single cases (Graham et al., 1994; Funnell, 1996; Macoir and Bernoer., 2002; Blazely et al., 2005) or in small series of sv-PPA patients (McKay et al., 2007). However, our cohort-based data add the information that item consistency is higher when analyzing lexical markers in addition to semantic markers. Blazely et al. (2005) reported that their patient had semantic impairments, as shown by performances on picture naming, single-word comprehension and word-picture matching tasks, along with surface dyslexia. This patient also showed impairments in a lexical decision task. However, while performances in the three semantic tasks correlated with each other, performances in the lexical decision task did not correlate significantly with performances in the semantic tasks. These results suggest, as ours do, that impairment in lexical decision is driven also by impairments other than semantic ones. However, in this study the authors did not explore item-by-item consistency between reading errors with irregulars and any other task, which did not allow for making inferences regarding the semantic vs. lexical mechanism underlying surface dyslexia in semantic dementia patients. Our cohort-based data add the information that item consistency in reading/writing of irregulars is higher when analyzing lexical markers (lexical decision task) then when analyzing semantic markers.

One might wonder whether the category decision task, using the same irregular items as the lexical decision task, allows for assessing semantic knowledge on lexically rejected words (NO-answers in lexical decision). Strictly serial models state that the access to semantic representations critically depends on the fact that a given item has been activated in the mental lexicon. Interactive models however (e.g., Rumelhart & McClelland, 1986; Joanisse & Seidenberg, 1999) propose that

degraded lexical representations allow for the activation of semantic information presumably via the involvement of an associative pathway directly connecting sound/letter patterns to semantic representations, eventually via 'hidden layers'. Without presuming the existence of such a direct associative pathway, our data indicate that degraded lexical representations in sv-PPA, leading to NO-answers in lexical decision, can allow for accessing correct semantic category representations for a given item. They more specifically highlight that similar proportions of lexically rejected and lexically non-rejected items result in correct living/non-living categorizations (69% and 71%, respectively in the written version; 68% and 73%, respectively in the auditory version).

4.1. Reconciliation with connectionist-inspired literature on dyslexia/dysgraphia in sv-PPA?

How can our findings be reconciled with previous studies attributing surface dyslexia to semantic breakdown and, anatomically, to damage to brain regions involved in semantic processing? Regarding behavioral results on sv-PPA, most authors implicitly accepted connectionist accounts without contrasting them against symbolic models and their predictions. Apparently in line with such connectionist approaches, the available sv-PPA cohort studies have reported significant correlations between reading/writing of irregular words and standard tests of semantics such as the Pyramids and Palm Trees Test or picture naming tasks (e.g., Brambati et al., 2009; Shim et al., 2012; Binney et al., 2016). Our results are compatible with such accounts stating that surface dyslexia/dysgraphia is related to semantic capacities as reflected by our item consistency analyses showing that 40% of semantic errors with a given item co-occur with reading/writing errors on that irregular item. However, item consistency was higher for lexical errors. The previous semantic-centered findings might in part be biased by the use of 'routine' tests which depend on multiple non-semantic factors involving lexical aspects, as well as attention and executive factors

which are minimized in our binary category decision task. In line with authors using such routine tests we replicated that scores on the verbal version, but not on the picture version, of the Pyramids and Palm Trees Test are slightly correlated with reading/writing with irregular words. One should note that this test is assumed to assess semantic performance but that its verbal version also depends on lexical access to the test items, requiring the complex processing of three words to find the association between two of them, while our task is a more direct semantic task that requires only the processing of one word at a time.

The most important point is, however, that no investigation on sv-PPA has provided direct comparisons between surface dyslexia and lexical vs. semantic markers, and no study has used item-specific consistency analyses for both lexical and semantic processing domains at a sv-PPA cohort level. Based on this stringent methodology we show that semantic failure plays a role, predicting surface dyslexia in almost half of the items, but we crucially provide novel evidence that lexical impairment is a better predictor and a more important contributor to surface dyslexia/dysgraphia. The latter finding is consistent with several case studies which have reported that semantic breakdown in the explored sv-PPA patients was not associated with reading errors on irregular words (Schwartz et al., 1979; Cipolotti and Warrington, 1995; Lambon Ralph et al., 1995; Blazely et al., 2005; Wilson and Martínez-Cuitiño, 2012). Such results dissociating surface dyslexia and semantics have recently been strengthened by a study on two sv-PPA cases showing a double dissociation with respect to reading performance on irregular words and lexical decision with pseudohomophones, such as the non-word ‘brane’ derived from the real word ‘brain’ (Boukadi et al., 2016). According to connectionist models, both lexical decision on such word-like non-words and reading of irregulars depend on the semantic system and therefore no dissociations between the two tasks are predicted. However, there was such a dissociation, and the authors thus

propose that their data are compatible with DRC models containing lexical representations, allowing for double damage dissociations within the lexical system itself, which comprises interconnected orthographical and phonological components. In summary, we do not state that surface dyslexia/dysgraphia is unrelated to semantic competency but our data temper this relationship. They indicate that the relationship was probably over-weighted culminating in the widely assumed view that specifically semantic failure causes surface dyslexia/dysgraphia without exploring whether lexical disorders might be the major causative factor.

Regarding the anatomical correlates of surface dyslexia, imaging studies on sv-PPA have primarily implicated semantic-related regions of the temporal cortex, namely left anterior areas (e.g., Brambati et al., 2009; Wilson et al., 2012). However, in sv-PPA atrophy is mainly located in such anterior areas whereas more posterior temporal regions, implementing lexical representations (e.g., Kotz et al., 2002; Graves et al., 2008; 2010), demonstrate lower atrophy variability. This pattern of atrophy in sv-PPA might constitute a bias in finding anatomo-functional correlations between surface dyslexia and brain regions other than anterior temporal regions, leading to non-significant correlation results with posterior temporal areas. Despite this possible bias, and in line with our data highlighting the crucial role of the lexicon, a recent cortical thickness study with one of the largest sv-PPA cohorts (N=33) has shown that more posterior temporal cortices are significantly correlated with surface dyslexia scores (Binney et al., 2016). In the same vein, Binder et al. (2016) have shown surface dyslexia without semantic impairment in stroke patients and their data of voxel-based lesion-symptom mapping suggested “that the posterior middle temporal gyrus may compute an intermediate representation linking semantics with phonology”. This so-called intermediate level represents presumably the mental lexicon which has been demonstrated to be implemented by such posterior temporal cortices (e.g., Kotz et al., 2002; Graves et al. 2008).

Nevertheless, the current antomo-functional uncertainty regarding surface dyslexia/agraphia encourages future imaging investigations using rigorously controlled stimulus materials for correlations in large cohorts of PPA patients and for functional MRI investigations in large populations of healthy adults.

Finally, a fundamental issue is whether our data are compatible with connectionist models of reading/writing such as the influential triangle PDP model (e.g., Plaut et al. 1996). The model claims that semantic impairment causes surface dyslexia/dysgraphia, and that the mental lexicon does not play any role because, in their view, it does not exist. Our data are at odds with this line of models by indicating that lexical impairment is critically related to surface dyslexia and dysgraphia. Connectionist modelers could, however, claim that lexical decision tasks, including controlled experimental designs containing no-neighbor non-words, tap semantics, just as category decision tasks do. From this point of view, one should predict significant correlations between the scores from both tasks (lexical decision and category decision), significant correlations between reading/writing of irregular words and both tasks, and item-specific consistency of reading/writing errors with error scores in both tasks. None of these predictions is validated by our data. By contrast, our results are in line with symbolic models such as DRC accounts proposing the existence of a mental lexicon and its major role in reading/writing deficits with irregular words (Coltheart et al., 2010). However, to adopt an equilibrated position, it should be mentioned that several connectionist models implement the notion of 'hidden layers' serving error back-propagation to adjust hidden layer units mediating between semantic, sound and orthographic features. Nevertheless, it has been argued that such hidden units might function as internal representations (Pinker and Prince, 1988), representing in reality the equivalent of aspects of the mental lexicon, and which might computationally model some mechanisms linked to genuine

lexical representations. Finally, it could be mentioned that various studies have investigated the existence of the mental lexicon showing its morphological, phonological and syntactic properties while demonstrating that these properties, and operations acting on them such as verb inflection, can not be fully simulated by connectionist hidden layer models. (see e.g., Pinker and Ullman, 2002).

5. Conclusion

Our findings refine the knowledge about language deficits in sv-PPA indicating that it is not only characterized by semantic but also by lexical impairment, and demonstrating that the lexical impairment is a crucial factor for surface dyslexia and dysgraphia. Our results also provide novel patient-cohort-based support for symbolic models of reading/writing processes such as DRC accounts whereas they are less compatible with connectionist models. Additional research is now required to specify the precise roles of semantic and lexical competencies for reading/writing in healthy subjects and patients, to enrich models of written language, and to clarify the linguistic targets of rehabilitation strategies.

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CHAPTER III

Transcranial stimulation: a new therapeutic approach?

III.1. Language boosting by transcranial stimulation in progressive supranuclear palsy

III.2. Modulation of language impairments in behavioral variant of Frontotemporal Dementia after transcranial direct current stimulation of the prefrontal cortex

III.3. Clinical characterization and non-invasive transcranial modulation of lexical and semantic language abilities in patients with the logopenic variant of Primary Progressive Aphasia

Language boosting by transcranial stimulation in Progressive Supranuclear Palsy

The following article is published by Neurology.

Résumé en français

La paralysie supranucléaire progressive (PSP) est une maladie neurodégénérative qui affecte essentiellement les noyaux gris centraux et le tronc cérébral. Cependant, plusieurs études ont également rapporté des atteintes au niveau des régions corticales, en particulier sur le cortex préfrontal dorsolatéral (CPFDL). Même si ces patients sont caractérisés par des troubles moteurs, il a aussi été montré qu'ils présentent d'importants troubles cognitifs et comportementaux, y compris une défaillance de la fonction exécutive et des capacités langagières. Au niveau du langage, des déficits au niveau de l'accès lexical et sémantique sont en corrélation avec une atrophie du CPFDL gauche. Plusieurs études utilisant la stimulation magnétique transcrânienne répétitive (SMTr) ou la stimulation transcrânienne à courant continu (STCC) ont montré une amélioration du langage induite par la stimulation dans l'aphasie après un Accident Vasculaire Cérébrale. En se basant sur le principe de la rivalité interhémisphérique et sur l'hypothèse que la stimulation anodale facilite l'activité neurale alors que la stimulation cathodale l'inhibe, plusieurs auteurs ont montré que la stimulation anodale gauche sur des zones liées au langage et la stimulation cathodale droite sur des régions homotopiques génère les effets les plus importants sur la récupération du langage. Des améliorations du langage avec des technologies de stimulation cérébrale transcrânienne ont aussi été rapportées dans des conditions neurodégénératives (par exemple, la maladie d'Alzheimer et les aphasies primaires progressives). Cependant, à ce jour, aucune étude n'a analysé d'effets similaires chez des patients atteints de PSP.

Dans cette étude nous avons évalué l'impact sur les performances langagières de la STCC anodale et cathodale livré sur le CPFDL gauche et droite, respectivement.

En utilisant un design croisé, en double-aveugle et contrôlé par placebo nous avons testé, sur une cohorte de 12 patients atteints de PSP, les effets de la STCC sur leurs troubles langagiers.

Au cours de trois sessions distinctes, nous avons évalué la capacité à stimuler les zones préfrontales liées au langage de l'hémisphère gauche avec une stimulation anodale gauche (excitatrice) ou cathodale droite (inhibitrice) sur le CPFDL, par rapport à une stimulation placebo. Les trois séances de stimulation ont été séparées d'une semaine et chaque séance a eu une durée de 20 minutes avec une intensité du courant de 1.59mA délivré par des électrodes rondes de 25cm^2. Des performances dans des tâches évaluant l'accès lexical / sémantique (*décision catégorielle, fluence littérale*) ont été enregistrées en tant que mesures de résultats comportementaux avant et immédiatement après chaque séance de stimulation. 15 sujets sains ont aussi été recrutés pour avoir des valeurs normatives pour les tâches.

Les patients PSP étaient significativement altérés par rapport aux sujets sains dans les deux tâches. De plus, les résultats contrastant les performances entre post-stimulation et pré-stimulation dans les différentes conditions de stimulation ont révélé une amélioration substantielle du langage en ce qui concerne la *décision catégorielle* après une stimulation cathodale droite. En parallèle, une analyse restreinte de la *fluence littérale* a montré des améliorations marginales à la suite d'une stimulation anodale gauche. Un modèle computationnel de la distribution du courant pendant la stimulation a corroboré l'impact escompté de la stimulation anodale gauche et cathodale droite sur le CPFDL.

Nos résultats fournissent des données probantes pour la première fois sur l'amélioration du langage induite par la STCC chez des patients PSP. Ces résultats apportent la preuve de concept de l'utilisation de la STCC dans cette maladie neurodégénérative et ouvrent la voie à de futurs régimes de stimulation sur plusieurs jours conduisant à des effets thérapeutiques plus durables, favorisés par la neuroplasticité.

ARTICLE CLASS OF EVIDENCE

Language boosting by transcranial stimulation in progressive supranuclear palsy

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Abstract

Objective

To explore whether transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) can improve language capacities in patients with progressive supranuclear palsy (PSP).

Methods

We used a sham-controlled double-blind crossover design to assess the efficiency of tDCS over the DLPFC in a cohort of 12 patients with PSP. In 3 separate sessions, we evaluated the ability to boost the left DLPFC via left-anodal (excitatory) and right-cathodal (inhibitory) tDCS, while comparing them to sham tDCS. Tasks assessing lexical access (letter fluency task) and semantic access (category judgment task) were applied immediately before and after the tDCS sessions to provide a marker of potential language modulation.

Results

The comparison with healthy controls showed that patients with PSP were impaired on both tasks at baseline. Contrasting poststimulation vs prestimulation performance across tDCS conditions revealed language improvement in the category judgment task following right-cathodal tDCS, and in the letter fluency task following left-anodal tDCS. A computational finite element model of current distribution corroborated the intended effect of left-anodal and right-cathodal tDCS on the targeted DLPFC.

Conclusions

Our results demonstrate tDCS-driven language improvement in PSP. They provide proof-of-concept for the use of tDCS in PSP and set the stage for future multiday stimulation regimens, which might lead to longer-lasting therapeutic effects promoted by neuroplasticity.

Classification of evidence

This study provides Class III evidence that for patients with PSP, tDCS over the DLPFC improves performance in some language tasks.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ANOVA = analysis of variance; **CI** = confidence interval; **DLPFC** = dorsolateral prefrontal cortex; **FAB** = Frontal Assessment Battery; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **MMSE** = Mini-Mental State Examination; **MNI** = Montreal Neurological Institute; **PPA** = primary progressive aphasia; **PSP** = progressive supranuclear palsy; **tDCS** = transcranial direct current stimulation; **TMS** = transcranial magnetic stimulation.

Progressive supranuclear palsy (PSP) is a neurodegenerative disease damaging mainly the basal ganglia, the midbrain, and the superior cerebellar peduncle.[1] However, several studies have also reported damage to cortical regions, particularly to the dorsolateral prefrontal cortex (DLPFC).[1–3]

The clinical features of the most frequent PSP variant, the Richardson syndrome, are parkinsonism, postural instability, and impairment of vertical eye saccades.[4] In addition, various investigations have shown cognitive disorders including a breakdown of executive function and language capacities.[5,6] Regarding language, patients have impaired access to lexical and semantic representations, causing a diminution of language initiation/fluidity.[1,6–10] Accordingly, patients with PSP demonstrate impaired performance on a range of lexical/semantic tests including synonym judgment, semantic associations, single-word comprehension, naming, and word fluency tasks.[6,11,12] Neuroimaging studies in patients with PSP have demonstrated correlations between such language disorders and atrophy levels in the left DLPFC.[1,5]

Despite growing insight into the mechanisms of motor and cognitive disorders in PSP, no validated therapy is available.[13] Regarding cognitive/language deficits, several authors have explored the use of anti-Alzheimer molecules without any positive effects.[13] Similarly, speech therapy approaches have not led to any validated protocol.[14] In this context, noninvasive neurostimulation aiming at boosting cognitive/language performance in brain-damaged patients may represent a promising perspective.

Several investigations using transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) have shown improvement of language recovery in poststroke aphasia.[15] Capitalizing on the principle of interhemispheric inhibition[16] and under the assumption that anodal stimulation facilitates neural activity whereas cathodal stimulation inhibits it,[17] several authors have shown that left-anodal stimulation over language-related areas and right-cathodal stimulation over homotopic right-sided regions generate the most positive effects on language recovery.[15,18,19] Moreover, long-lasting effects persisting for several months after multiday stimulation regimens linked to neuroplasticity open avenues for future therapeutic applications.[19] Stimulation studies have provided evidence for improvement of language performance in neurodegenerative conditions such as Alzheimer disease[20] and primary progressive aphasias (PPA).[21–23] However, many of these investigations did not implement a double-blind or a sham-controlled design, limiting their ability to report genuine effects on language networks and performance. Recently, a double-blind sham-controlled tDCS study in the semantic variant of PPA reported improvement of semantic processing specifically in the verbal domain, following anodal and cathodal stimulation over the left and the right anterior temporal lobes, respectively.[23] Such a rigorous methodology yielding positive results paves the way to explore similar approaches in other neurodegenerative conditions with impaired language function, such as PSP.

We used a double-blind, sham-controlled, crossover design on a well-characterized cohort of patients with PSP applying single sessions of anodal and cathodal tDCS over the left and right DLPFC, respectively. Lexical and semantic access and language initiation/fluidity were evaluated with a "category judgment" and a "letter fluency" task prior to and following tDCS. To demonstrate potential language-specific improvement, we also applied a control task tapping non-language-related executive functioning.

Methods

Participants

Twelve patients with PSP were recruited at the National Reference Center for Rare Dementias and PSP, Pitié-Salpêtrière Hospital, Paris, France. The diagnosis was established by expert clinicians following international diagnostic criteria.[24] All patients had progressive disease evolution including predominantly axial parkinsonism, postural instability leading to falls during the first year of the disease, and impairment of vertical eye saccades. All patients also presented impairment of executive functions and decreased verbal fluency. Patients were included only when psychotropic medication such as antidepressant, anxiolytic, or antipsychotic drugs, or dopaminergic molecules, have been stopped at least 3 months before the inclusion to avoid any medication-induced biases of the results. Such biases were also minimized by our study design in which all patients received the 3 stimulation modalities (left-anodal/right-cathodal/sham), in a counterbalanced order permutation. Exclusion criteria were (1) psychiatric or neurologic diseases other than PSP; (2) contraindications for MRI or tDCS such as intracranial ferromagnetic devices, scalp/skull lesions, or epilepsy; and (3) major depression (Montgomery-Åsberg Depression Rating Scale [MADRS] > 20[25]) or major cognitive disorders (Mini-Mental State Examination [MMSE] < 15[26]; Frontal Assessment Battery [FAB] < 10[27]). Fifteen healthy controls were

also included to determine normative performance levels in the experimental language tasks. They were recruited via an announcement that healthy volunteers are needed for a research program, and they mostly were spouses or friends of the patients. Controls and patients with PSP had similar characteristics for handedness, sex, age, and years of education (χ^2 test for sex: $p > 0.05$; Mann-Whitney tests for age and years of education: both $p > 0.05$). All participants were native French speakers. Demographic data are summarized in table 1.

Standard protocol approvals, registrations, and patient consents

The study received approval from the local ethics committee (RCB-2013-A00734-41) and written informed consent was obtained from all participants. A clinical trial identifier number was not obligatory and not requested for this pretherapeutic proof-of-concept study.

General study design

We applied a double-blind sham-controlled crossover design in which each patient underwent 3 separate tDCS sessions: anodal and cathodal tDCS over the left and right DLPFC, respectively, and sham stimulation over the left DLPFC. To evaluate the effects of each tDCS modality, stimulation was immediately preceded and followed by experimental tasks assessing lexical and semantic access, language fluidity/initiation, and executive functions. Given that the period of offline effects of a single tDCS session is about 20–30 minutes,[28] we did not apply follow-up evaluations in this exploratory proof-of-concept study.

The order of the 3 stimulation sessions was counterbalanced across the patient cohort to avoid order biases (6 order permutations × 2 patients for each order). A computer-generated randomization list was created before the inclusions, and 12 sequentially numbered sealed envelopes containing the 12 (6 × 2) orders of the 3 stimulation sessions were saved in a research file box. Following the inclusion of a patient, the researcher responsible for the stimulation sessions opened the envelope without revealing the order information to any other person involved in the study. tDCS sessions were separated 7 days apart to prevent unlikely carryover effects.[28] In contrast to TMS protocols, the lack of lasting scalp sensations made patients totally unaware of the tDCS condition (anodal/cathodal/sham). To warrant a double-blind design, different researchers supervised the application of tDCS and of the experimental tasks.

Table 1 Demographic data of patients with progressive supranuclear palsy (PSP) and healthy controls (mean ± SD)

	Patients with PSP	Healthy controls
No. of participants	12	15
F/M	6/6	8/7
Age, y, mean ± SD	68.58 ± 6.35	64.13 ± 7.49
Handedness, R/L	12/0	15/0
Years of education, mean ± SD	14.25 ± 3.22	14.93 ± 2.69
Symptom duration, y, mean ± SD	4.33 ± 2.19	—

Brain stimulation

tDCS procedures were the same as previously described by Teichmann et al.[23] An MRI-guided stereotaxic frameless neuronavigation system (Brainsight, Rogue Research, Canada) guided tDCS electrode placement to ensure the shortest straight path to the cortical target. Stimulation targets for anodal and cathodal tDCS of the left and right DLPFC corresponded to the Montreal Neurological Institute (MNI) coordinates (x = −36, y = 32, z = 47) and (x = 39, y = 32, z = 45),[20] respectively, whereas a contralateral supraorbital electrode (right and left supraorbital region, respectively) was used as return. The scalp location of active tDCS electrodes corresponded to ~F3 (left-anodal) and ~F4 (right-cathodal) according to the 10–20 EEG reference system, and the contralateral supraorbital return electrodes were placed on ~AF8 and AF7, respectively. Active stimulation was delivered with round sponge electrodes (5.65 cm diameter, 25 cm^2 surface, Neuroelectrics SPONSTIM 25) at an intensity of 1.59 mA (current density 0.06 mA/cm^2). The current was kept at this intensity during 20 minutes before being ramped down along 30 seconds. During sham stimulation, the current was ramped up and down during 30 seconds at the initial and final phase of the session to emulate the transient skin itching sensations characterizing active stimulation.

To ensure safety and assess tolerance to stimulation, patients completed a tDCS adverse effects questionnaire[29] that rates side effects within a set of the most frequent effects reported in tDCS studies (e.g., itching, tingling, skin redness).

Computer simulations of current density distribution

A finite element method model was developed on a detailed standardized head volume (ICBM-NY) to determine the peak electric field, current density, and their distribution on the cortical surface. A mean anatomical MRI volume using data from 152 individuals (ICBM152/MNI152) was segmented into 6 conductive volumes: air, skin, skull, CSF, gray matter, and white matter for modeling. Lingering errors in continuity and detail were corrected manually within the image volumes at a resolution of 0.5 mm^3. MNI targets of the right and left DLPFC areas were coregistered to the ICBM-NY model in SPM8 to recreate the tDCS experimental conditions of the study.

Two tDCS conditions were modeled with scalp electrodes targeting the aforementioned MNI coordinates (shortest straight path to target): anodal and cathodal tDCS over the

left and right DLPFC, respectively. Stimulation electrodes and sponge pads (5.65 cm diameter, 25 cm^2 surface) were modeled in SolidWorks (Dassault Systems Corp., Waltham, MA) and imported into ScanIP for meshing. An adaptive tetrahedral meshing algorithm was used in ScanIP M-2017.06 (Simpleware, Exeter, UK) to generate meshes with approximately 10 million quadratic elements. Finite element method models were created in COMSOL multiphysics 5.1 (COMSOL, Inc., Burlington, MA) using electrostatic volume conductor physics with material conductivities defined as follows (in S/m): air, 1×10^{-15}; skin, 0.465; skull, 0.01; CSF, 1.65; gray matter, 0.276; white matter, 0.126; electrode, 5.99×10^{7}; saline-soaked sponge, 1.4. The former values were the same as previously published modeling work drawing on data from a combination of in vivo and in vitro measurements' employed in neurodegenerative patients.[23]

Internal boundary conditions between tissue layers were implemented to simulate direct current stimulation and assigned the continuity condition ($n^*[J1 - J2] = 0$), to solve the Laplace equation ($\nabla^*[\sigma \nabla V] = 0$). The surfaces of the cathodes were grounded ($V = 0$), while the surfaces of the anodes were assigned inward normal current densities calculated to produce 1.59 mA of stimulation. All other exterior surfaces were electrically insulated. The resulting cortical electric field was interpreted as a correlate for modulation. The radial electric field was calculated as the vector projection of the cortical electric field onto the cortical surface normal ($n \cdot E$).

General cognitive/language assessment

Assessment with standardized tests contributed to PSP diagnosis and to the constitution of a relatively homogenous cohort with patients having similar levels of cognitive impairment and disease duration. The general cognitive assessment included the MMSE,[26] the FAB,[27] Trail-Making Test A,[30] an evaluation of aphasia severity (Boston Diagnostic Aphasia Evaluation[31]), a picture naming test (D080[32]), and a verbal fluency test (phonemic and category fluency).[33] Healthy participants were tested with the MMSE and the FAB. Test scores are summarized in table 2.

Experimental tasks

Experimental language tasks were designed to tap semantic and lexical access, which contributes to language initiation/fluidity. They allowed, unlike standard aphasia tests, for the matching of the stimuli on linguistic variables between different intratask conditions and between version 1 and version 2 of the tasks (prestimulation or poststimulation).

The category judgment task was applied to assess access to semantic representations. Participants judged whether a given word item belonged to a "living" or a "nonliving" semantic category. The material included 2 versions (prestimulation and poststimulation) to avoid retest effects. Both versions contained 20 words representing living items and 20 words representing nonliving items. Words representing living and nonliving items, and words of both versions of the task, were matched for lexical frequency, number of letters, and number of phonemes (all Fs < 1).[34] Each stimulus was displayed in the center of a computer screen for 6 seconds. Participants were asked to press the left trackpad button for living items, and the right button for nonliving items, using respectively the index and the middle fingers of their dominant hand. The order of living and nonliving stimuli was randomized.

Table 2 General cognitive/language assessment, mean ± SD

	Patients with PSP	Healthy controls	Normative thresholds
MMSE	25.80 ± 3.0	29.33 ± 0.72	≥27
FAB	14.30 ± 2.50	17.67 ± 0.49	≥16
TMT-A	90.4 ± 20.7	—	<40
BDAE: aphasia severity scale	3.60 ± 0.89	—	>4
Category fluency (fruits/2 min)	14.33 ± 6.53	—	≥15
Phonemic fluency (P/2 min)	13.0 ± 1.41	—	≥15
DO80	74.30 ± 5.03	—	>75

Abbreviations: BDAE = Boston Diagnostic Aphasia Examination; DO80 = picture naming test; FAB = Frontal Assessment Battery; MMSE = Mini-Mental State Examination; PSP = progressive supranuclear palsy; TMT-A = Trail-Making Test version A.

The letter fluency task was used to assess lexical access and language initiation/fluidity. Participants were asked to generate orally in 1 minute as many words as possible beginning with a given letter (C or P). To limit retest effects, patients performed this task prior to and following stimulation either with the letter C (version 1) or P (version 2). Words beginning with C or P are similar in terms of number of items and they have a similar cumulative lexical frequency in French (both Fs < 1).[33]

To control for potential biases linked to executive dysfunction, independently from language deficits, we also tested tDCS effects on a spatial sequence generation task assessing executive control/attention capacities. Participants were asked to generate in 1 minute the highest number of sequences made of 4 items (white dots) within a set of 15 items arranged in a triangular configuration. They were requested to sequentially select on a tactile screen each item with the index finger of their dominant hand, and avoid repeating the same sequence or using items appearing in blue (blue dots). Two versions of the test with different spatial arrangements of white and blue dots were used during prestimulation and poststimulation.

The 2 language tasks were programmed with E-Prime software (Psychology Software Tools, Pittsburgh, PA) and were presented on a laptop computer (HP EliteBook 8770w). The

stimuli for the spatial sequence generation task were presented on a touch-sensitive screen tablet (HP Envy 8 x2). The order of version 1 and version 2 of each test was counterbalanced, with half of the patients receiving version 1 before tDCS (version 2 following tDCS) and half of the patients receiving version 2 before tDCS (version 1 following tDCS). The order of the tests was blocked: (1) letter fluency task, (2) spatial sequence generation task, (3) category judgment task. The tasks were completed in ~15 minutes, a period covered by the offline effects of 20 minutes of tDCS.[28]

The primary research questions were to explore whether tDCS over the DLPFC improves performance of patients with PSP in (1) the category judgment task (semantic access) or (2) in the letter fluency task (lexical access), while assigning a level of evidence corresponding to a Class III trial.

Data availability statement

Anonymized data, statistical methods, and experimental material not entirely published within the article will be shared by request from any qualified investigator.

Results

Computational model of current density distribution

Computer simulations predicted that both active tDCS stimulation strategies (left-anodal, right-cathodal) differentially modulate activity in the lateral and rostral aspects of their respective DLPFC targets. Directional current flow also indicated opposite modulatory effects.[35] The model characterized left-anodal stimulation as driving enhancements of activity across the left DLPFC and adjacent areas (where current flow is radially inward) and relative decreases (where current flow is radially outward) for right-cathodal tDCS. Moreover, as intended, both tDCS configurations (anodal tDCS and cathodal tDCS over the left and right DLPFC, respectively) generated an interhemispheric imbalance of prefrontal activity, with higher levels in left than right DLPFC.

Further supporting the efficacy of our electrode montage, the magnitude of the peak electric field and current density at each of the 2 MNI locations reached intensities (left and right DLPFC targets: 0.65 V/m and 0.18 A/m^2) comparable to those generated in prior tDCS studies showing preclinical efficacy, including investigations with substantiated neurophysiologic support.[36] The polarity of stimulation (anodal vs cathodal) was dependent on the orientation of the electric field with the cortical surface, which led to mixed polarities between the electrodes. However, currents in the regions of peak stimulation underneath the anode and cathode were predominately in the expected orientation (inward for anodal, outward for cathodal). Finally, our modeling work showed that the area of influence of tDCS fields spread across a cortical area, which encompassed the MNI targets of the left and right DLPFC. Results are illustrated in figure 1.

Experimental tasks at baseline: Patients vs controls

Analyses of variance (ANOVAs) showed that patients with PSP performed more poorly than healthy controls in the 2 language tasks: category judgment (75.8% ± 16.1% correct, 95% confidence interval [CI] 69.6%–80.2% [patients]; 98.8% ± 1.2% correct, CI 97.5%–99.1% [controls]; $F_{1,25}$ = 30.673, $p < 0.001$, CI of difference 18.1%–28.8%) and letter fluency (6.5 ± 4.9 words, CI 4.6–7.6 [patients]; 21.2 ± 5.8 words, CI 19–23.4 [controls]; $F_{1,25}$ = 48.989, $p < 0.001$, CI of difference 12.4–17.7). In the category judgment task, reaction times were slower in patients than in controls (1,615 ms ± 448 ms, CI 1,512 ms–1,825 ms [patients], 938 ms ± 145 ms, CI 879 ms–999 ms [controls]; $F_{1,25}$ = 30.357, $p <$ 0.001, CI of difference −896 ms to −564 ms). Performance in the spatial sequence generation task was poorer in patients than in controls (7 ± 2.9 sequences, CI 6–8 [patients]; 17.9 ± 2.9 sequences, CI 17.5–19.8 [controls]; $F_{1,25}$ = 165.8, $p <$ 0.001, CI of difference 10.1–13.2). Results are illustrated in figure 2.

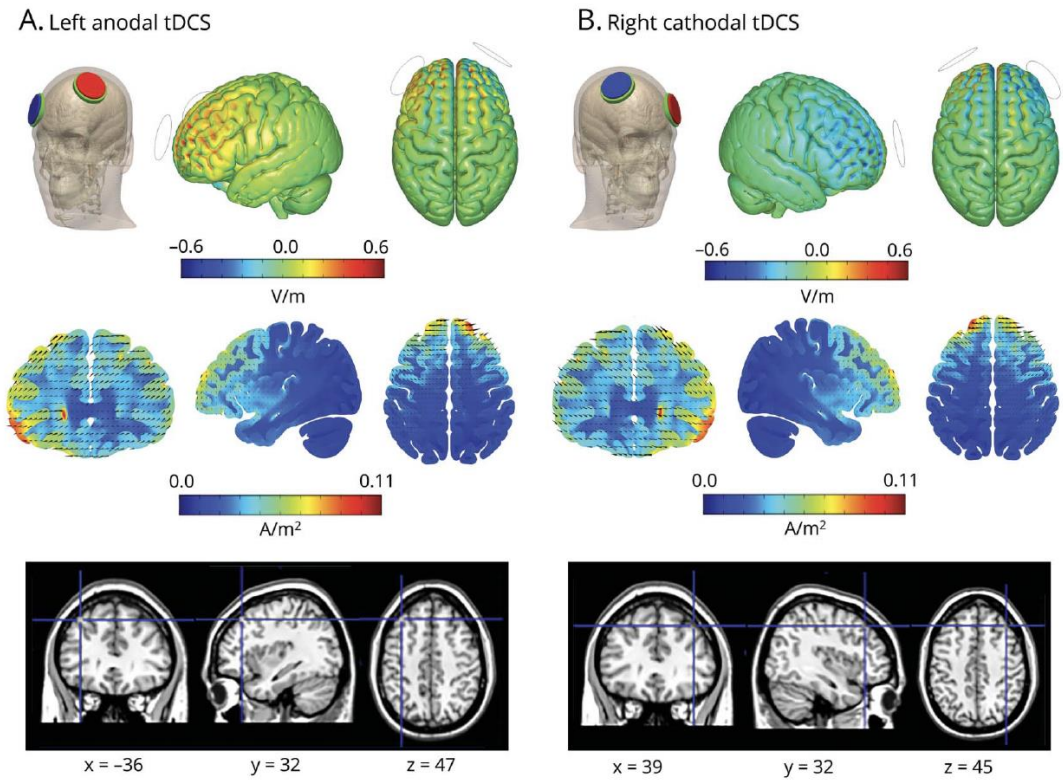
tDCS and language performance

ANOVAs contrasted prestimulation and poststimulation performance by comparing left-anodal and right-cathodal with sham stimulation. The independent variables were time point (prestimulation, poststimulation) and tDCS condition (left-anodal, right-cathodal, sham). Performance accuracy or reaction times were the dependent variables. Incorrect responses were excluded from the analyses of reaction times. Results are illustrated in figure 3 and table 3.

Results for the category judgment task showed a significant time point × tDCS condition interaction ($F_{2,22}$ = 5.850, p = 0.009). Restricted analyses demonstrated performance improvement following right-cathodal tDCS (81.7% ± 15.8% correct, CI 71%–91.5%), compared to prestimulation performance (71.7% ± 15.2% correct, CI 61.9%–81.1%; $F_{1,11}$ = 12.878, p = 0.004, CI of difference 3.4%–16.1%). In contrast, no effects between prestimulation vs poststimulation performance were found for sham stimulation (poststimulation 76.3% ± 18.8% correct, CI 63.9%–87.9%; prestimulation 75.2% ± 15.2% correct, CI 65.5%–84.8%; $F < 1$) or for left-anodal tDCS (poststimulation 76.2% ± 17.3% correct, CI 65.2%–87.1%; prestimulation 78% ± 17.7% correct, CI 66.8%–89.2%; $F < 1$). Results of the restricted analyses remained significant after correction for multiple comparisons using Bonferroni corrections. Baseline performance measured during the prestimulation test session was similar for the left-anodal, right-cathodal, and sham condition ($F_{2,33}$ = 0.497, p = 0.613). Left-anodal, right-cathodal, or sham tDCS did not show significant effects for reaction times (all Fs < 1).

Results for the letter fluency task showed no significant time point × tDCS condition interaction (F = 0.735, p = 0.467) but restricted analyses indicated improvement of poststimulation performance following left-anodal tDCS (7.3 ± 4.9 words, CI 4.2–10.5) compared to prestimulation performance (5.5 ± 4.5

Figure 1 Modeling of electric field and current density for anodal and cathodal transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC)



Predicted radial electric field and current density magnitude modeled for round 25 cm^2 sponge electrodes with a contralateral supraorbital reference on a standard head (ICBM-NY) for the 2 active electrode montages. (A) Left-anodal DLPFC tDCS. (B) Right-cathodal DLPFC tDCS, both with a contralateral supraorbital reference. Each panel presents an accurate account of relative electrode position and size with regards to head and scalp features. (Top) Anatomical model of electrode relative size and positioning, and radial electric field (V/m) distribution on cortical surface (by convention, the color scale was normalized so that cathodal [outward] electric field was presented in blue hues and anodal [inward] electric field in red hues); (middle) current density magnitude (A/m^2) and flow direction (current density magnitude was plotted in 2D slices with uniformly distributed arrows sized proportionally to the local current density magnitude); (bottom) coregistered coronal and sagittal MRI centered on Montreal Neurological Institute target coordinates (x = −36, y = 32, z = 47) and (x = 39, y = 32, z = 45) for left and right prefrontal targets, respectively. Note that whereas right-cathodal tDCS induced peak outward electrical field in the right prefrontal lobe, left-anodal tDCS induced opposite effects in a similar location of the left prefrontal lobe. The regions in which the effects of anodal or cathodal tDCS were modeled encompassed the coordinates of the intended cortical targets and colocalized tightly with them.

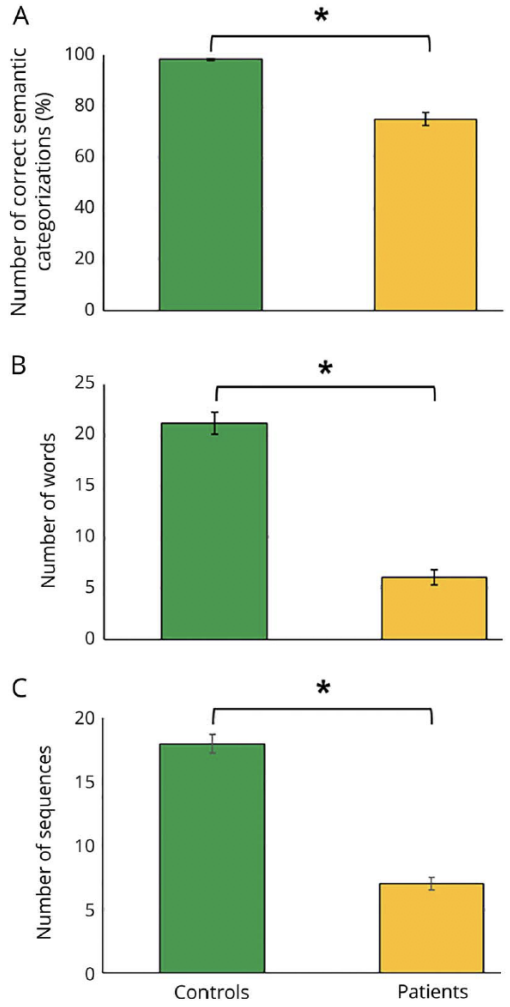
words, CI 2.6–8.4; $F_{1,11} = 6.969$, $p = 0.023$, CI of difference 0.3–3.4). In contrast, right-cathodal tDCS (prestimulation 6 ± 4.5 words, CI 3.1–8.9; poststimulation 7.1 ± 4.4 words, CI 4.4–9.9) and sham stimulation (prestimulation 6.8 ± 4.7 words, CI 3.8–9.8; poststimulation 7.5 ± 5.7 words, CI 3.8–11.2) did not modify performances (both Fs < 1). Results of the restricted analyses remained significant after correction for multiple comparisons using Bonferroni corrections. Baseline performance measured during the prestimulation test session was similar for the left-anodal, right-cathodal, and sham condition ($F_{2,33} = 0.259$, $p = 0.773$).

For the executive control task (spatial sequence generation) there was no time point × tDCS condition interaction ($F < 1$). Moreover, restricted analyses showed no differences between poststimulation and prestimulation performance for left-anodal (prestimulation 6.9 ± 3.5 sequences, CI 4.7–9.1; poststimulation 7.3 ± 4.9 sequences, CI 4.1–10.4), right-cathodal (prestimulation 6.6 ± 2.7 sequences, CI 4.9–8.3; poststimulation 7.3 ± 2.8 sequences, CI 5.3–9.2), and sham stimulation (prestimulation 7.5 ± 2.8 sequences, CI 5.7–9.3; poststimulation 7 ± 3.4 sequences, CI 4.8–9.2) (all Fs < 1).

To further strengthen these results, we checked for unlikely carryover effects of the 3 one-week-distanced tDCS sessions[28] by comparing the 3 prestimulation baselines for the 2 efficient tDCS modalities (left-anodal for letter fluency, right-cathodal for category judgment). Friedman tests showed that there were no differences among the 3 prestimulation performances (category judgment $\chi^2[2] = 2.79$, $p = 0.25$; letter fluency $\chi^2[2] = 4.33$, $p = 0.12$), demonstrating the absence of carryover biases.

We also checked that depression levels have not influenced the stimulation outcomes by performing Pearson correlations between depression scores (MADRS) and stimulation-driven performance improvements in the category judgment and the letter fluency task. There was no significant correlation between depression scores and performance improvements of category judgment ($r = -0.297$, $p = 0.35$) and letter fluency ($r = 0.018$, $p = 0.96$).

Figure 2 Performance of patients with progressive supranuclear palsy and healthy controls in the experimental tasks (mean values and standard error bars)



(A) Category judgment task. (B) Letter fluency task. (C) Spatial sequence generation task.

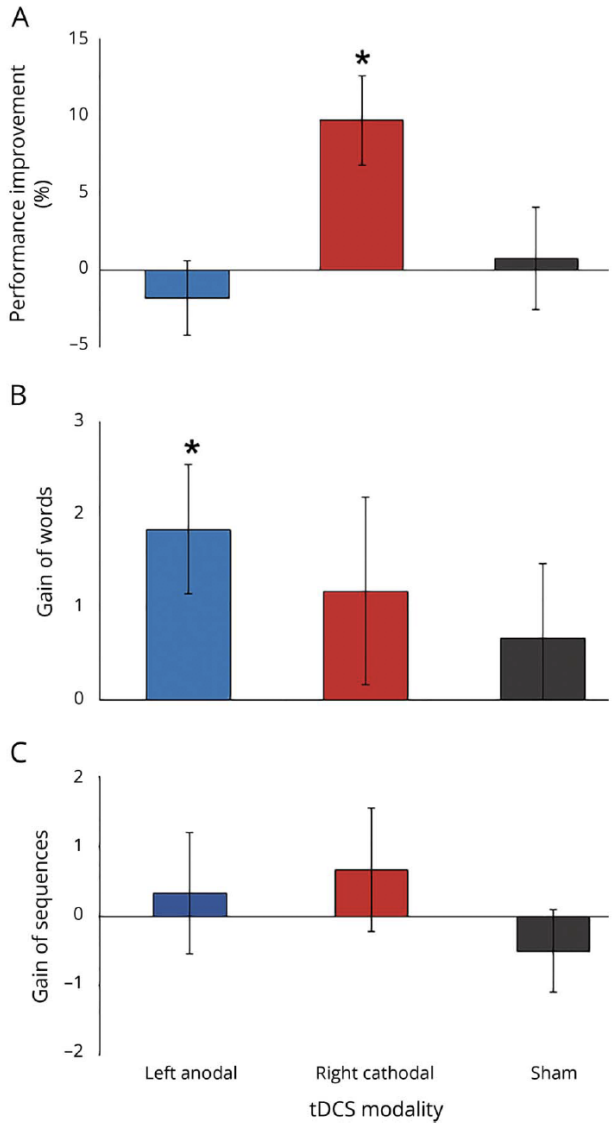
No side effects or any discomfort, as assessed by the tDCS adverse effects questionnaire,[29] were reported by any patient during or after the stimulation sessions.

Discussion

We explored the ability of tDCS to modulate language impairments in a cohort of patients with PSP using a double-blind sham-controlled crossover design. According to the principle of interhemispheric inhibition, we tested 2 stimulation strategies: anodal tDCS over the left DLPFC to directly boost the activity of language-related prefrontal regions, and cathodal tDCS over the right DLPFC to suppress inhibitory interhemispheric influences exerted by right prefrontal over left prefrontal systems. Our results show improvement of semantic access following right-cathodal tDCS as measured by the category judgment task. They also indicate that left-anodal tDCS improves lexical access and language initiation/fluidity as measured by the letter fluency task. In contrast, tDCS had no influence on executive capacities as assessed by the spatial sequence generation task. Furthermore, modeling of current distribution demonstrated that both anodal and cathodal tDCS reached sufficient peak current on the intended targets to influence adjacent prefrontal regions within the targeted hemisphere. Both tDCS strategies increased interhemispheric differences of prefrontal activity while boosting the left DLPFC. Our findings provide evidence for language improvements in patients with PSP via noninvasive neurostimulation and set the stage for therapeutic uses of tDCS with multiday regimens aiming at longer-lasting language effects by promoting neuroplasticity. Our results also enrich current knowledge about the role of the left DLPFC in language processing, and especially of lexical and semantic access mechanisms.

The issue whether transcranial stimulation can modulate language-related brain networks in neurologic diseases remains largely unsolved given contradicting results and methodologic shortcomings of most of the previous studies on poststroke or degenerative aphasia. The majority of these studies did not use double-blind or sham-controlled designs, and the different stimulation modalities such as anodal and cathodal tDCS, or high- and low-frequency TMS, were not counterbalanced in crossover designs. In addition, TMS studies using sham-controlled designs could not apply an effective sham condition given the hard-to-cancel sensory side effects, allowing patients to easily distinguish active from sham TMS.[37] The present study using a double-blind, sham-controlled, and counterbalanced crossover design aimed at clarifying whether tDCS can modulate language processing and its underlying networks to generate a rationale for its therapeutic application. Our findings demonstrated statistically significant effects on language processing by modulating prefrontal brain networks, as shown by our behavioral results with the support of modeling data on tDCS current distribution. They also strengthen prior findings by authors who highlighted the need for a rigorous methodology in pretherapeutic transcranial stimulation studies, which is indispensable for demonstrating statistically significant tDCS-induced language effects.[23] Our data furthermore indicate that stimulation effects are linked to the modulation of language-related processes rather than to nonspecific factors such as effects on general executive functioning. The probable language specificity in our study is suggested by the absence of tDCS effects on the non-language-related executive control task (spatial sequence generation). One should however note that tDCS generates effects on relatively large cortical regions, which could have modulated the activity of language-unrelated executive components of the left prefrontal cortex. Such putative modulations, not captured by the spatial sequence generation task, encourage future investigations using various executive tasks to explore whether tDCS-driven

Figure 3 Gain of function in the experimental tasks for the poststimulation/prestimulation contrast, comparing left-anodal and right-cathodal to sham transcranial direct current stimulation (tDCS) (mean values and standard error bars)



(A) Category judgment task. (B) Letter fluency task. (C) Spatial sequence generation task. Statistically significant gain of function for performance (poststimulation – prestimulation) is observed for the category judgment task after right-cathodal tDCS and the letter fluency task following left-anodal tDCS. Neither left-anodal nor right-cathodal tDCS had statistically significant effects on performances in the spatial sequence generation task testing executive control processes.

Table 3 Mean ± SD absolute values for prestimulation and poststimulation performances, for each task and stimulation modality

	Category judgment (total of 40 items)	Letter fluency (number of words)	Spatial sequence generation (number of sequences)
Prestimulation anodal	31.3 ± 6.8	5.5 ± 4.5	6.9 ± 3.5
Poststimulation anodal	30.6 ± 6.6	7.3 ± 4.9	7.3 ± 4.9
Prestimulation cathodal	28.7 ± 5.8	6.0 ± 4.5	6.6 ± 2.7
Poststimulation cathodal	32.6 ± 6.2	7.1 ± 4.4	7.3 ± 2.8
Prestimulation sham	30.2 ± 5.8	6.8 ± 4.8	7.5 ± 2.8
Poststimulation sham	30.5 ± 7.2	7.5 ± 5.8	7.0 ± 3.4

boosting of the left DLPFC might also improve some non-language-related executive capacities.

How does tDCS modulate the activity of cortices and brain networks underpinning language/semantic processing? In the present investigation, stimulation may have exerted a direct effect on language-related regions of the left prefrontal lobe following left-anodal tDCS, whereas similar effects were also indirectly achieved following right-cathodal tDCS via the suppression of interhemispheric inhibitory interactions between right/left DLPFC systems. This explanation finds support in our modeling study of current distribution in prefrontal regions revealing opposite local effects for anodal and cathodal tDCS on the left and right DLPFC, respectively. The left DLPFC, which was boosted in activity by both active stimulation strategies, has been shown to contribute to several language-related processes such as language activation/initiation and access to the mental lexicon and the semantic system.[38,39] However, this left prefrontal region does not host per se lexical or semantic representations. Nonetheless, it might contribute to the activation of search/retrieval processes for representations implemented in interconnected distant cortical areas of the left hemisphere such as the anterior temporal cortex for semantic information[40] or the temporal–parietal region for lexical representations.[41] Thus, in addition to direct effects on prefrontal regions, tDCS probably also modulates the activity of remote language areas via structural connectivity linking the stimulated left prefrontal cortices and the left temporal–parietal junction via the left arcuate fasciculus,[42] and anterior temporal cortices via the uncinate fasciculus.[42] This explanation is also coherent with recent fMRI studies indicating that anodal tDCS increases brain excitability in the targeted cortical area and modulates its functional connectivity with distant brain regions.[43] More specifically, an fMRI investigation has shown that anodal tDCS over the left DLPFC during a verbal fluency task increased functional connectivity between frontal and inferior parietal regions, which are part of the lexicon-related temporal–parietal junction.[44] Likewise, improvement of letter fluency in Parkinson disease after left-anodal DLPFC tDCS[45] suggests activity modulation of the left striatum contributing to lexical processing.[46] However, additional studies are needed to investigate the modulation of functional connectivity and the effects of tDCS on remote cortical regions.

Our study also allows for a comparison of effects between right-cathodal vs left-anodal tDCS. Regarding right-cathodal tDCS, the notion that local activity can be manipulated by suppressing transcallosal inputs from the opposite hemisphere relies on mutually inhibitory interhemispheric projections.[16] The modulation of interhemispheric interactions by noninvasive neurostimulation has been exploited in healthy participants and brain-damaged patients targeting right and left prefrontal, parietal, and temporal systems related to visuospatial attention,[47] verbal/spatial working memory,[48] or language/semantic performance.[15,21,23] Our results confirm that both tDCS strategies generate statistically significant language effects, yet in different domains. Semantic access (category judgment) was improved after right-cathodal tDCS whereas lexical access and language initiation/fluidity (letter fluency) was sensitive to left-anodal stimulation. These findings substantiate the validity of both left-anodal and right-cathodal tDCS approaches regarding language performance. However, they cannot provide an explanation regarding the differential effects of distinct stimulation strategies on distinct language processes.

Our findings also shed light on the role of prefrontal language systems. The results of the category judgment task revealing disorders of semantic access are consistent with investigations showing semantic difficulties in PSP.[6,9–12] In addition, our tDCS data demonstrate that semantic dysfunction can be improved by modulating left DLPFC activity. This finding is coherent with studies in healthy adults showing that the left DLPFC is activated in fMRI paradigms using semantic tasks.[49] Furthermore, probable tDCS effects on the connectivity with remote semantic-related areas is consistent with the fact that white matter tracts critical for semantic processes such as the uncinate fasciculus are damaged in PSP.[50] The results of the letter fluency task showing impaired performance in patients confirm that patients with PSP have verbal fluency deficits and deficient lexical access mechanisms.[9,10] Thus, in accordance with anatomo-functional correlation studies in PSP,[1,5] our data strengthen the view that the left DLPFC is a key region for the activation of language processes. More specifically, our findings suggest that the left DLPFC is part of a system controlling search mechanisms in the lexicon and in the semantic system, which are implemented by remote brain regions including the temporal–parietal junction and anterior temporal cortices.

tDCS delivered over the DLPFC efficiently seems to generate transitory modulations of left hemispheric language networks dedicated to several aspects of linguistic/semantic processing in patients with prefrontal lesions. This suggests pretherapeutic evidence for the improvement of language initiation and lexical and semantic access in PSP. The proof-of-concept provided by our study has implications for future uses of noninvasive neurostimulation as a therapeutic strategy in neurodegenerative language disorders. To achieve this goal, and to strengthen our findings, double-blind and sham-controlled trials with multiday tDCS regimens engaging enduring plasticity phenomena will be necessary to confirm therapeutically meaningful long-lasting effects in large PSP cohorts, or in other prefrontal pathologies affecting language processing.

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Continued

Appendix (continued)

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Modulation of language impairments in behavioral variant of Frontotemporal Dementia after transcranial direct current stimulation of the prefrontal cortex

Résumé en français

La variante comportementale de la démence frontotemporale (DFT) est une maladie neurodégénérative caractérisée par une atrophie bilatérale du cortex préfrontal, notamment des régions dorsolatérales, ventromédiales et orbitofrontales, régions qui sous-tendent les fonctions exécutives et contribuent à la régulation du comportement. La DFT entraîne une détérioration progressive du comportement et des capacités exécutives et une rupture de l'initiation / activation du langage, y compris des mécanismes de recherche dans le lexique mental, comme le montrent les déficits dans des tâches de dénomination et de fluence verbale, qui sont sous-tendues par le cortex préfrontal dorsolatéral gauche (CPFDL). À ce jour, aucun traitement efficace pour les troubles cognitifs de la DFT n'est actuellement validé. L'augmentation de la population âgée entraînant une plus grande prévalence des maladies neurodégénératives, il existe actuellement un besoin crucial de nouvelles approches thérapeutiques. Une de ces approches est la stimulation transcrânienne, y compris la stimulation transcrânienne à courant continu (STCC). La stimulation transcrânienne a généré des résultats prometteurs dans diverses maladies affectant les réseaux langagiers. Des données sur les maladies dégénératives ont démontré la capacité de la stimulation du CPFDL à favoriser l'accès lexical dans l'aphasie primaire progressive, la maladie d'Alzheimer, la maladie de Parkinson et la paralysie supranucléaire progressive. Deux études ont exploré les effets de la STCC sur la DFT, mais le petit nombre de patients a produit un niveau de preuve limité, ce qui encourage donc des investigations supplémentaires sur cette maladie.

La présente étude visait à évaluer les effets modulateurs d'une seule session de STCC appliquée sur le CPFDL sur l'initiation / l'activation du langage chez des patients atteints de DFT. Sur la base du principe d'inhibition interhémisphérique selon lequel les connexions transcalleuses entre les deux hémisphères cérébraux induisent une inhibition réciproque de l'activité corticale controlatérale, nous avons appliqué trois séances de stimulation individuelle: (a) stimulation anodale sur le CPFDL gauche, pour réactiver les processus langagiers mis en œuvre par les régions péri-lésionnelles (b) la stimulation cathodale sur le CPFDL droit, pour réduire l'inhibition exercée

par les systèmes de l'hémisphère droit sur le réseau langagier dominant gauche et (c) la stimulation placebo.

Utilisant un design croisé, en double-aveugle et contrôlé par placebo et une cohorte de 12 patients DFT, nous avons évalué la capacité de moduler l'activité du CPFDL gauche via une stimulation anodale gauche et cathodale droite, et nous les avons comparés à une stimulation placebo en trois sessions espacées d'une semaine. Chaque séance a eu une durée de 20 minutes avec une intensité du courant de 1.59mA délivré par des électrodes de 25cm^2. Une tâche de fluence littérale et une tâche de dénomination ont été appliquées immédiatement avant et après les sessions de stimulation en tant que marqueurs de la modulation potentielle du langage. Une tâche de génération de séquences spatiales évaluant les capacités de contrôle / attention exécutives a également été testée pour contrôler les biais potentiels liés au dysfonctionnement exécutif. Pour avoir des valeurs normatives pour chaque tâche, 15 sujets sains ont aussi été recrutés.

Les patients atteints de DFT étaient altérés dans toutes les tâches expérimentales initiales, comme le montre la comparaison avec les sujets sains. Les performances contrastées en post-stimulation par rapport à la pré-stimulation n'ont montré aucune amélioration dans aucune des tâches quelle que soit la modalité de stimulation. Un modèle computationnel de la distribution du courant a corroboré l'impact attendu de la STCC anodale gauche et cathodale droite sur le CPFDL ciblé.

Notre étude n'a pas pu fournir de preuve de concept pour l'amélioration du langage par le biais de la STCC dans des patients atteints d’une DFT. Cependant, nos résultats, combinés à des études antérieures, suggèrent fortement que la recherche sur l'efficacité de la STCC dans des maladies neurodégénératives affectant le langage devrait également prendre en compte des questions supplémentaires telles que la gravité du déficit du langage, des facteurs anatomiques, notamment le degré d'atrophie, et l'application de la STCC à des régions cibles du réseau langagier qui soient relativement intactes.

Modulation of language impairments in behavioral variant of Frontotemporal Dementia after transcranial direct current stimulation of the prefrontal cortex

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Abstract

Objective: The behavioral variant of frontotemporal dementia (bv-FTD) is a neurodegenerative disease characterized by bilateral atrophy of the prefrontal cortex, including dorsolateral, ventromedial and orbitofrontal regions. It leads to a gradual deterioration of behavior, executive capacities, a breakdown of language initiation/activation and impaired search mechanisms in the mental lexicon. To date, two studies have explored the modulation of language deficits in bv-FTD patients with transcranial direct current stimulation (tDCS), yet with inconsistent results. **Methods:** Using a sham-controlled double-blind crossover design in a cohort of bv-FTD patients (n=12), we explored the impact on language performance of a single session of tDCS delivering anodal or cathodal tDCS, over the left and right DLPFC, respectively, compared to sham stimulation. A *Letter fluency* task and a *Picture naming* task were performed immediately prior and following 20 minutes of tDCS, to assess modulatory effects on language. A *Spatial sequence generation* task measuring executive control/attention capacities was also tested to control for potential biases linked to the modulation of executive dysfunction. **Results:** Bv-FTD patients were impaired in all evaluation tasks at baseline compared to healthy controls. Moreover, a computational Finite Element Model of current distribution corroborated the intended impact of left-anodal and right-cathodal tDCS on the targeted DLPFC regions. However, none of the three tasks showed statistically significant evidence of language improvements caused by active tDCS stimulation compared to sham. **Conclusions:** Our pre-therapeutic study failed to provide proof-of-concept for language improvements by left anodal or right cathodal prefrontal tDCS in bv-FTD patients. Our finding strongly suggests however that research evaluating the modulatory role of tDCS in neurodegenerative language impairments must carefully weigh the influence of variables such as baseline language severity and the degree of cortical atrophy affecting the stimulated

region. The delivery of tDCS on relatively spared regions of the language network instead of areas already affected by atrophy should be strongly considered.

Key words: Frontotemporal dementia, language impairment, dorsolateral prefrontal cortex, transcranial direct current stimulation (tDCS), non-invasive neuromodulation, plasticity, neurodegenerative diseases

Introduction

The behavioral variant of frontotemporal dementia (bv-FTD) is an early onset (<65 years of age) neurodegenerative disease significantly impacting patients' daily life (Knopman and Roberts, 2011). It is characterized by bilateral atrophy of the prefrontal cortex, encompassing dorsolateral, ventromedial and orbitofrontal areas (Rosen et al., 2002; Seeley et al., 2008; Whitwell et al., 2009), regions known to subtend executive processes and contribute to the regulation of behavior (Cummings, 1993; Peters et al., 2006).

According to revised diagnosis criteria by Rascovsky et al. (2011), bv-FTD leads to a gradual deterioration of behavior resulting in apathy, decrease of social convenience, impulsivity and disinhibition. Additionally, executive capacities and language production are severely impaired (Kramer et al., 2003; Le Ber et al., 2006; Ranasinghe et al., 2016; Rascovsky et al., 2011). Behavioral FTD patients present degraded communication abilities, caused by a progressive breakdown of language initiation/activation and word search mechanisms in the mental lexicon. These symptoms can be objectivated as difficulties in naming and verbal fluency tasks (Hardy et al., 2016), which are contributed by left dorsolateral prefrontal systems (Sanjuan et al., 2010; Valero-Cabré et al., 2019). To date, pharmacological trials in bv-FTD have failed to demonstrate significant benefits (e.g., Vercelletto et al., 2011; Boxer et al., 2013), and no effective treatment for cognitive impairment is currently validated. Speech therapy has shown benefit for language dysfunction, but no proof of generalization to untrained items or long-lasting improvements (Cadório et al., 2017).

With the increase of the elderly population and the higher prevalence of neurodegenerative diseases, a crucial need for non-pharmacological neuromodulation therapies is emerging. Non-invasive brain stimulation technologies, such as Transcranial Magnetic Stimulation (TMS) and

transcranial Direct Current Stimulation (tDCS) have shown the ability in healthy individuals to modulate brain systems and improve cognitive functions such as perception, attention, language, decision making or memory (e.g. Cattaneo et al., 2011; Chanes et al., 2013; Floel et al., 2012). This technique uses a mild electrical field conveyed between two surface electrodes to electrically polarize regions of the cerebral cortex and modulate resting membrane potential of exposed neurons, rendering them more or less prone to discharge action potentials and engage in synaptic transmission (Nitsche and Paulus, 2000; Suemoto et al., 2014). Neurodegenerative diseases encompassing large cortical areas such as bv-FTD might prove particularly suited to the spatially broad action of tDCS compared to the exquisite focality characterizing TMS applications (Torres et al., 2013). Moreover, thanks to its low cost, excellent safety profile, and portability, this technique holds promise to increase activity in the atrophic cortical regions and enhance cognitive function in neurodegenerative disorders.

Transcranial DCS has already generated beneficial outcomes in several diseases affecting language networks. In post-stroke aphasia for example, the stimulation of left hemisphere language-related regions boosted the recovery of naming abilities (Cotelli et al., 2011; Wu, Wang and Yuan, 2015). Moreover, delivered to the dorsolateral prefrontal cortex (DLPFC), which is one of the most affected regions in bv-FTD, tDCS has shown to induce facilitation of verbal fluency (e.g. Sanjuan et al., 2010) and improvement of lexical access (e.g., Fertonani et al., 2010). In several neurodegenerative diseases, tDCS stimulation of the DLPFC has promoted lexical access, such as in Primary Progressive Aphasia (Trebbastoni et al., 2013; Roncero et al., 2017), Alzheimer's disease (Cotelli et al., 2008; Roncero et al., 2017), Parkinson's disease (Pereira et al., 2013) and Progressive Supranuclear Palsy (Valero-Cabré et al., 2019). However, to date, only two studies have investigated the effects of tDCS in bv-FTD, with inconsistent outcomes (Huey et al.,

2007; Agarwal et al., 2016). All in all, the low number of patients tested and the fragile level of evidence encourage further investigations.

The present study sought to evaluate the modulatory effects of a single tDCS session applied over the left or right DLPFC on language initiation/activation in bv-FTD patients. We capitalized on interhemispheric inhibition principles (Ferbert et al., 1992), upon which transcallosal bilateral connections mediate rivalrous inhibitory interactions of cortical activity between the two hemispheres. In such connectivity framework, we tested and compared across 3 independent stimulation sessions: (a) anodal stimulation over the left DLPFC aiming to improve language processes implemented by left hemisphere peri-lesional regions; (b) cathodal stimulation over the right DLPFC to reduce the inhibition that right hemisphere systems exert on the left dominant language network, and (c) sham tDCS to rule out improvements caused by placebo effects or intrasession learning effects. A *Letter fluency* task and a *Picture naming* task were used to evaluate tDCS effects on language initiation/activation, whereas a nonverbal executive control task was used to tease apart language-specific effects from an impact on executive processes.

Materials and Methods

Participants

Twelve bv-FTD patients were recruited at the National Reference Center for "Rare Dementias" of the Pitié-Salpêtrière Hospital, Paris, France. All participants were native French speakers. The diagnosis was established by expert clinicians following international diagnostic criteria for bv-FTD (Rascovsky et al., 2011), including progressive deterioration of behavior and executive capacities characterized by at least 3 of the following 6 criteria: disinhibition, loss of empathy, apathy, perseverative or compulsive behaviors, hyperorality and executive dysfunction,

including low verbal fluency. Diagnosis was also supported by neuroimaging (MRI) signs such as prefrontal atrophy (Rascovsky et al., 2011). None of the patients were under medication interfering with central nervous system activity during their participation in the study.

Exclusion criteria were (i) Psychiatric disorders or neurologic diseases other than bv-FTD; (ii) Contra-indications to MRI or tDCS, such as the presence of intracranial ferromagnetic devices, scalp or skull lesions or epilepsy; and (iii) Major depression (MADRS >20 [Montgomery Asberg Depression Rating Scale], Montgomery and Asberg, 1979), or major cognitive disorders (MMSE <15 [Mini-Mental State Examination], Folstein et al., 1975; FAB <10 [Frontal Assessment Battery], Dubois et al., 2000). Fifteen healthy controls, with similar characteristics as patients for handedness, gender, age and years of education, were used to determine normative performance levels in our evaluation tasks. The study received approval from the local Ethics Committee (Protocol STIMLANG, Ile-de-France I, Paris, France) and written informed consent was obtained from all the patients and healthy controls. Demographic data are summarized in Table 1.

Table 1. Demographic data of bv-FTD patients and healthy controls (Mean ± Standard deviation)

	Bv-FTD patients	**Healthy controls**
Number of participants	12	15
Sex (Women, Men)	4W/7M	8W/7M
Handedness (R/L)	12R	15R
Age	63.08 ± 11.70	64.13 ± 7.49
Years of education (years)	14.91 ± 3.73	14.93 ± 2.69
Symptom duration	3.04 ± 2.26	--

Study design

We applied a double-blind, sham-controlled crossover design in which each bv-FTD patient of our cohort underwent 3 independent tDCS sessions in 3 separate weeks consisting in: anodal tDCS delivered over the left DLPFC, cathodal tDCS over the right DLPFC and sham stimulation over the left DLPFC. Each stimulation session was preceded and immediately followed by a series of computer-based behavioral paradigms to evaluate the impact of each stimulation condition tested. The order of the 3 stimulation sessions was counterbalanced across patients to avoid order biases (6 order permutation, 2 patients for each order). Stimulation sessions were set a week apart to prevent unlikely carry-over effects and ensure independency of interventions. At difference to TMS protocols, the lack of accompanying tactile scalp sensations or auditory patterns characterizing tDCS made patients totally unaware of the stimulation condition (anodal, cathodal or sham) delivered on each session. The double-blind character of our design was warranted by asking two different investigators to be in charge either of tDCS application or behavioral evaluations of language and executive functions.

Brain stimulation

For brain stimulation, we followed the exact same tDCS procedures previously described in different populations of neurodegenerative patients (Teichmann et al., 2016, targeting the right and left anterior temporal lobes in sv-PPA patients; Valero-Cabré et al., 2019, targeting the right and left DLPFC in PSP patients). In short, we guided electrode placement on the scalp of each patient minimizing the straight path to reach from the skin surface a well-defined cortical target by means of an MRI-guided stereotaxic frameless neuronavigation system (Brainsight, Rogue Research, Canada). Left anodal and right cathodal tDCS of DLPFC regions targeted the following MNI (Montreal Neurological Institute) coordinates [x=-36, y =32, z =47] and [x=39, y=32, z=45]

(Cotelli et al., 2008; Valero-Cabré et al., 2019), respectively. A contralateral supraorbital electrode (right and left supraorbital regions, respectively) was used as return electrode on each montage. The location of active electrodes corresponded approximately to ~F3 (for left anodal DLPFC) and ~F4 (right cathodal DLPFC) sites of the 10-20 EEG reference system, whereas the contralateral supraorbital return electrode was placed either on AF8 and or AF7. Stimulation was delivered through round sponge electrodes (5.65cm diameter, 25cm^2 surface, Neuroelectrics [NE026a] SPONSTIM 25) at an intensity of 1.59 mA (current density of 0.06 mA/cm^2). Current was ramped up for 30 seconds and kept on at 1.59 mA during 20 minutes before being ramped down for 30 seconds. Emulating the same transient skin itching sensations characterizing the first and last 10-20 seconds of active stimulation, the sham tDCS condition was ramped up and down during 30 seconds at the initial and final phase of the 20-minute stimulation blocks.

To ensure safety, and gauge the level of comfort and tolerance to stimulation, patients were asked to fill a '*questionnaire* of *tDCS adverse effects'* (Brunoni et al., 2011) based on a likert scale assessing patients' sensations in the most frequent adverse effects reported for tDCS.

Computer simulations of current density distribution

A Finite Element Method model was developed on a detailed standardized head volume (ICBM-NY) to determine the peak electric field, current density, and their distribution on the cortical surface. Current density magnitude was overlaid in MRI sections with uniformly distributed arrows sized proportionally to local levels of current density. The two tDCS conditions applied in this study were modeled (Figure 1). Find details on the modeling procedures of DLPFC stimulation with identical parameters in Valero-Cabré et al. (2019).

General cognitive/language assessment

Assessment with standardized tests contributed to the diagnosis of bv-FTD and to the constitution of a relatively homogenous cohort with patients having similar levels of cognitive impairment and disease duration. The general cognitive assessment included the MMSE (Folstein et al., 1975), the FAB (Dubois et al., 2000), the Trail Making Test A and B (Reitan, 1958), an evaluation of aphasia severity (Boston Diagnostic Aphasia Evaluation) (Mazaux and Orgogozo, 1982), a picture naming test (D080, Deloche and Hannequin, 1997) and a verbal fluency test comprising phonemic and category fluency (Cardebat et al., 1990). Healthy participants were tested with the MMSE and the FAB. Test scores are summarized in Table 2.

Table 2. General cognitive/language assessment (Mean scores ± Standard deviation)

	Bv-FTD patients	**Healthy controls**	**Normative thresholds**
MMSE	25 ± 4.53	28.33 ± 0.72	≥ 27
FAB	14 ± 2.07	17.67 ± 0.49	≥ 16
BDAE – aphasia severity scale	4 ± 0.4	--	> 4
Phonemic fluency (P/2min)	7 ± 4.47	--	≥ 15
Category fluency (animals/2min)	13 ± 5.44	--	≥ 15
DO80	35 ± 4.03	--	> 75
TMT A	61 ± 27.29	--	≤ 40
TMT B	178 ± 90.61	--	≤ 92

Evaluation tasks

Each stimulation session was preceded and followed by language performance assessments aiming to monitor potential modulatory effects of tDCS following vs preceding stimulation. In order to limit the confounding of learning effects between the pre- and post-stimulation, each test

had two computerized versions matched according to a series of psycholinguistic variables, presented in counterbalanced order across our 12 participants. A *Letter fluency* task was used to assess the initiation/activation of language and lexical access. Participants were asked to generate orally in one minute as many words as possible beginning with a given letter ("C" [version 1] or "P" [version 2]), displayed on the computer screen and provided orally by the examiner (Figure 2A). Words beginning with "C" or "P" are similar in terms of number of items and they have a similar cumulative lexical frequency in French (both Fs < 1) (New et al., 2004).

A *Picture naming* task explored the activation of access mechanisms to lexical and semantic representations. The material included the naming of 40 images from two databases of images (Bonin et al., 2003; Snodgrass and Vanderwart, 1980) (Figure 2B). For both versions of the test, the material was matched for image visual complexity, word lexical frequency (New et al., 2004) and word and image familiarity. Each image was displayed on the computer screen for 8 seconds, after which the lack of a response was counted as an incorrect answer. The number of correct answers is a marker of lexico-semantic access abilities and reaction time (RT) was used as a marker of language initiation skills.

To control for potential biases linked to the modulation of executive dysfunction, independently from language deficits, the impact of tDCS on a *Spatial sequence generation* task assessing executive control/attention capacities was also tested. Participants were asked to generate in 1 minute the highest number of sequences made of 4 items (white dots) within a set of 15 items arranged in a triangular configuration (Figure 2C). They were requested to sequentially select on a tactile screen each item with the index finger of their dominant hand and avoid repeating the same sequence or using items appearing in blue (blue dots). The order of the tests preceding

or following the tDCS sessions was blocked as follows: 1) *Letter fluency* task, 2) *Spatial sequence generation* task and 3) *Picture naming* task.

The two language tasks were programmed with E-Prime software (Psychology Software Tools, Pittsburgh, PA) and presented on a laptop computer (HP EliteBook 8770w, USA). The stimuli for the *Spatial sequence generation* task were presented on a touch-sensitive screen tablet (HP Envy 8 x2). Patients were sitting in front of the computer that automatically recorded their responses in the presence of an examiner. The cumulative duration of the 3 tasks was consistent with the period during which the effects of tDCS remained active and significant (approximately ~20 minutes) according to observations made on the primary motor cortex and cortico-spinal tracts (Priori et al., 2003).

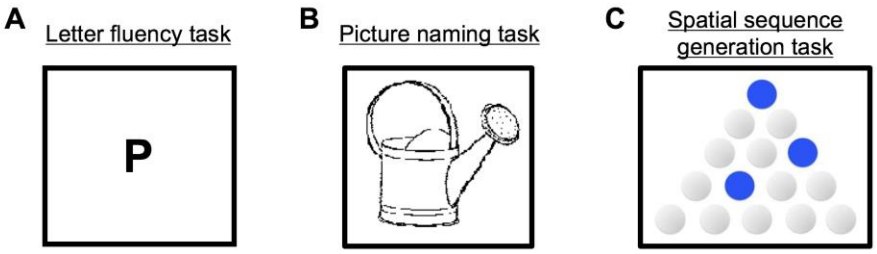

Figure 2. Illustration of the three tasks used to evaluate language and executive functions in our study. (A) In the *Letter fluency* task patients are asked to give the maximum number of words beginning with the letter presented in the screen (and said orally) in 1 minute. (B) In the *Picture naming* task patients are asked to name the image in the screen as fast and accurately as possible. (C) In the *Spatial sequence generation* task patients are asked to generate in 1 minute the highest number of different sequences made of 4 dots, without using the blue dots.

Statistical analysis

First, performance levels (behavioral scores and reaction times) at baseline (pre-stimulation sessions) for the cohort of 12 bv-FTD patients was compared with those of the 15

healthy controls, to specify the language impairment in the patient cohort. For this, a non-parametric Wilcoxon signed-rank test was used due to the non-normality of data distribution.

To verify the absence of an inter-session learning effect, baseline performances for the three sessions were compared using the non-parametric Friedman test. Regarding stimulation effects, the results obtained in the different tasks (scores and reaction times) before and immediately after tDCS were compared using the Wilcoxon signed-rank test for each stimulation modality: left-anodal, right-cathodal and sham. The total changes in each task (post-stimulation – pre-stimulation performances) was compared between the 3 stimulation conditions using the Friedman test.

Results

Computational model of current density distribution

Both active tDCS stimulation strategies (left-anodal and right-cathodal) were predicted to differentially modulate activity in the lateral and rostral aspects of the targeted DLPFC, with magnitude of the peak electric field and current density at each of the two MNI target locations reaching significant intensities (left and right DLPFC prefrontal target: 0.65 V/m and 0.18 A/m^2). The direction of the current flow also indicated opposite modulatory effects (Bikson et al., 2015). Mixed polarities were found between the electrodes showing that stimulation polarity (anodal vs. cathodal) depended on the orientation of the electric field with the cortical surface. Results are illustrated in Figure 1.

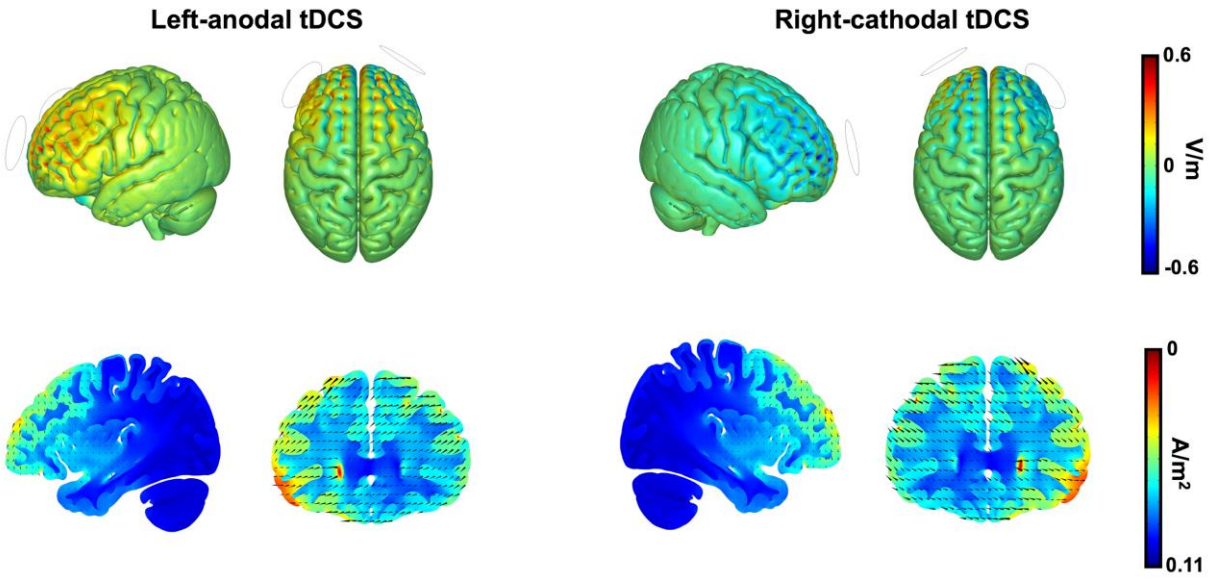

Figure 1. Predicted radial electric field (top panel) and current density magnitude (bottom panel) modeled for round 25 cm^2 sponge electrodes on a standard head (ICBM-NY) for the 2 active electrode montages. For the top panel the color scale was normalized so that cathodal [outward] electric field was presented in blue hues and anodal [inward] electric field in red hues). In the lower panel, current density magnitude was plotted in 2D slices with uniformly distributed arrows sized proportionally to the local current density magnitude. Electrodes were placed, for the left and right prefrontal targets, in the Montreal Neurological (MNI) coordinates ($x = -36, y = 32, z = 47$) and ($x = 39, y = 32, z = 45$), respectively, and with a contralateral supraorbital reference.

Evaluation tasks at baseline: patients versus healthy controls

The comparison of the scores and the reaction times of the 15 healthy controls and the 12 bv-FTD patients showed, as expected, that patients performed significantly poorer than healthy controls in the 3 evaluation tasks used to assess the impact of tDCS on the right or left DLPFC (all p-values < 0.001). Results are illustrated in Figure 3.

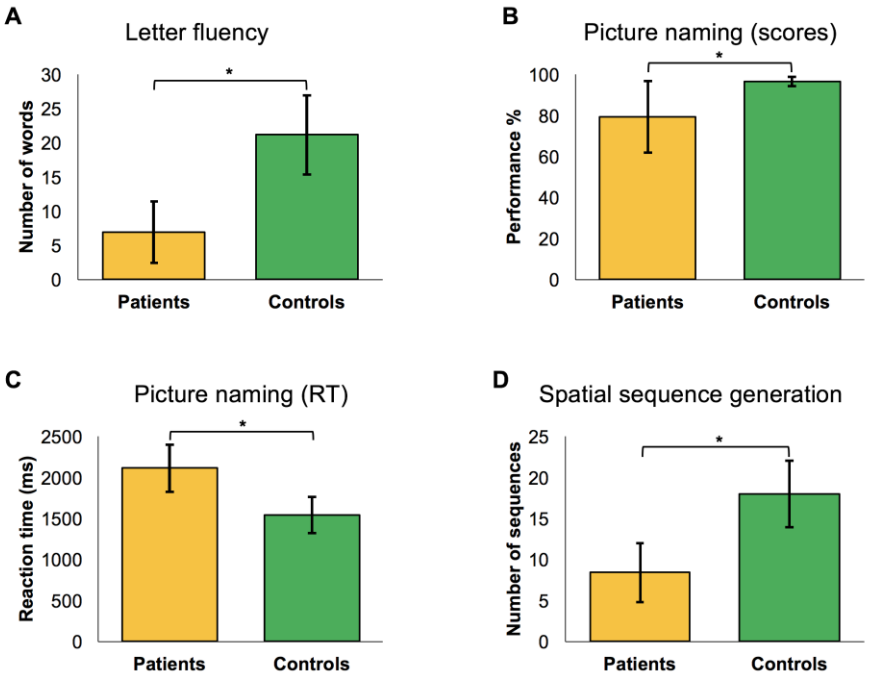

Figure 3. Pre-stimulation baseline performance for bv-FTD patients and equivalent healthy controls in the three tasks and outcome measures employed in our study to analyze impact on behavior: (A) *Letter fluency* task (number of words), (B) *Picture naming* task (accuracy) (C) *Picture naming* task (reaction times) and (D) *Spatial sequence generation* task (number of sequences). Patients showed poorer performances than healthy controls in all tasks. All values are presented as mean ± standard deviation of the mean (standard deviation bars).

Impact of tDCS on language performance and executive processes

The comparison between the number of words produced at baseline in the three sessions revealed no significant difference ($\chi^2(2) = 0.706$, $p = 0.703$), ruling out across-session learning biases that could have influenced our comparisons or rendered our 3 isolated tDCS session (tested once a week across three weeks) not independent. Nonetheless, the difference between the number of words produced in the *Letter fluency* task immediately before and after stimulation did not reach statistical significance, regardless of stimulation modality (left-anodal: $Z = -1.615$, $p = 0.106$; right-cathodal: $Z = -1.932$, $p = 0.053$; sham: $Z = -0.245$, $p = 0.807$). Similarly, no statistically

significant differences in post vs. pre-stimulation levels between the 3 tDCS conditions were found ($\chi^2(2) = 2.909$, $p = 0.234$) (Figure 4A).

Regarding the *Picture naming* task, the comparison between the scores and RTs at baseline in the 3 sessions revealed no significant difference (scores: $\chi^2(2) = 3.619$, $p = 0.164$; RT: $\chi^2(2) = 4.167$, $p = 0.125$). Nonetheless, no statistically significant differences were found between pre- and post-stimulation performance for any stimulation modality neither for scores nor reaction times (left-anodal: scores - $Z = -1.459$, $p = 0.145$; RT - $Z = -0.706$, $p = 0.480$; right-cathodal: scores - $Z = -1.433$, $p = 0.152$; RT - $Z = -0.706$, $p = 0.480$; sham: scores - $Z = -1.434$, $p = 0.152$; RT - $Z = -1.726$, $p = 0.084$). Our comparisons also failed to reveal statistically significant differences in post- minus pre-tDCS differences between the 3 stimulation modalities (scores: $\chi^2(2) = 4.044$, $p = 0.132$; RT: $\chi^2(2) = 0.167$, $p = 0.920$) (Figure 4B and 4C).

For the *Spatial sequence generation* task (control task assessing effect on executive function) baseline performance was similar for the left-anodal, right-cathodal and the sham tDCS condition ($\chi^2(2) = 3.244$, $p = 0.197$), supporting as for our two language tasks, the lack of across session learning effects and the independency of the 3 stimulation sessions.

Once more, no statistically significant difference was found between pre- and post-stimulation performance for any stimulation modality (left-anodal: $Z = -0.257$, $p = 0.797$; right-cathodal: $Z = -0.920$, $p = 0.358$; sham: $Z = -0.154$, $p = 0.877$). No statistically significant differences were found with regards to post- vs. pre-tDCS differences between the 3 stimulation modalities ($\chi^2(2) = 1.316$, $p = 0.518$) (Figure 4D).

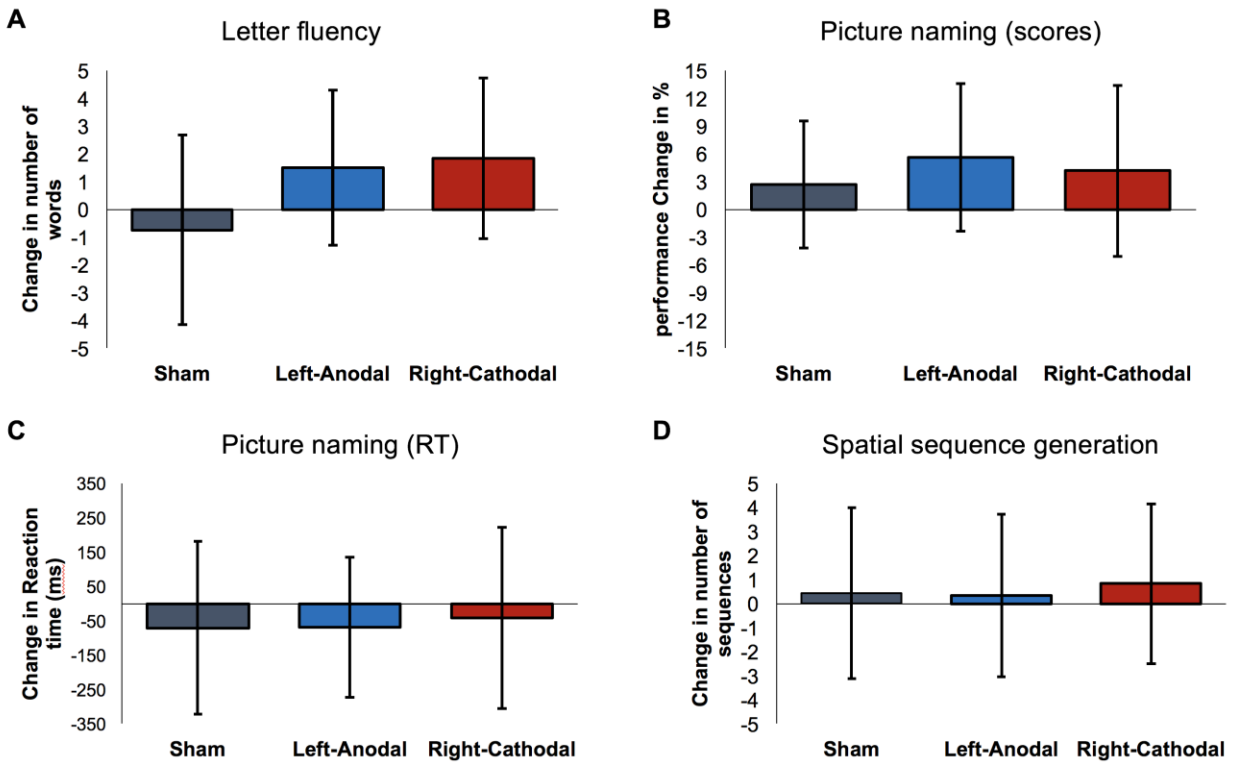

Figure 4. Performance change in (A) the L*etter fluency* task (number of words); (B) the *Picture naming* task (accuracy); (C) the *Picture naming* task (reaction times) and (D) the *Spatial sequence generation* task (number of sequences), calculated as the contrast between post vs. pre-stimulation, comparing left-anodal, right-cathodal and sham tDCS. All values are presented as mean ± standard deviation of the mean (standard deviation bars). Note that no significant change of performance (all $p>0.05$) was found for any tDCS condition in none of the three tasks evaluated in our study.

Discussion

Given the encouraging results obtained with transcranial stimulation in post-stroke aphasia and in several neurodegenerative diseases affecting language, we here explored the ability of single tDCS sessions to influence language-related networks in bv-FTD. Paralleling prior studies with successful outcomes in early onset focal neurodegenerative diseases (Teichmamn et al. 2016; Valero-Cabré et al. 2019), we applied a double-blind sham-controlled crossover design and compared two stimulation strategies: anodal tDCS delivered over the left DLPFC aiming to

directly stimulate the activity of language-related prefrontal regions; and cathodal tDCS over the right DLPFC intending to suppress interhemispheric inhibitory interactions exerted by this region on left prefrontal regions hence boosting activity in the latter.

Baseline evaluations before any tDCS condition had been delivered yielded significantly lower performance in language tasks for bv-FTD patients as compared to matched healthy controls. This result is not necessary novel but it strengthens similar evidence provided by studies reporting verbal fluency and lexical access deficits in patients with bv-FTD (Kramer et al., 2003; Sanjuan et al., 2010; Ranasinghe et al., 2016). Most important, it reinforces the claim that the left DLPFC is a region involved in activation of language processes (Klaus and Schutter, 2017; Valero-Cabré et al., 2019) and emphasizes the need to adequately diagnose and attempt to contain language dysfunctions in bv-FTD patients.

Nonetheless, contrary to what we predicted and at opposing clinical success shown by tDCS in post-stroke and degenerative aphasia, we were unable to find statistically significant modulation of language performance in bv-FTD following a single session of anodal or cathodal tDCS over the left and right DLPFC, respectively. The current negative result is worth-reporting, as non-significant outcomes are nearly as important as positive results to limit the strong bias respect to positive outcomes in scientific literature and improve our understanding on if and how tDCS should be optimally used in such conditions. Nonetheless, how to explain the lack of efficiency treating a symptom when very similar (Teichmann et al., 2016) or quite identical (Valero-Cabré et al., 2019) tDCS strategies and experimental designs yielded evidence of briefly lasting outcomes on language tasks?

A thorough evaluation of the studies using transcranial stimulation in cognitive disorders such as language in the context of cerebro-vascular or neurodegenerative diseases shows that,

taken together, these approaches resulted in heterogeneous outcomes (see Sanches et al., submitted for details). The use of heterogenous populations of patients and incomplete experimental designs (sometimes flawed or biased) emphasize the importance of a rigorous methodology to be able to demonstrate potential efficiency. The outcomes of the current investigation suggest that tDCS as it was delivered and evaluated in the current pre-clinical study might not be as promising on bv-FTD as it has been proven to be on other conditions such as sv-PPA (Teichmann et al., 2016) or PSP (Valero-Cabré et al., 2019), hence putting in standby plans for large cohort-based therapy trials. However, this conclusion is not to be considered definitive but rather be used to open a necessary discussion to identify which reasons might limit the effects of tDCS in bv-FTD patients.

Two reasons seem particularly important in the light of our results. First, the lack of language improvement could be the result of weak cortical modulatory effects following the delivery of a single tDCS session, unable to reach a minimal threshold of activity change required to significantly change language performance. Supporting this hypothesis, it has been suggested that cumulative effects obtained with multi-day stimulation regimes give rise to higher magnitude and lasting modulations, linked to the induction of cerebral plasticity phenomena (Monte-Silva et al., 2013). Accordingly, significant improvements in verbal fluency have been reported following anodal tDCS over the DLPFC in Parkinson's disease (Manenti et al., 2016), Primary Progressive Aphasia (Cotelli et al., 2014; Gervits et al., 2014) and also bv-FTD (Agarwal et al., 2016), when delivered daily for 10 consecutive stimulation sessions. Similar to our outcomes, hence highlighting the influence of the number of accrued stimulation sessions, Huey and colleagues (2007) failed to find significant improvements on verbal fluency after a single anodal tDCS session over the DLPFC in patients with advanced bv-FTD.

A second factor that might limit tDCS efficiency in well-controlled trials with language-impaired patients is the degree in the severity of language impairments, hence the stage at which the neurodegenerative condition is proposed for tDCS treatment. Pereira et al. (2013), for example, found improvements in phonemic fluency after a single anodal tDCS session over the DLPFC in patients with Parkinson's disease. Nonetheless, baseline performance in this study was relatively preserved (17 words/minute) compared to our cohort (7 words/minute).

A directly related factor that probably limits tDCS efficiency is the degree of cortical atrophy affecting the area targeted by tDCS, hence the spared neuronal resources available for modulation. Valero-Cabré et al. (2019) have recently used a double-blind sham-controlled design to explore stimulation effects on a cohort of patients with Progressive Supranuclear Palsy (PSP) and reported improvements in lexical access and language initiation/fluidity (as measured by a *letter fluency* task) following a single session of anodal tDCS over the left DLPFC. However, PSP is characterized by intense damage in subcortical structures and relatively mild levels of atrophy in the DLPFC, leaving spared prefrontal neural resources that can be more efficiently boosted by tDCS, than in bv-FTD patients with severely atrophic prefrontal cortices. Strengthening the plausibility of this explanation, a tDCS resting state functional MRI study in Parkinson's disease patients, characterized by predominant subcortical damage, reported improvements in verbal fluency improvements following anodal stimulation over the left DLPFC along with an increased functional connectivity between frontal and inferior parietal regions (Pereira et al., 2013). Taken together, these outcomes suggest that anatomical factors such as the severity of cortical atrophy (and the functional impairments that at the excitability, metabolic and neurochemical levels derived from such) influence the efficiency of tDCS.

In this same vein, it has been shown that the volume of the cerebrospinal fluid (CSF) in the subdural space, gyral depth and the distance between the surface tDCS electrode (anode or cathode) and the cortical target accounted for up to 50% of the spatial variability in electric field strength (Datta et al., 2012; Opitz et al, 2015). Kim et al. (2014) modeled individually the current density induced by stimulation over the left DLPFC in a cohort of healthy adults and reported performance improvements in a working memory task which correlated with the magnitude of the predicted current density at target. These findings suggest that inconsistent behavioral outcomes of non-invasive brain stimulation (either tDCS or TMS) might be importantly influenced by interindividual differences in head and brain structures, which might be even more variable in patient populations (see Wagner et al., 2007; Wagner et al., 2009; O'Brien et al., 2016, for extensive discussion). On this basis, we hypothesize that the excessive degree of DLPFC atrophy shown by bv-FTD patients at the time of diagnosis may be one of the main causes that limits the impact of tDCS. It follows that more effective therapeutic approaches (instead of focusing on highly damage DLPFC areas with scarce viable resources to modulate) should identify and target relatively spared cortical areas within language networks involved in lexical/semantic access and verbal fluency. To this regard, neuroimaging evidence supports a role for prefrontal, parietal and temporal areas in the networks contributing to such language processes (e.g., Badre, 2008; Biesbroek et al., 2016). Moreover, in bv-FTD, the temporal-parietal junction and the anterior temporal cortex, involved in lexical (Migliaccio et al., 2016) and semantic representations (Rice, Lambon Ralph and Hoffman, 2015), respectively, remain relatively spared and should be alternatively tested as tDCS targets.

The use of well-designed double-blind sham-controlled pre-therapeutic studies is indispensable to search proof-of-concept of transcranial stimulation in neurological disease, and

on such basis, justify more costly, high-risk, large-scale clinical trials aiming at probing lasting therapeutic effects. As successfully achieved for other neurodegenerative diseases (Teichmann et al., 2016; Valero-Cabré et al. 2019), we here aimed to show brief lasting improvements of language impairments in bv-FTD patients with a single tDCS session targeting the DLPFC (the most affected area in these patients). Our study failed to provide such proof-of-concept. However, together with other prior investigations, our results highlight the need to factor in the baseline magnitude of language impairments, and consider the degree of cortical atrophy on targeted regions; hence to identify in larger bv-FTD populations the window of baseline severity at which patients might be optimally responsive to stimulation, and consider application of tDCS to relatively undamaged regions of the language network.

Such individual-patient approach, might call for a selection of candidates to a specific tDCS therapeutic protocol according to their individual anatomical parameters (e.g., skin and skull thickness, degree of atrophy/cortical thickness, CSF volume etc.), and clinical profile of disease severity. Nonetheless, on very similar basis, a 'personalized precision medicine' framework with individually profiled therapy based on several variables (among them symptom severity and degree of atrophy) may gain ground in brain stimulation. In parallel, biophysically inspired computational models of tDCS generated current fields, individualized to each patients' head and brain structure, may help tailor the electrode montages and stimulation parameters most suited to optimize outcomes (Huang et al., 2017; Opitz et al., 2018).

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Clinical characterization and non-invasive transcranial modulation of lexical and semantic language abilities in patients with the logopenic variant of Primary Progressive Aphasia

Résumé en français

La stimulation transcrânienne à courant continu (STCC) est une technique non invasive de stimulation cérébrale capable de moduler l'activité corticale et de promouvoir la neuroplasticité. Un nombre croissant d'études s'intéressent de plus en plus à l'utilisation de la STCC en tant que technique thérapeutique dans les maladies neurodégénératives. Cela tient au fait que, à ce jour, de telles maladies n'ont pas de traitement validé et que de nouvelles approches thérapeutiques pouvant donner de l'espoir aux patients et à leur environnement sont donc nécessaires. Un domaine qui a montré des résultats encourageants considérables concerne les déficits au niveau du langage. S'appuyant sur le principe d'inhibition interhémisphérique selon lequel les liaisons transcalleuses entre les deux hémisphères cérébraux induisent une inhibition réciproque de l'activité corticale controlatérale, ainsi que sur l'hypothèse que la stimulation anodale favorise l'activité neurale pendant la stimulation cathodale l'inhibe, de nombreuses études chez des patients neurodégénératifs ont appliqué une stimulation anodale sur l'hémisphère gauche, dominant du langage, et une stimulation cathodale sur les zones homotopiques droites, générant des effets positifs. La variante logopénique des Aphasies Primaires Progressives (APP-vl) affecte principalement le cortex temporal moyen/postérieur et pariétal inférieur gauches, englobant la jonction temporo-pariétale (JTP), et provoque une altération de l'accès aux représentations lexicales, reflétée par difficultés de récupération des mots, et une diminution de la mémoire de travail verbale. Certaines études ont également suggéré que les déficits chez ces patients pourraient s'étendre à d'autres niveaux du processus d'accès lexical, affectant également les représentations sémantiques.

Dans cette étude nous avons visé à évaluer les effets modulateurs d'une seule session de STCC délivrée sur la JTP sur l'accès lexical et sémantique chez des patients atteints d'une APP-vl.

Pour explorer la capacité de la stimulation transcrânienne à courant continu (STCC) à moduler le traitement du langage dans l'APP-vl, nous avons stimulé une cohorte de 12 patients en utilisant un design croisé, en double-aveugle et contrôlé par placebo. Nous avons appliqué la STCC anodale et cathodale sur la JTP gauche et droite, respectivement, et les avons comparés à une stimulation placebo, en trois sessions espacées d'une semaine. Chaque séance a eu une durée de 20 minutes avec une intensité du courant de 1.59mA délivré par des électrodes rondes de 25cm^2. Une tâche de fluence littérale, une tâche de dénomination et une tâche d'association sémantique ont été appliquées immédiatement avant et après les sessions de stimulation en tant que marqueurs de la modulation potentielle de l'accès lexical et sémantique. Pour avoir des valeurs normatives pour chaque tâche, 15 sujets sains ont aussi été recrutés.

Les patients étaient altérés dans toutes les tâches expérimentales initiales, comme le montre la comparaison avec les sujets sains. Les performances contrastées en post-stimulation par rapport à la pré-stimulation n'ont montré aucune amélioration du langage dans aucune des tâches et dans aucune des modalités de stimulation. Un modèle computationnel de la distribution du courant a corroboré l'impact attendu de la STCC anodale gauche et cathodale droite sur la JTP ciblée.

Dans notre étude, la STCC n'a pas entraîné d'amélioration du langage chez les patients avec une APP-vl. Cependant, notre étude a permis de mettre en évidence des aspects importants à prendre en compte lors de la planification d'un protocole de stimulation, tels que l'influence de l'état neuronal pendant la stimulation sur les effets de la même et l'importance du choix de la région du cerveau à stimuler. Nous encourageons les recherches futures sur les effets de la STCC en tant que traitement possible des déficits du langage dans ls APP-vl.

Clinical characterization and non-invasive transcranial modulation of lexical and semantic language abilities in patients with the logopenic variant of Primary Progressive Aphasia

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Abstract

Objective: We here further characterized lexical and semantic clinical deficits in patients with the logopenic variant of Primary Progressive Aphasia (lv-PPA) compared to healthy individuals. We then explored the ability of a single session of transcranial Direct Current Stimulation (tDCS) over the Temporo-Parietal Junction (TPJ) to modulate impairments of language processing. **Methods:** The language abilities of lv-PPA patients (n=12) and age matched controls (n=15) were assessed and compared by means of a *Letter fluency* task, a *Picture naming* task and a *Semantic association* task. Then, using a sham-controlled double-blind crossover design, we evaluated in lv-PPA patients the impact of anodal and cathodal tDCS over the left and right TPJ, respectively, compared to sham tDCS. Patients were tested in the above-mentioned tasks immediately prior and following tDCS, and performance outcomes were used as markers demonstrating the modulation of lexical and semantic access impairments. **Results:** At baseline, lv-PPA patients showed impairments on all three experimental tasks compared to healthy controls. A computational Finite Element Model of current distribution corroborated the intended impact of left-anodal and right-cathodal tDCS on the targeted TPJ region. Nonetheless, contrasting post vs. pre-stimulation performance across tDCS conditions did not yield evidences of language improvement for any of the tasks. **Conclusions:** Our study suggests that both lexical and semantic representations are affected in lv-PPA. Additionally, we failed to find evidence supporting an effect of tDCS on language improvements for lv-PPA patients. Outcomes allow us to highlight a series of important variables when planning stimulation protocols (e.g. state-dependency of stimulation effects, need for multiday-regimes and adequate choice of the brain target). Although results were not encouraging, further research needs to be carried over on therapeutic uses of tDCS in lv-PPA.

Keywords: Logopenic Primary Progressive Aphasia, language, transcranial direct current stimulation (tDCS), function modulation

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain neuromodulation technology which has shown promise modulating human cortical activity (Paulus et al., 2013; Rahman et al., 2013) and promoting neuroplasticity via long-term potentiation (LTP) or long-term depression (LTD) -like processes (Nitsche and Paulus, 2000). It uses a weak constant electrical current passed between at least two electrodes, an anode and a cathode (Nitsche and Paulus, 2000).

Depending on stimulation modality, the so called active electrode (either the anode or the cathode) is placed on a scalp area overlying the region of interest, whereas the return is placed in a distant site, to avoid current shunting through the skin (Bikson et al., 2012). The flow of current between electrodes polarizes extended cortical areas by impacting the concentration of ion charges in the extracellular space around neurons, hence shifting the resting membrane potentials towards or away from their firing threshold. It is generally assumed that neurons in the region under the anode become more excited (resting membrane potentials closer to threshold) hence more prone to fire in response to weak inputs. Opposite, the resting membrane potential of neurons under the cathode is shifted away from threshold rendering neurons inhibited and less prone to fire (Rahman et al., 2013). Importantly, tDCS has also been shown to affect not only the regions that are directly under the electrodes, but also distant connected regions, thus influencing brain connectivity (Keeser et al., 2011; Kwon et al., 2008).

A growing body of studies has been evaluating potential uses of tDCS as cognitive contention therapy in several neurodegenerative diseases (Boggio et al., 2009; Elder et al., 2016; Teichmann et al., 2016; Valero-Cabré et al., 2019). Studies addressing such applications, bringing new hope to patients and their families, is skyrocketing given the lack of other validated therapies. Additionally, at difference with focal non-invasive brain stimulation techniques, such as

transcranial magnetic stimulation (TMS), the wide spatial range of modulatory action (Torres et al., 2013), high portability, low risk, ease of use and reasonable cost makes of tDCS the technique of choice for clinical applications in neurodegenerative diseases (Elder and Taylor., 2014).

A domain in which tDCS has been drawing considerable attention and encouraging outcomes relates to neurodegenerative language impairments. Interventions have found support in the principles of interhemispheric rivalrous interactions (well characterized for motor and visuo-spatial attention systems), upon which transcallosal connectivity between cerebral hemispheres exerts mutually inhibitory effects (Ferbert et al., 1992) and on premises that anodal and cathodal tDCS increased and inhibited respectively neural activity, and that periodical modulation of brain activity would engage long-term adaptive plasticity.

Consequently, a handful of studies have tested either anodal tDCS stimulation over a language dominant left hemisphere region and/or cathodal tDCS stimulation over right homotopic areas, reporting beneficial effects (i.e. Cotelli et al., 2014; Manenti et al., 2015a, 2015b; Teichmann et al., 2016; Tsapkini et al., 2014, 2018; Valero-Cabré et al., 2019). This literature is also being challenged however by negative findings (Huey et al., 2007; Hung et al., 2017; Sanches et al., in preparation) which sets limits to the ability of tDCS to modulate language-related networks in neurodegenerative diseases, and calls for specific indications (likely symptom-, disease-, brain damage- and severity-dependent).

Primary Progressive Aphasia is an early onset neurodegenerative disease with (<65 years of age) characterized by impaired language and communication abilities (Mesulam et al., 2014). To date, three main variants have been identified, including the logopenic variant (lv-PPA) (Teichmann et al., 2013), which affects mainly the left posterior temporal and inferior parietal cortices, encompassing the temporo-parietal junction (TPJ) (Gorno-Tempini et al., 2011).

Clinically it is characterized by impairment accessing lexical representations, such as single-word retrieval difficulties, and dwindling verbal working memory resources (Gorno-Tempini et al., 2011; Teichmann et al., 2013). Some studies have also suggested that deficits in these patients might extend into other levels of the lexical access process, affecting also semantic representations (Leyton et al., 2013; Rogalski et al., 2008; Teichmann et al., 2013). As for other neurodegenerative diseases, there is a lack of validated therapies able to slow down damage progression (Boxer et al., 2013) and speech therapy shows little effects containing language decline (Savage et al., 2014).

A few studies have already explored the effects of multiday-regimes of tDCS coupled to language rehabilitation in patients with lv-PPA and reported lasting positive outcomes in different language tasks (Ficek et al., 2018; Gervits et al., 2016; Roncero et al., 2017; Tsapkini et al., 2014, 2018). Recently, two double-blind sham-controlled tDCS studies reported task specific language improvements in the semantic variant of Primary Progressive Aphasia (Teichmann et al., 2016) and in Progressive Supranuclear Palsy patients (Valero-Cabré et al., 2019) following the delivery of anodal and cathodal stimulation over the left and the right anterior temporal lobes and the left and right dorsolateral prefrontal cortices, respectively. Opposite, a recent study in behavioral variant of Frontotemporal Dementia patients, targeting the left and right dorsolateral prefrontal cortices failed to find any impact of tDCS on any language task (Sanches et al., in preparation).

We here mimicked the designed employed in some of these precedent studies (Teichmann et al., 2016; Sanches et al., in preparation; Valero-Cabré et al., 2019) and applied, to a well-characterized cohort of lv-PPA patients, a double-blind, sham-controlled, crossover design with single sessions of anodal and cathodal tDCS over the left and the right TPJ, respectively. Prior and immediately following stimulation, we evaluated lexical and semantic access with a *Letter fluency, Picture naming* and *Semantic association* tasks. We aimed to contribute to a better characterization

of the extent of lexical and semantic language deficits in lv-PPA, probe the potential role the TPJ in such symptoms and assess the ability of tDCS stimulation alone (i.e., without the confounding of language rehabilitation) to modulate language performance in lv-PPA patients.

Materials and Methods

Patients

Twelve lv-PPA patients who satisfied the International Diagnostic Criteria of PPA (Gorno-Tempini et al., 2011) established by expert clinicians, were recruited at the National Reference Center for "PPA and Rare Dementias" of the Pitié-Salpêtrière Hospital in Paris, France. All patients showed isolated or largely predominant language impairments, presenting with the core features of word-finding difficulties and sentence repetition impairments in the absence of agrammatism, motor speech impairments and single-word comprehension impairments.

The clinical diagnosis was additionally supported with clinical MRI acquisitions which yielded for all patients signs of posterior peri-sylvian or parietal atrophy, predominantly in the left hemisphere. During their participation, none of the patients were under medication which could have been likely to interfere with central nervous system function. Non-inclusion criteria were as follows: (i) Psychiatric disorders or neurologic diseases other than lv-PPA; (ii) Contra-indications for MRI or tDCS such as the presence of cranial and intracranial ferromagnetic artifacts or devices, scalp or skull lesions or having suffered epileptic events; and (iii) Major depression (MADRS > 20 [Montgomery Asberg Depression Rating Scale], Montgomery and Asberg, 1979), or major cognitive disorders (MMSE < 15 [Mini-Mental State Examination], Folstein et al., 1975; FAB < 10 [Frontal Assessment Battery], Dubois et al., 2000). Fifteen healthy controls, with similar characteristics to our patient population for handedness, gender, age and years of education (Chi-

square test for gender: p >0.05; Mann-Whitney test for age and years of education: both p >0.05), were also included to determine normative performance levels in our language tasks. All participants were native French speakers. The study received approval from the local Ethics Committee (*Comité Coonsultatif de Protection de Personnes, Ile-de-Frace I, Protocol STIMLANG*) and written informed consent was obtained from all the patients and healthy controls prior to their participation. Demographic data are summarized in Table 1.

Table 1. Demographic data of lv-PPA patients and healthy controls (mean ± standard deviation)

	Lv-PPA patients	**Healthy controls**
Number of participants	12	15
Sex (Women, Men)	6W/6M	8W/7M
Age (years)	70.5 ± 2.6	64.1 ± 7.4
Handedness (R/L)	12/0	15/0
Years of education (years)	14.1 ± 1.0	14.9 ± 2.7
Symptom duration (years)	4.3 ± 0.7	--

Study design

We applied a double-blind sham-controlled crossover design, in which each patient underwent three independent tDCS sessions, a week apart: anodal tDCS over the left TPJ, cathodal tDCS over the right TPJ, and sham stimulation over the left TPJ. Each stimulation session was preceded and immediately followed by a set of language tasks to evaluate the efficiency of tDCS to modulate access to lexical and semantic representations. The order of the three stimulation sessions was counterbalanced across the twelve patients to avoid order biases (6 permutations x 2 patients per permutation order), and the sessions were one week apart to prevent any unlikely carry-over effects of the stimulation. In contrast to TMS protocols, the lack of lasting scalp sensations characterizing tDCS made patients totally unaware of the specific condition being

applied (anodal, cathodal or sham). To warrant a double-blind procedure, two different researchers supervised the application of tDCS and of the language evaluation tasks.

Brain stimulation

Using custom-made software based on SPM 12 (Statistical Parametric Mapping 12, Wellcome Department of Cognitive Neurology, UK, running on Matlab 2016b, Mathworks, USA), stimulation targets in the left and a right TPJ for anodal and cathodal tDCS were labelled on the MRI of each patient at Montreal Neurological Institute (MNI) coordinates [x=-64, y =-38, z =6] and [x=64, y=-38, z=6] (Roiser et al., 2013), respectively. A return electrode was placed in the contralateral supraorbital region (right and left supraorbital, respectively). The scalp location of the active tDCS electrodes corresponded to ~CP5 (for left TPJ) and ~CP6 (for right TPJ) sites according to the 10-20 EEG reference system, whereas the contralateral supraorbital return electrodes were placed on EEG coordinates AF8 and AF7, respectively.

During anodal and cathodal tDCS, current intensity was linearly increased during 30 seconds to reach a maximum of 1.59mA, delivered through round sponge electrodes (5.65cm diameter, 25cm^2 surface, NEuroelectrics [NE026a] SPONSTIM 25), ensuring a current density of 0.06 mA/cm^2, similar to the one applied in previous studies (Teichmann et al., 2016; Tsapkini et al., 2014; Valero-Cabré et al., 2019). Current was kept at this intensity for 20 minutes before being ramped down for 30 seconds. For the sham session, the current was ramped up and down during 30 seconds at the initial and final phase of the session, to emulate the transient skin itching sensations characterizing active stimulation.

During the stimulation sessions patients performed a simple visuo-motor task running in a laptop (HP EliteBook 8770w, USA), consisting in pressing the space bar every time a slowly

moving black dot (~1 cm diameter) contacted the edge of a surrounding rectangle (10 x 5 cm) centered in the middle of the screen, with a real-time score counting successes and potential misses. As in prior studies (Teichmann et al., 2016; Sanches et al., in preparation; Valero-Cabré et al., 2019), the task was planned to ensure patients maintained vigilance through all the stimulation time. To assess the tolerance of patients to stimulation, before and immediately after each tDCS session patients were asked to complete a 'tDCS adverse effects questionnaire' (Brunoni et al., 2011) documenting patients' sensations in a set of the most frequent adverse effects reported in tDCS studies (find a detailed description of the stimulation procedure see Teichmann et al., 2016).

Computer simulations of current density distribution

The software SimNIBS 2.1.2 was used to calculate the electric field induced by tDCS based on a Finite Element Model (FEM) (https://simnibs.drcmr.dk/), on a standardized head volume (MNI-152) to determine the peak electric field strength and the peak values of the normal component of the electric field, and their distribution on the cortical surface. The tDCS stimulation electrodes and conditions were set-up on the head model using the Graphical User Interface (GUI) with the exact same parameters employed during the stimulation sessions. Electrodes were modeled as a 1mm thick rubber electrode + 4mm thick round 25 cm^2 sponges. The two tDCS conditions applied in this study were modeled.

Conductivity values were set as follows (in S/m): skin, 0.465; skull, 0.010; CSF, 1.654; gray matter, 0.275; white matter, 0.126; eye balls, 0.500; eye region, 0.250; electrode rubber, 29.4; electrode saline, 1.4. Transcranial DCS current intensity was set at 1.59mA.

Both the electric field strength and the normal component of the electric field values in the targeted TPJ were extracted.

General cognitive/language assessment

Assessment with standardized tests allowed the establishment of lv-PPA diagnosis and the composition of a relatively homogenous cohort with patients presenting similar levels of cognitive impairment and disease duration. The general cognitive assessment included the MMSE (Folstein et al., 1975), the FAB (Dubois et al., 2000), and the MADRS (Montgomery and Asberg, 1979). The language assessment was composed of an evaluation of aphasia severity, a sentence-repetition test and a single-word comprehension test (Boston Diagnostic Aphasia Evaluation) (Mazaux and Orgogozo, 1982), a picture naming test (D080, Deloche and Hannequin, 1997) and a verbal fluency test comprising phonemic and category fluency (Cardebat et al., 1990). Healthy participants were tested with the MMSE and the FAB. Test scores are summarized in Table 2.

Table 2. General cognitive / language assessment (mean scores ±standard deviations)

	Lv-PPA patients	**Healthy controls**	**Normative thresholds**
MMSE	21.8 ± 1.1	29.33 ± 0.72	≥ 27
FAB	11.6 ± 0.8	17.7 ± 0.1	≥ 16
MADRS	9.7 ± 0.9	--	≤ 6
BDAE – aphasia severity scale	3.75 ± 0.2	--	> 4
Category fluency (fruits/2 min)	8.9 ±4.2	--	≥ 15
Phonemic fluency (P/2 min)	10 ± 3.4	--	≥ 15
DO80	63.2 ± 8.5	--	>75
Sentence repetition BDAE	10.2 ±1.9	--	≥ 4
Single-word comprehension BDAE	65.8 ± 7.6	--	≥ 68

Language evaluation tasks

In the *Letter fluency* task participants were asked to produce orally as many words as possible beginning with a given letter (“C” or “P”), within a limited time of one minute. The letters were displayed on the computer screen and provided orally by the examiner (Figure 1A). Patients

performed this task prior and following stimulation either with the letter “C” (Version 1) or “P” (Version 2), to reduce any test/re-test effects. Words beginning with “C” or “P” are similar in terms of numbers of items and have a similar cumulative lexical frequency in French (both Fs < 1) (New et al., 2004).

In the *Picture naming* task participants were asked to name 40 images, issued from two image databases (Bonin et al., 2003; Snodgrass and Vanderwart, 1980), as quickly and accurately as possible. Each image was displayed on the computer screen for 8 seconds, after which a lack of response was counted as an incorrect answer (Figure 1B). Patients performed two different versions of the task prior and after stimulation to reduce any test/re-test effects. For both versions of the test, the material was matched for the visual complexity of the images, lexical frequency of words (New et al., 2004) and the familiarity of words and images (all Fs < 1). The number of correct responses and the reaction time (RT) for each response were automatically recorded by the computer.

In the *Semantic Association* task three words were simultaneously presented on a screen, a test item (center top of the computer screen), a semantically related target (bottom, left or right), and an unrelated distractor (bottom right or left) (Figure 1C). In half of the stimuli the target was located at the left bottom side of the screen (distractor on the right), and in the other half the target was presented at the right bottom side (distractor on the left). Participants were asked to indicate as accurately and as quickly as possible which of the two items at the bottom of the screen (target, distractor) was related to the test item (top of the screen). Two equivalent versions of the task, each version composed of 26 stimuli, were used to avoid test/re-test effects between pre- and post-stimulation evaluations. Importantly, test items, targets and distractors of the two versions, were matched for lexical frequency, number of letters and concept familiarity (all Fs < 1) (New et al.,

2004). Within each version targets and distractors were matched for lexical frequency, number of letters and concept familiarity (all Fs < 1).

The evaluation order of the tests was blocked in the following way: 1) *Letter fluency* task, 2) *Picture naming* task and 3) *Semantic association* task. All stimuli were presented on a laptop computer (HP EliteBook 8770w, USA) using commercial stimulus presentation software (*E-Prime*, Psychology Software Tools, USA). Patients were sitting in front of the computer, that automatically recorded their answers in the presence of an examiner. The testing procedure required about 15 minutes to be completed, a period that corresponds to the post-stimulation period usually covered by the after-effects of 20 minutes of tDCS (Priori et al., 2003). The same testing and evaluation materials and procedures were also applied to healthy controls, who did not undergo tDCS.

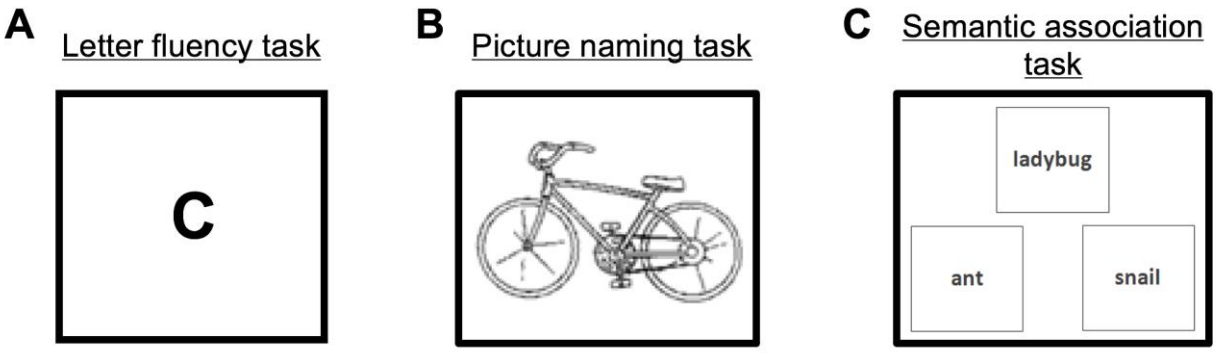

Figure 1. Illustration of the three tasks used to evaluate language functions in our study. (A) In the *Letter fluency* task patients are asked to give, in 1 minute, the maximum number of words beginning with the letter presented in the screen (and said orally). (B) In the *Picture naming* task patients are asked to name the image in the screen as fast and accurately as possible. (C) in the *Semantic association* task patients are asked to choose from the two words at the bottom of the screen the one that is more associated with the word presented at the top of the screen.

Voxel-based morphometry

T1 weighted MRI had been previously acquired for all 12 patients and for 11 out of the 15 healthy controls, on a Siemens 3 Tesla VERIO TIM or on a Siemens 3T TRIO TIM, at Pitié-Salpêtrière hospital. Image processing and statistical analyzes were performed using the software SPM 12 (Wellcome Department of Cognitive Neurology, UK), running on Matlab 2016b (Mathworks, USA). Image preprocessing included the following steps: segmentation, spatial normalization, modulation and smoothing. T1 images were segmented and normalized in a template space using DARTEL. The normalized and modulated segments were then smoothed using a Gaussian kernel of 10mm full-width-at-half-maximum (FWH). Voxel-based morphometry (VBM) was used to compare gray matter volumes between healthy controls and PPA patients using a two-sample t-test design. Age, gender and total intracranial volume were introduced as nuisance variables. We tested two statistical thresholds: $p < 0.05$ with family-wise error (FWE) correction for multiple comparisons, and a threshold of $p < 0.001$, uncorrected. This uncorrected threshold was accepted given the relatively small sample size of the two groups.

Statistical analysis

Due to the non-normality of data distribution, to characterize language impairments in the patient cohort, performance at baseline (scores and reaction times of the pre-stimulation sessions) for the of 12 lv-PPA patients were compared with those of the 15 healthy controls using a non-parametric Wilcoxon signed-rank test.

Then, patients' baseline performances for the three sessions were compared using the non-parametric Friedman test, to check for the absence of an inter-session learning effect. The results obtained in the different tasks (scores and reaction times) before and immediately after tDCS were compared using the Wilcoxon signed-rank test for each stimulation modality: left-anodal, right-

cathodal and sham, to assess stimulation effects. To compare the efficacy of the different stimulation modalities, the 'net gain' (or 'net improvement') for each task (calculated as post-stimulation *minus* pre-stimulation performance levels or scores) were compared across the three stimulation conditions using the Friedman test.

Results

Voxel-based morphometry

Compared to healthy controls, the patterns of significant gray matter atrophy present in our cohort of lv-PPA patients encompassed the left TPJ and a portion of the left middle/posterior temporal cortex and the inferior parietal cortex (Figure 2).

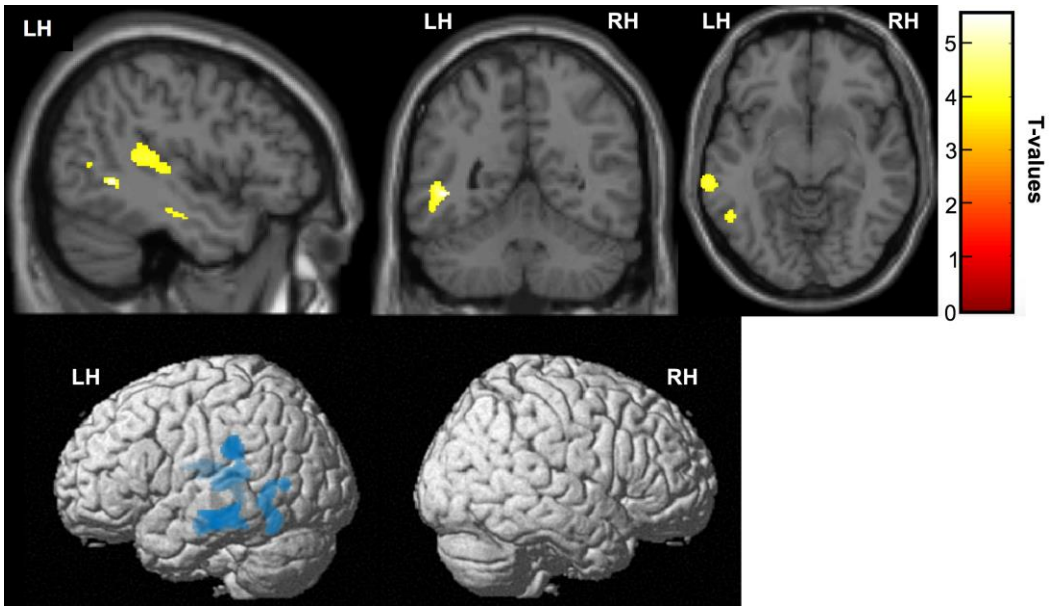

Figure 2. Voxel-based morphometry (VBM) comparisons between the lv-PPA patients (n=12) and healthy controls (n=11) ($p < 0.001$, uncorrected). (Top panel, from left to right) Sagittal slice, coronal slice and axial slice. A cluster of voxels in the MNI coordinates [x = -45, y = -52, z = -2] (left posterior temporal cortex) survived with a statistical threshold of $p < 0.05$ corrected for multiple comparisons. The color bar represents T-values. (Bottom panel) 3D reconstruction of the brain with the regions that presented gray matter loss in our lv-PPA cohort, as compared to healthy controls, colored in blue (left and right hemispheres). LH – left hemisphere, RH – right hemisphere.

Language tasks at baseline: patients vs. healthy controls

Logopenic PPA patients showed significantly lower accuracy scores in all the three evaluation tasks compared to healthy controls (all p-values < 0.001). Regarding reaction times, patients were also significantly slower than healthy controls in the *Semantic association* task (Z = -2.74, p = 0.003), whereas similar differences did not reach significance for the *Picture naming* task (p > 0.05). Results are shown in Figures 3 and 4.

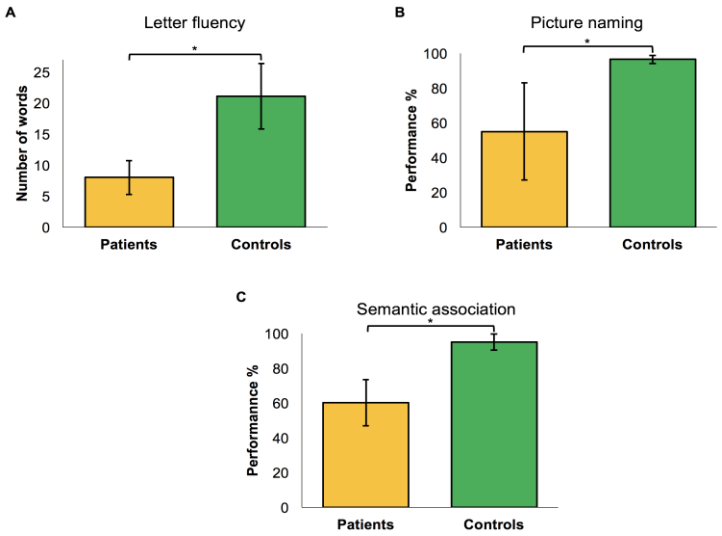

Figure 3. Pre-stimulation baseline performance of lv-PPA patients and healthy controls (mean values and standard deviations) in the language tasks: (A) *Letter fluency* task, (B) *Picture naming* task (C) *Semantic association* task. Patients showed poorer performances than healthy controls in all tasks.

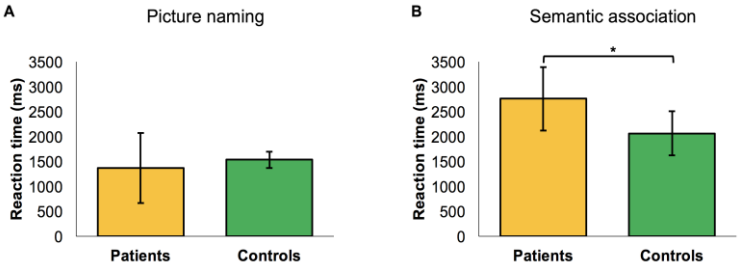

Figure 4. Pre-stimulation reaction times of lv-PPA patients and healthy controls (mean values and standard deviations) in the experimental tasks: (A) *Picture naming* task (B) *Semantic association* task. Patients were slower than healthy controls in the *Semantic association* task but not in the *Picture naming* task. Note that only for the *Semantic association* task, but not for the *Picture naming* task, lv-PPA patients were significantly slower than controls.

Computational model of current density distribution

Computer simulations predicted that both anodal and cathodal tDCS modulate the lateral aspects of the targeted TPJ also extending to the posterior temporal and inferior parietal cortices. Further demonstrating the efficacy of our electrode montage, electric field strength at each of the two MNI target locations reached meaningful values in both locations (left TPJ: 0.57 V/m, right TPJ: 0.61 V/m) (Figure 5A). Directional current flow produced opposite modulatory effects as shown by the normal component of the electric field maps (Figure 5B). The normal component of electric field also reached meaningful values at the two MNI targets (left TPJ: 0.26 V/m; right TPJ: -0.27 V/m) (Figure 5B).

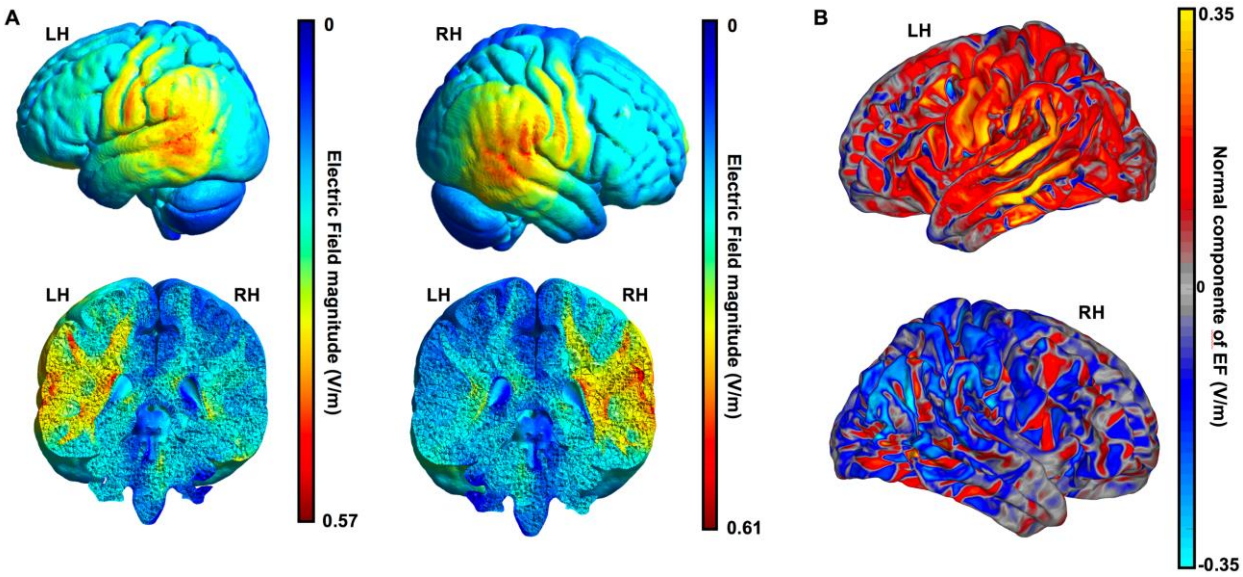

Figure 2. Predicted electric field magnitude and distribution modeled for round 25 cm^2 sponge electrodes on a standard head (MNI152) for the two active electrode montages: (A) (Left panel) Montage with the anode over the left TPJ (left-anodal tDCS) and (Right panel) Montage with the cathode over the right TPJ (right-cathodal tDCS), both with a contralateral supraorbital reference. The top panel of A shows the anatomical model of electric field strength (V/m) and distribution on cortical surface; the bottom panel of A shows the electric field strength on a coronal slice, centered on MNI target coordinates [x = -36, y = 32, z = 47] and [x = 39, y = 32, z = 45] for left and right TPJ targets, respectively. (B) Maps for the normal component of the electric field, for the left-anodal montage (top) and for the right-cathodal montage

(bottom). Notice that whereas left anodal tDCS (top) induced inward currents in the left TPJ and adjacent areas, right cathodal tDCS (bottom) induced opposite effects in the right TPJ. LH – left hemisphere, RH – right hemisphere.

Effects of stimulation on language performance

Base-line performance measured during the pre-stimulation test session was similar for the three stimulation sessions (*Letter fluency* task: $\chi^2(2) = 2.205$, $p = 0.332$; *Picture naming* task: $\chi^2(2) = 1.721$, $p = 0.423$; *Picture naming* task (RT): $\chi^2(2) = 2$, $p = 0.368$; *Semantic association* task: $\chi^2(2) = 3.244$, $p = 0.197$; *Semantic association* task (RT): $\chi^2(2) = 0.383$, $p = 0.826$). Nonetheless, unexpectedly, no significant effects of stimulation were found for any of the three language tasks (accuracy and reaction times) in any of the tested tDCS modalities (all p-values > 0.05) (Figures 6 and 7).

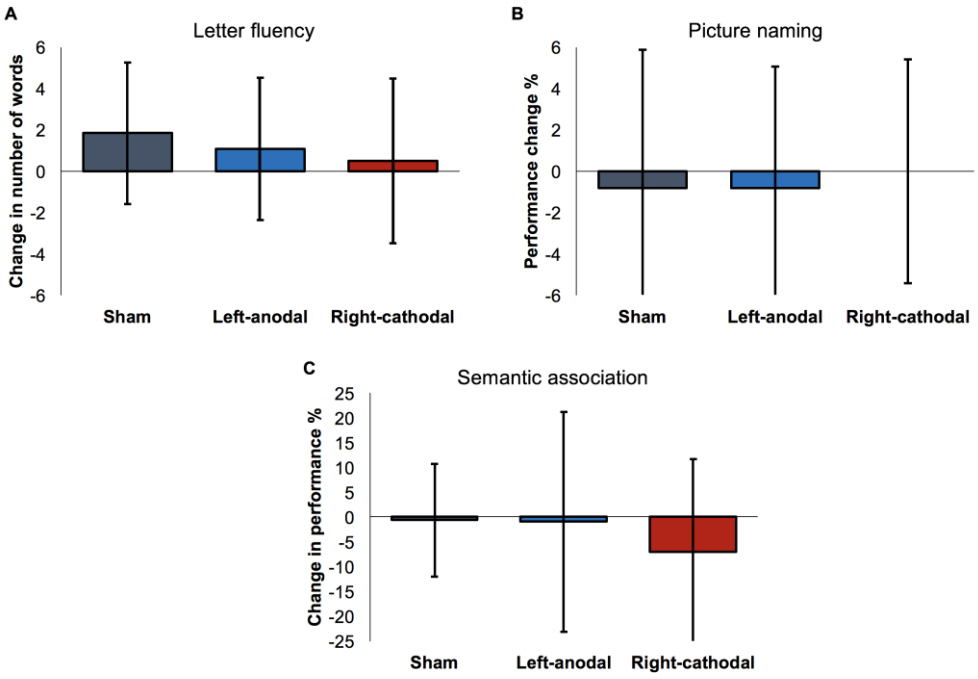

Figure 6. Changes between pre- and post-stimulation for performances (mean values and standard deviations): (A) *Letter fluency* task (B) *Picture naming* task and (C) *Semantic association* task. No significant performance improvement was found for any task (all $p > 0.05$).

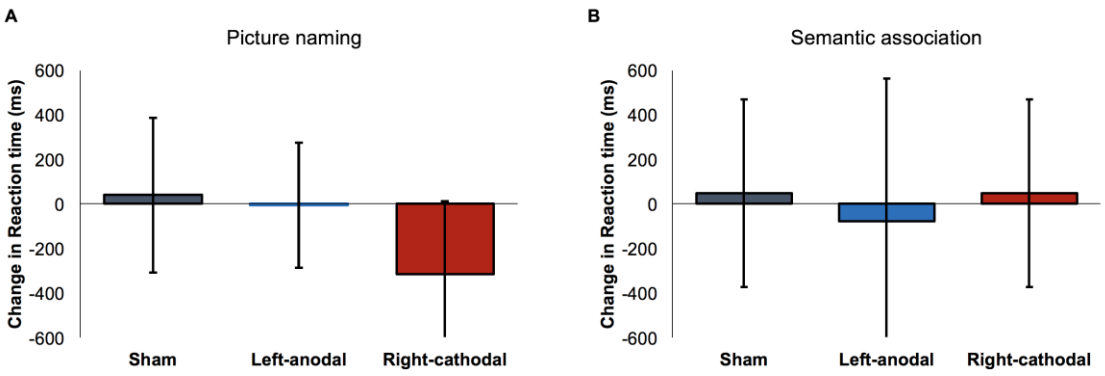

Figure 7. Changes between pre- and post-stimulation for reaction times (mean values and standard deviations): (A) *Picture naming* task and (B) *Semantic association* task. No significant improvement was found for any task (all $p > 0.05$).

Discussion

Transcranial direct current stimulation has been gaining visibility in the field of neurodegenerative diseases as a novel therapeutic tool for this class of untreatable neurological pathologies (i.e. Boggio et al., 2009). As it is the case for lv-PPA patients showing deficits in word-retrieval (Gorno-Tempini et al., 2011), language abilities are often affected in these conditions. Nonetheless, a few tDCS studies have now brought new hope to this domain and reported beneficial outcomes on different aspects of language function in lv-PPA (Ficek et al., 2018; Gervits et al., 2016; Roncero et al., 2017; Tsapkini et al., 2014;2018) and other early onset neurodegenerative diseases, such as the semantic variant of PPA (Teichmann et al., 2016) or Progressive Supranuclear Palsy (Valero-Cabré et al., 2019).

On the basis of such promising results, we here sought to explore the ability of single tDCS sessions to act on language-related deficits in a cohort of 12 lv-PPA patients and provide pre-therapeutic 'proof-of-concept' and identify the valid strategies before undergoing highly demanding clinical trial with multiday stimulation regimes. Using a double-blind sham-controlled

crossover design and following the principle of interhemispheric inhibition, we evaluated the efficacy of two stimulation strategies: the delivery of anodal tDCS over the left TPJ to directly facilitate the activity of language-related regions impaired by atrophy and the use of cathodal tDCS over the right TPJ to suppress interhemispheric inhibitory influences from this area onto left hemisphere regions contributing to language processing. Evaluation of baseline performance before any tDCS session was delivered showed that lv-PPA patients had significantly lower performance in the three chosen language tasks than healthy participants. However, contrary to what we initially predicted, our results did not reveal statistically significant modulations of language performance immediately following a single session of active tDCS, neither left anodal nor right cathodal, in lv-PPA patients.

Logopenic PPA patients have been classically characterized by impairments in the phonological/orthographic code, mainly influencing lexical representations (Gorno-Tempini et al., 2011). However, compared to healthy controls, our results yielded lower performances in both the *Picture naming* task, a marker for both lexical and semantic access and in the *Semantic association* task, which requires intact semantic access abilities (Rogalski et al., 2008; Teichmann et al., 2013), contributing to the further characterization of language deficits in this neurodegenerative disease. The characteristic pattern of cortical atrophy in lv-PPA at initial stages confines damage to the posterior temporal and inferior parietal regions (left > right) (Gorno-Tempini et al., 2011). Additionally, from this location, damage progression spreads to more medial and rostral portions of the left temporal lobe (Leyton et al., 2019). Importantly, the patterns of cortical atrophy in our cohort of lv-PPA revealed by our analyses are totally coherent with such reports.

Our analyses yielded strong impairment in the *Letter fluency* task, which are usually associated with dysfunctions of working memory, self-monitoring and phonological memory

(Schwartz et al., 2003; Troyer et al., 1998) which correlate with damage to frontal regions (Brickmann et al., 2005; Henry and Crawford, 2004; Vonk et al., 2019). However, the significant baseline impairments found for this task in lv-PPA patients compared to healthy controls and the lack of atrophy signs in frontal regions suggests that middle/posterior regions of the temporal cortex might have a more important role in this task that what is usually attributed by correlational studies.

Regarding stimulation, we chose to stimulate the left TPJ since this region has been characterized as the most damaged in lv-PPA patients (Gorno-Tempini et al., 2011). Moreover, previous studies have shown that the stimulation of atrophic brain regions could help boost their activity and deficits related to those regions (Roncero et al., 2017; Teichmann et al., 2016; Valero-Cabré et al., 2019). The computational model predicting effective strength and distribution of tDCS current fields around the TPJ areas and the maps of significantly atrophic areas verified in the patients of our cohort overlapped quite significantly, hence suggesting that our electrode montage targeted the right anatomical regions. In that case, why at difference with prior reports (Ficek et al., 2018; Gervits et al., 2016; Roncero et al., 2017; Tsapkini et al., 2014; 2018) our study failed to demonstrate efficacy improving language deficits in lv-PPA populations? Three main explanations may apply.

First, the above-mentioned studies showing positive results combined stimulation with an *online* language-related task. To this regard, it has been well-established in sensory systems that the modulatory effects of neurostimulation (magnitude and direction) can be determined by the patterns of ongoing activity on the targeted region and associated networks at the time of delivery (Silvanto et al., 2008). In neurodegenerative diseases and for high-level and sophisticated cognitive processes such as language, interactions between activating tasks and transcranial stimulation

remain complex. Hence it remains unclear how ongoing tasks could help optimize final behavioral outcomes driven by stimulation. Moreover, when transcranial stimulation and language tasks are combined, it becomes difficult to disentangle their individual contributions, or rule out the possibility that task training or stimulation alone are playing the active key role. This risk is particularly sensitive in multiday treatment regimes, without adequate patient groups followed in parallel undergoing only task training or stimulation. For this reason, in our study we focused on evaluating the single effects of stimulation, without the co-adjuvant action of additional boosting by language tasks during or following stimulation. Nonetheless, as suggested by prior studies (Ficek et al., 2018; Gervits et al., 2016; Roncero et al., 2017; Tsapkini et al., 2014; 2018) for lv-PPA, the coupling of tDCS with a related-language task might provide an extra-edge necessary for recovery.

Second, another factor could be the higher magnitude and longer lasting modulation with cumulative neuromodulation effects of multi-day stimulation regimes engaging neural plasticity (Monte-Silva et al., 2013). Solid evidence shows that some neurodegenerative diseases experience brief and transient cognitive improvements with a single stimulation session. Hence such signs of pre-clinical response are employed to set ‘proof-of-concept’, identify optimal stimulation target, and test montages in cross-over designs using the same population of patients, before considering evaluation of multiday stimulation regimes (Boggio et al., 2009; Ferrucci et al., 2008; Marceglia et al., 2016; Teichmann et al., 2106; Valero-Cabré et al., 2019). Nonetheless, this two-step process might not always be the optimal choice. Indeed, successful studies in lv-PPA population reported to date have applied up to two weeks of daily tDCS sessions (Ficek et al., 2018; Gervits et al., 2016; Roncero et al., 2017; Tsapkini et al., 2014; 2018), suggesting that longer stimulation periods are required for a measurable impact.

Third and last, most of the successful studies stimulated with specific tDCS montages the left Inferior Frontal Gyrus (Ficek et al., 2018; Tsapkini et al., 2014:2018) or the left fronto-temporal region (Gervits et al., 2016), which are contributors to language processing and less likely to be damaged in lv-PPA patients (Badre et al., 2008; Leyton et al., 2019). Naming, as in a *Picture naming* task, requires contributions from multiple and distant brain regions located in the left temporal and left frontal lobes (Migliaccio et al., 2016; Price, 2010). Thus, targeting left frontal regions might be a better strategy than stimulating regions that are directly correlated with this task (Leyton et al., 2009) but also severely atrophied, hence less responsive.

In conclusion, despite the lack of evidence supporting a beneficial effect of tDCS in language performances for lv-PPA patients with our design, our result should not be discouraging. Instead, our study allowed to detect and highlight important aspects that need to be considered when planning effective stimulation protocols for neurodegenerative diseases. More specifically, we call the reader's attention onto three issues that require further exploration: (1) state-dependency of tDCS effects and their manipulation with concurrent tasks; (2) the need for multiday-stimulation regimes able to engage higher magnitude and longer lasting effects, and eventually plasticity; and (3) the choice of optimal targets among those contributing to language with the highest level of viable neurons to boost.

With regards to state-dependency, successful neurostimulation studies in lv-PPA that implemented a language task during stimulation (Ficek et al., 2018; Gervits et al., 2016; Roncero et al., 2017; Tsapkini et al., 2014; 2018) failed to compare such combined intervention with the isolated effects of stimulation or the task alone, which is a must to identify the active agents of a therapeutic change. With regards to stimulation regimes, it needs to be assumed that some conditions might require several days of periodical stimulation regimes to produce 'proof-of-

concept', hence a negative result in single session pre-clinical studies should not be a discouraging end point, but the start of further testing. Finally, with regards to the selection of cortical targets, one should consider the possibility of avoiding highly atrophic regions and consider long range intra- inter-hemispheric connectivity to intact regions that are part of a same network. We encourage future research in the effects of tDCS as a possible therapy for language deficits in lv-PPA, using double-blind sham-controlled designs and implementing important aspects less explored until now.

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CHAPTER IV

Influence of individual anatomy in current flow during tDCS: models matter

Predictive clinical value of MRI based biophysical models of cortical tDCS fields in the semantic variant of primary progressive aphasia

Résumé en français

L'utilisation croissante de la stimulation transcrânienne en courant continu (STCC) dans les études cliniques a mis en évidence l'importance de la recherche sur les facteurs individuels déterminant les effets de la STCC. La distribution et l'intensité du courant dans le cerveau est déterminé non seulement par la dose de la stimulation et le montage des électrodes, mais également par les caractéristiques anatomiques et des tissus sous-jacents, tels que la distance rectiligne de la peau à la cible cérébrale, la forme du crâne, le volume et l'épaisseur corticale, entre autres. Les champs électriques induits lors de la stimulation chez l'homme ne sont pas faciles à évaluer directement et des approches de modélisation sont donc fréquemment utilisées pour étudier les distributions et les amplitudes du champ électrique dans le cerveau humain en fonction de l'imagerie par résonance magnétique structurelle (IRM) individuelle. Il a été montré que dans des conditions de stimulation identiques, les résultats comportementaux de la STCC ne sont pas cohérents entre les sujets. Étant donné les fortes altérations structurelles du cerveau au cours du vieillissement pathologique, la distorsion que l'anatomie individuelle peut produire sur la distribution du courant électrique et son impact possible sur les résultats cliniques, il est important de prendre en compte de tels facteurs dans la conception de protocoles de stimulation pour les patients neurodégénératifs, pour optimiser leur efficacité et améliorer la sélection des patients qui pourraient le plus bénéficier de ces thérapies.

Dans cette étude, nous analysons les données d'une cohorte de patients souffrant de la variante sémantique de l'aphasie progressive primaire (APP-vs), une maladie neurodégénérative qui affecte principalement le lobe temporal antérieur gauche et altère les capacités langagières, touchant particulièrement les connaissances conceptuelles. Notre objectif était d'explorer l'impact de l'atrophie cérébrale et des caractéristiques anatomiques individuelles chez ces patients sur la distribution et la quantité de courant atteignant leur surface corticale au cours de la STCC, ainsi qu'étudier les caractéristiques anatomiques pouvant mieux expliquer toute variabilité éventuelle des mesures de champ électrique. Enfin, nous avons étudié comment les différences dans les mesures du champ électrique ont eu une incidence sur les résultats des patients dans une tâche

d'association sémantique (AS) suivant une séance de STCC et comment la sévérité de la maladie du patient, mesurée ici en tant que les performances de base dans la tâche d'AS, peut également influer sur la réponse d'un sujet à la stimulation.

Les données utilisées sont issues d'une cohorte de 17 patients avec APP-vs qui avaient été inclus dans un protocole de stimulation ou ils ont subi une séance unique de stimulation anodale pour évaluer ses effets dans une tâche d'AS. La stimulation a été délivrée avec l'anode sur le lobe temporal antérieur gauche et la cathode sur la région supraorbitale droite, pendant 20 minutes et avec une intensité de 1.59mA. Avant et immédiatement après la séance de stimulation les patients ont réalisé une tâche d'AS. Des modèles computationnels de la distribution et intensité du courant ont été produits pour chaque patient en utilisant le logiciel de simulation SimNIBS 2.1.2 et l'IRM individuel de chaque patient. Nous avons étudié les corrélations entre la force du champ électrique et la valeur de la composante normale du champ électrique dans une région d'intérêt, le cortex temporal gauche, et les paramètres anatomiques d'épaisseur corticale et volume de liquide céphalo-rachidien (LCR) sur cette région et l'épaisseur du crâne + peau. Nous avons aussi réalisé une régression linéaire multiple avec la valeur de la composante normale du champ électrique et la sévérité de la maladie (performances en ligne de base dans la tâche d'AS) en tant que variables explicatives de la variabilité de l'amélioration dans cette tâche.

Nous avons trouvé une corrélation positive entre les deux mesures du champ électrique et l'épaisseur corticale du lobe temporal gauche et une corrélation négative entre ces deux mesures et le volume de LCR dans cette région. Notre modèle de régression linéaire montre que les valeurs de la composante normale du champ électrique et la sévérité de la maladie expliquent 48% de la variabilité de l'amélioration après la séance de stimulation.

Nous renforçons ici l'importance de l'utilisation de ces modèles computationnels au préalable des protocoles de stimulation, essentiellement lors du travail avec des populations de patients neurodégénératifs, étant donnée l'influence de l'atrophie cérébrale marqué sur la distribution et l'intensité du courant qui atteint le cerveau. Ces modèles pourraient aider à individualiser les paramètres de stimulation pour chaque patient, permettant ainsi des meilleurs résultats lors des protocoles de stimulation.

Predictive clinical value of MRI based biophysical models of cortical tDCS fields in the semantic variant of primary progressive aphasia

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Keywords: computational models, predicted electrical field, current distribution, non-invasive transcranial brain stimulation, brain neuromodulation, transcranial Direct Current stimulation (tDCS), primary progressive aphasia, cortical atrophy, neurodegenerative diseases, simulations.

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Abstract

Individual anatomical features and properties of the underlying tissues have been shown to influence the distribution and intensity of the current in the brain during transcranial direct current stimulation (tDCS). Computational modeling approaches are now frequently used to study the distribution and amplitude of the electric field in the human brain as a function of individual structural magnetic resonance imaging (MRI). Given the strong structural alterations of the brain during pathological aging, the distortion that individual anatomy can produce on the distribution of electrical current and its possible impact on clinical outcomes, it is important to take into account such factors in the design of stimulation protocols for neurodegenerative patients, to optimize their effectiveness. In this study, we analyze data from a cohort of semantic variant of primary progressive aphasia patients (sv-PPA) to explore the impact of individual anatomical features in these patients on the distribution and amount of current reaching their cortical surface during tDCS. Finally, we investigated how differences in electrical field measurements affected patient outcomes in a semantic association task following a tDCS session and how the severity of the patient's disease can also affect the response of a subject to stimulation. We found a positive correlation between the electric field strength and the normal component of the electric field and the cortical thickness of the left temporal lobe and a negative correlation between these two electric field measurements and the volume of CSF in this region. Our linear regression model shows that the values of the normal component of the electric field and the severity of the disease account for 48% of the variability in improvement after the stimulation session. Our results reinforce the importance of using computational models in advance of stimulation protocols when working with neurodegenerative patient populations given the influence of cerebral atrophy on the distribution and intensity of the current that reaches the brain.

Introduction

The growing use of transcranial direct current stimulation (tDCS) in clinical studies has brought to the fore the importance of individual factors determining tDCS effects. Transcranial DCS fields result into complex spatial distribution patterns of the electric current flow across superficial and deep neural structures, which hinders an accurate strategy to target specific brain areas with sufficient field strength (Opitz et al., 2015).

Current patterns reaching the cortex are significantly altered from those applied to the scalp due to the biophysical properties of tissue layers between the skin and the cortical gray matter (Datta et al., 2009). A great part of the applied current shunts directly from anode to cathode through the skin, hence failing to penetrate through the skull and entering the brain (Rampers et al., 2013). The precise distribution of current fields and the pattern of current flow through the brain is determined not only by the electrode montage and the stimulation intensity (or current density and total dose) but very particularly by underlying anatomical features (Bikson et al., 2012; Datta et al., 2011), such as the skull shape, skin-to-brain straight distance, cortical volume and thickness, sulcal and gyri geometry (Bikson et al., 2012; Wagner et al., 2007). There is indeed evidence that the thickness of the skull, the volume of the cerebrospinal fluid (CSF) in the subdural space and the distance between the tDCS skin electrodes and the target region in the cortical surface account for up to 50% of the spatial variation of the electric field strength (Datta et al., 2012; Opitz et al., 2015; Russell et al., 2013).

The skull is the least conducting medium in the human head, and its thickness strongly determines the amount of current that succeeds in entering the brain (Opitz et al., 2015). Usually, higher field strengths can be found below cortical areas overlaid by thin skull regions, a factor that is important for dosage considerations over intended brain target region (Opitz et al., 2015). On

the contrary, CSF is the highest conductive medium in the human head, provoking a dispersion of currents. Accordingly, brain cortical regions underlying thinner layers of CSF are exposed to higher field strength than those overlain by wide subdural spaces (Miranda et al., 2013; Opitz et al., 2015).

Electric fields (EF) induced during tDCS stimulation cannot be easily measured in humans directly, hence modelling approaches are frequently used to study their spatial distribution and magnitude (Alekseichuk et al., 2019). Computational Finite Element Models (FEM) can be used to estimate the spread and intensity of current fields based on individual structural magnetic resonance imaging (MRI), including all major tissue classes, specific conductivity assumptions and electrode properties (Antonenko et al., 2019; Saturnino et al., 2015). These models account in advance for variability factors as those mentioned above, hence they could allow to tailor individually optimal stimulation settings and approaches (Wagner et al., 2014; Wagner et al., 2007) needed to reach a certain level of current on a given cortical location, necessary to sufficiently modulate local excitability and change behavior.

Such models consider cortical anatomical anisotropies (e.g. sulci, gyri, or areas of atrophy and lesions etc.), the biophysical properties (conductivity) and the volume of the layers of tissue that tDCS fields need to cross through before reaching a cortical target. On that basis, they estimate the cortical site of peak current, the radial spatial distribution of the electric field, which determine focality, and current peak density. Off-the-shelf biophysically-based computational models for tDCS (SimNIBS, Thielscher et al., 2015; BONSAI, Truong et al., 2014; or ROAST, Huang et al. 2019) are now freely available for users. On the basis of a high-resolution MRI from each patient and the segmentation of its different tissue layers, these tools help define if tDCS magnitudes and distribution differ across individuals, and how these differences may affect clinical outcomes.

Transcranial DCS modeling studies often place their focus on field strength as the main outcome measure (Rampers et al., 2019). Nonetheless, although changes in membrane polarization increase with electric field strength (Bikson et al., 2004), the direction of the electric field (defined as a vector) relative to the orientation of the neuraxes (i.e., neuronal longitudinal axis defined by a straight line between the soma and the axon terminal) of impacted neurons plays an essential role (Rahman et al., 2013). With regards to this issue, it has been shown that the electric field predominantly affects neural cells oriented parallel to it (Radman et al., 2009), whereas those that are perpendicularly oriented relating to the electric field will be less influenced (Ye et al., 2011). So, knowledge about the relative orientation of the electric field with regards to neurons is paramount to accurately predict the end result of tDCS stimulation (Miranda et al., 2013) or optimize electrode montages and stimulation parameters to boost impact.

The electric field is a vector that has both a norm (which represents the magnitude or strength of the field) and a direction in space (Saturnino et al., 2019). The direction of the electric vector has a tangential and a normal component. The tangential component represents current that runs parallel to the cortical surface, while the normal component represents current that flows orthogonally to the cortical surface (Saturnino et al., 2019) and is the one conventionally considered to cause most of the physiological effects (Antonenko et al., 2019; Bindman et al.,1964).

It has been noted that under identical tDCS stimulation conditions, behavioral/clinical outcomes evaluating an impact on behaviors can show quite substantial variable effects across the subjects of a group. This might be partly caused by inter-individual differences in the head and brain anatomy (either individual features in healthy participants or brain damage in patients) affecting the distribution and strength of the current that reaches each individual brain. Mahdavi

et al. (2017) modeled current distributions and magnitudes in three head models corresponding to a young and an elder healthy individual, and an old subject presenting mild cognitive impairment (MCI). These authors showed decreased gray matter volume in the MCI model which resulted in a reduction of the magnitude of the current in the brain. Likewise, Kim et al. (2014) used computational models and showed that, for healthy participants who after tDCS over the left dorsolateral prefrontal cortex experienced significant improvements in working memory, models predicted significantly larger field strengths on the targeted regions than for subjects who did not show improvements in working memory. In the same vein, current flow distribution in post-stroke patients has been shown to be strongly affected by the structural anisotropies generated by brain lesions (O'Brien et al., 2016; Wagner et al., 2009). Nonetheless, interestingly, authors have also shown that it is possible to modulate current patterns through a careful selection of electrode montages (Datta et al., 2011; Opitz et al., 2015).

Pathological aging is responsible for strong structural brain alterations of individual anatomy, such as cortical and subcortical atrophy, the thinning of the cortex, and an enlargement of epidural space filled with a higher volume of highly conductive CSF. Such changes induce variable distortion of electrical currents across patients, enhancing response variability and reducing the likelihood of beneficial clinical outcomes. It is hence important to take such factors into account for the design of stimulation protocols for neurodegenerative patients.

We here analyzed data from a cohort of patients diagnosed with the semantic variant of Primary Progressive Aphasia (sv-PPA), a neurodegenerative disease that mainly affects the left anterior temporal lobe (ATL) and impairs language abilities, particularly touching conceptual knowledge (Gorno-Tempini et al., 2004). We aimed to explore how individual anatomical features and brain atrophy in these patients affected the distribution and the amount of current that reached

their cortical surface during tDCS and which anatomical features could better explain any possible variability in electric field measures. We also investigated how differences in electric field magnitude and distribution impacted clinical outcomes following tDCS in a *Semantic association* task and how the disease severity of the patient, here measured as baseline performances in the semantic association task, can also influence a subjects' response to tDCS.

Materials and Methods

Dataset

Data were obtained from n=17 patients diagnosed with sv-PPA (Table 1 for demographic details), who participated in a protocol in which they received a single session of anodal tDCS to gauge its modulatory effects in a *Semantic association* task.

Table 1. Demographic data of the sv-PPA patients (mean ± standard deviation).

	Sv-PPA
Number of patients	17
Female / Male	8 / 9
Mean age (years)	67.6 ± 7.2
Age Range (Max-Min)	53-82
Years of education	13.9 ± 3.5
Handedness (R/L)	17R / 0L
Symptom duration (years)	2.8 ± 1.4

Briefly, each patient performed a baseline (pre-tDCS) evaluation of performance levels in a *Semantic association* task (Figure 1). This was followed by 20 minutes of stimulation (at 1.59 mA using round 25cm^2 electrodes, current density 0.06 mA/cm^2) with the anode placed on a scalp

location minimizing the shortest straight path towards the left ATL (Montreal Neurological Institute [MNI] coordinates: x=-52, y=2, z =-28, located between sites FT7 and FT9 in the 10-20 EEG system) and the cathode over the right supraorbital region (located at AF7 position in the 10-20 EEG system). Immediately after the end of the stimulation, patients underwent a post-tDCS evaluation block of the *Semantic association* task, using a different version to avoid intrasession learning biases.

Prior to the evaluation session, patients underwent an MRI acquisition to identify and label the targeted ATL coordinates. T1-3D Scans were obtained less than one month before the stimulation session using a 3T scanner (VERIO system, SIEMENS, Germany) with a 32-channel head coil including anatomical 3D T1-weighted MPRAGE images (magnetization prepared rapid acquisition gradient echo; TR=2.3s; TE=4.18ms; flip angle=9°; TI=900ms; voxel size=1x1x1mm3; 176 slices). Images were registered in MNI space and the left ATL was identified and labeled by means of a 5mm sphere on the coordinates [x = -52, y = 2, z = -28], using SPM8 (http://www.fil.ion.ucl.ac.uk/spm).

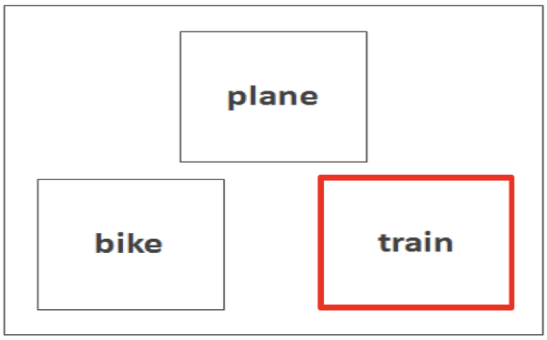

Figure 1. Illustrative items of a representative trial of the *Semantic association* task performed by sv-PPA patients, prior and immediately after the 20 minutes left ATL anodal tDCS session. Patients had to choose which of the two bottom words (right or left) was best associated with the target word presented on the top of the screen, by pressing the right or left keys on a laptop keyboard.

A frameless stereotaxic neuronavigation software (Brainsight, Rogue System, Canada) was used to identify the target region and guide the placement of the active tDCS electrode. Correct and consistent electrode placement was achieved by aligning the center of the active electrode (in the current dataset case the anode) with the orthogonal projection of the MNI-defined target towards the closest skin area overlaying the temporal bone. As indicated above, this procedure ensured for each patient the shortest path-length between the electrode surface and the target location in the cortical surface of the ATL.

Electric field simulations

The software SimNIBS 2.1.2 was used to calculate the electric field induced by tDCS based on a Finite Element Model (FEM) and individualized head models derived from the structural MR images (https://simnibs.drcmr.dk/). SimNIBS was chosen since it is one of the most used free simulation software and it automatically calculates both electric field strength values and values for the normal component of the electric field. First, the T1-weighted anatomical images were used to create individualized tetrahedral FEM head meshes of each subject, using the SimNIBS routine 'headreco'. This procedure uses the Statistical Parametric Mapping (SPM12) to first segment the MRI into six tissue types (skin, skull, CSF, gray matter, white matter and air) and then the FEM mesh is generated by filling in tetrahedrons between the tissue surfaces (Geuzaine and Remacle, 2009).

The tDCS stimulation electrodes and conditions were then set-up on each head model using the Graphical User Interface (GUI) with the exact same parameters employed during the stimulation sessions. Electrodes were modeled as a 1mm thick rubber electrode + 4mm thick round 25 cm^2 sponges. The anode was placed as indicated above over the left ATL [x = -52, y = 2, z = -

28] and the cathode over the right supraorbital region (AF7 location in the 10-20 EEG system) of each model. Electrode locations (i.e., the center coordinates and orientations of the modeled electrodes) for each patient were precisely placed on the generated FEM head mesh on the basis of the head anatomical positions documented for each tDCS session on individual cross-sectional & 3D-T1 MRI images with MRI-based neuronavigation software employed to accurately place electrodes on each patient.

Conductivity values were set as follows (in S/m): skin, 0.465; skull, 0.010; CSF, 1.654; gray matter, 0.275; white matter, 0.126; eye balls, 0.500; eye region, 0.250; electrode rubber, 29.4; electrode saline, 1.4. Transcranial DCS current intensity was set at 1.59mA. The electric field strength (normE) and the normal component of the electric field (E.normal) were calculated for each patient in their native meshes and the individual results were transformed to the normalized space 'fsaverage' provided by Freesurfer.

Anatomical measures

We focused on three outcome measures: cortical thickness, CSF volume and scalp/skull thickness. Cortical thickness and CSF were chosen since these two measures were shown to greatly influence current magnitudes and distribution and are features that are strongly altered in neurodegenerative brains, we hypothesize then that they should be the most influential in these patients. Scalp/skull thickness determines the amount of current that actually enters the brain, reaching the cortical surface, and seems thus important to study its influence in electric field measures.

Cortical thickness and CSF volume were computed using the computational anatomy CAT12 toolbox (http://www.neuro.uni-jena.de/cat/), an extension of SPM12. Cortical thickness

and CSF volume for specific regions of interest were obtained based on the *Neuromorphometrics* atlas (to label the different regions). We computed the mean values for cortical thickness and CSF volume in the left Temporal Pole, left Superior Temporal, Middle Temporal and Inferior Temporal Gyrus. Scalp/skull thickness was defined as the Euclidean distance between the center of the anode placed on the scalp region overlying the left ATL and the CSF/bone interface. The distance was measured using FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/).

Data analyses

In order to test our hypothesis that inter-individual differences in the estimated electric field induced in our targeted region scaled with differences in individual anatomical parameters, we extracted individual fields from a defined region-of-interest (ROI). Our target ROI was defined based on the Desikan-Killiany atlas (Desikan et al., 2009) as the junction between the left Superior Temporal Gyrus, the left Middle Temporal Gyrus and the left Inferior Temporal Gyrus. By doing so, we ensured that specific brain coordinates on which the stimulation electrode exerted strongest effects were included in our analysis. Both electric field strength and the normal component of the electrical field were extracted and correlated separately with anatomical measures.

We first studied the links between two features of the electrical field (EF) modeled for an ROI including the temporal lobe, hence encompassing the above-mentioned left ATL target: (a) EF peak strength or 'normE' and (b) EF normal component or 'E.normal'; and the following three head-brain anatomical features shown to greatly influence tDCS generated electrical fields: (1) cortical thickness (2) CSF volume, and (3) scalp/skull thickness. We did so by applying a permutation test (Groppe et al., 2011) based on Pearson's correlation coefficient, with 5000 permutations, between pairs of parameters. Since this is a hypothesis-driven study we accepted

uncorrected p-values as significant (Kim and Bang, 2016), however, we also used the max statistic method to adjust p-values in a way that controls the family-wise error rate, and we present these p-values corrected for multiple correlations. The null hypothesis of the permutation test is that the correlation obtained with the initial order in the variables is as likely as the correlation obtained with random permutations. The value of the peak electric field strength (across the whole brain or within our selected ROI) was estimated excluding the 0.1% highest values to avoid the influence of outliers.

Furthermore, in order to explore which variables could explain a patients' response to tDCS, we performed a multiple linear regression using performance improvements in the *Semantic association* task from pre- to post-tDCS as the dependent variable and disease severity (from which we took baseline performances in the *Semantic association* task as a marker), the 'normE' and the 'E.normal' values as explanatory variables.

Results

Electric field strength in ROI ('normE')

Electric field strength in the left temporal lobe (the selected ROI encompassing our tDCS target, i.e., the ATL) reached quite distinctive levels of activity, which varied considerably across our participants between 0.289 V/m and 0.522 V/m (Figure 2 and Figure 2Alt). In all patients of our cohort, peak electric field strength values ('normE') were identified in a ventral frontal region (inferior orbitofrontal cortex), hence outside of the selected left temporal lobe ROI or outside the boundaries of the ATL which was our target region.

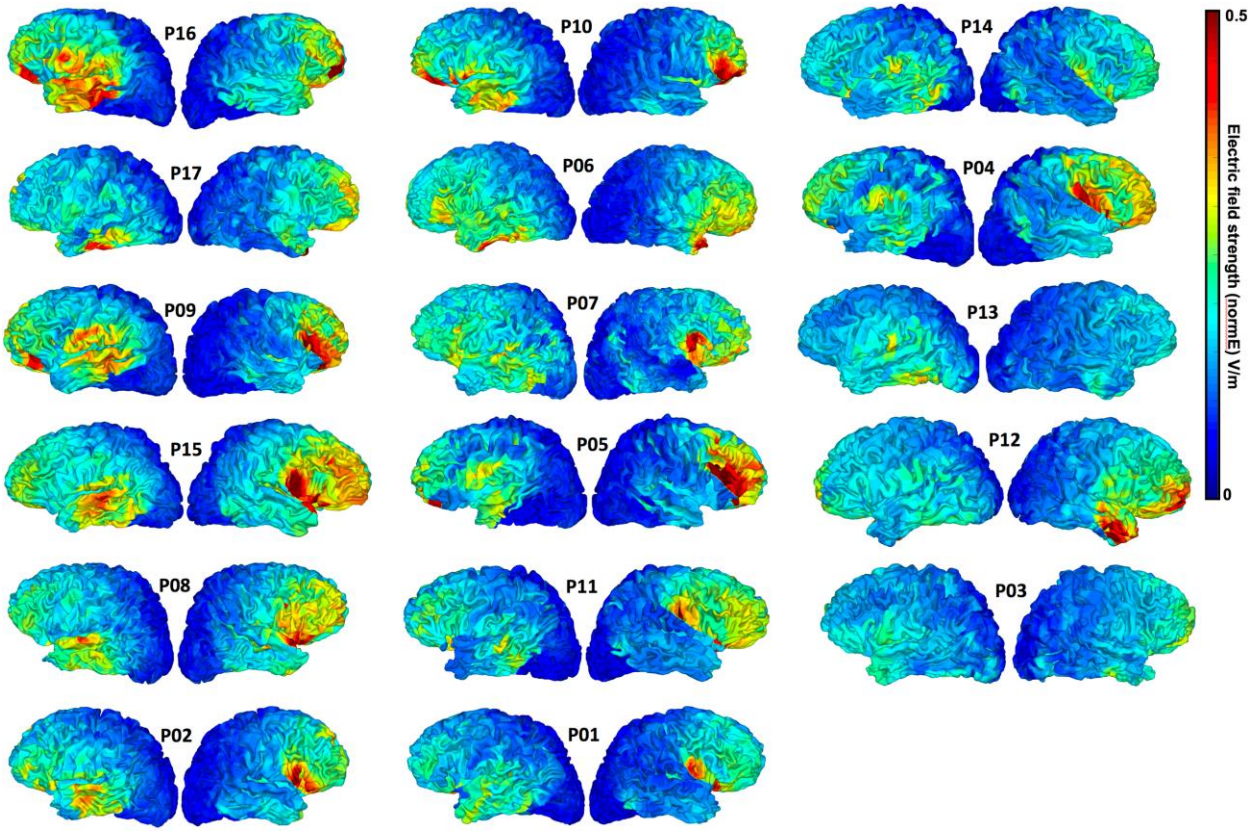

Figure 2. Electric field strength ('normE') for each individual patient presented in their native space (from P1 to P17) on a 3D reconstruction of each individual brain (left and right hemispheres). Patient models are presented in decreasing levels of maximum 'normE' values at our selected ROI (i.e., the whole left temporal lobe) from top to bottom and left to right in the figure. Notice that the maximal peak 'normE' values were found in a ventral frontal location (~the inferior orbitofrontal cortex) which is not easily visible in the presented captions. Color bar represents electrical field strength 'normE' in V/m.

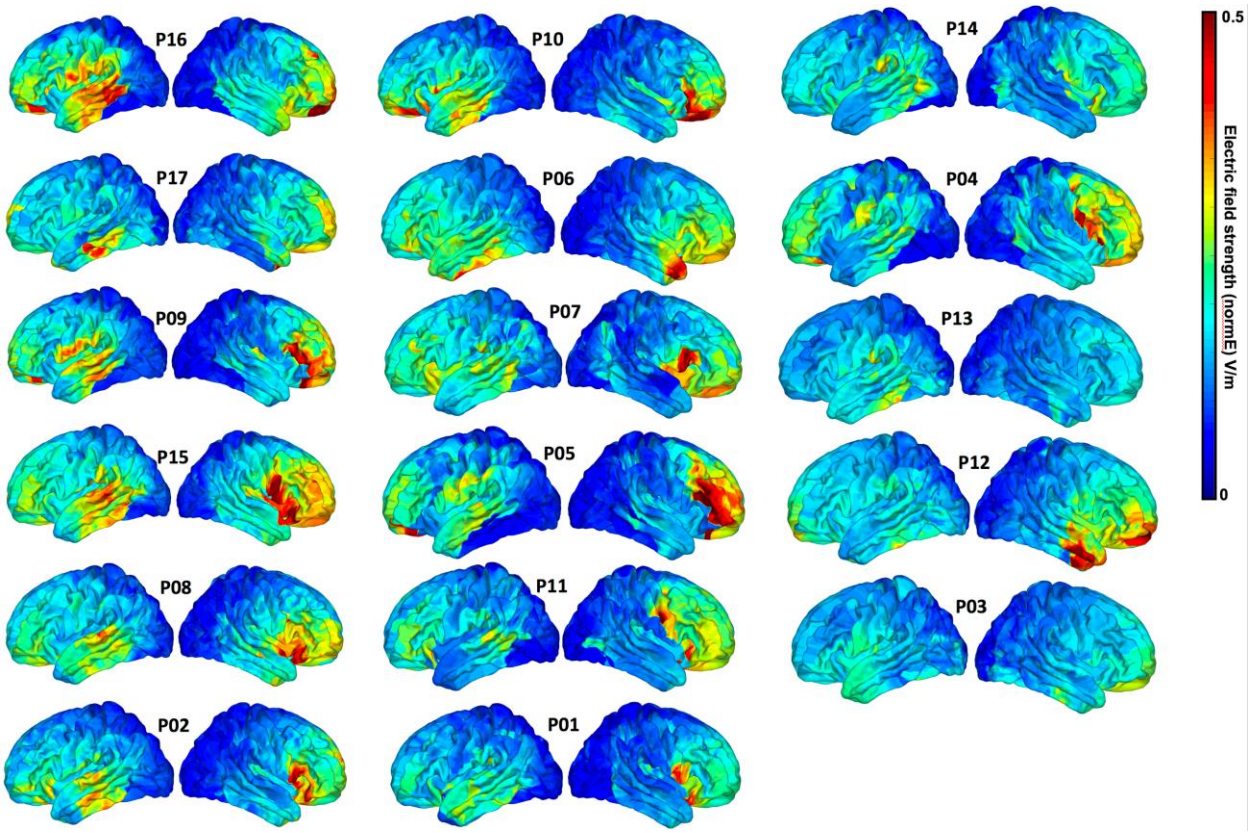

Figure 2Alt. Electric field strength ('normE') for all patients (from P1 to P17) in the 'fsaverage' normalized space provided by Freesurfer on a 3D reconstruction of each individual brain (left and right hemispheres). Patient models are presented in decreasing levels of maximum 'normE' values at the left temporal lobe ROI (from top to bottom and left to right in the figure). Notice that the maximal peak 'normE' values were found in the inferior orbitofrontal cortex, hence outside the above-mentioned ROI, which being a ventral region is not easily visible in the presented captions. Color bar represents electrical field strength values 'normE' in V/m.

Peak values of electric field strength in the temporal cortex showed a significant positive correlation with cortical thickness in this same cortical area, suggesting that the higher the thickness the higher the electric field strength (Figure 3A): r = 0.564, p = 0.015 (uncorrected), p = 0.046 (corrected). Additionally, a marginally significant negative correlation was found between electric field strength and CSF volume in the temporal cortex (Figure3B): r = -0.539, p = 0.026

(uncorrected), p = 0.070 (corrected). However, no significant correlation was found between electric field strength and scalp/skull thickness (Figure 3C): r = -0.423, p = 0.09 (uncorrected), p = 0.227 (corrected).

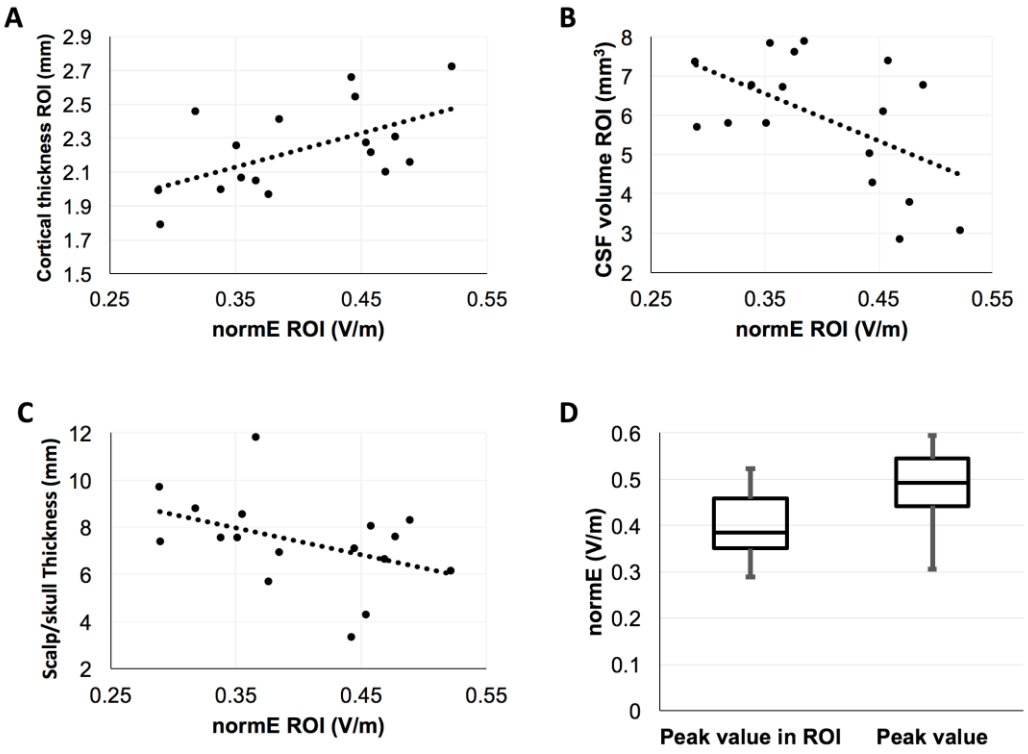

Figure 3. Correlations between peak electric field strength ('normE') values in the left temporal lobe for the three anatomical measures: cortical thickness, CSF volume and scalp/skull thickness. Three main outcomes are to be noted: (A) A significant positive correlation with cortical thickness on the selected ROI (B) A marginally significant negative correlation with CSF volume in the left temporal lobe (C) A lack of significant correlation with scalp/skull thickness globally or around the same above-mentioned ROI. (D) Boxplot representing the variability of electric field strength peak values in the ROI and in the whole brain (maximum, minimum and median).

Normal component of the electric field (E.normal)

The maximal peak values for the normal component of the electric field 'E.norm' were found this time within the boundaries of our pre-designated ROI, the left temporal lobe, in our

cohort of 17 sv-PPA patients. Values varied between 0.203 V/m and 0.387 V/m (Figure 4 and Figure 4Alt).

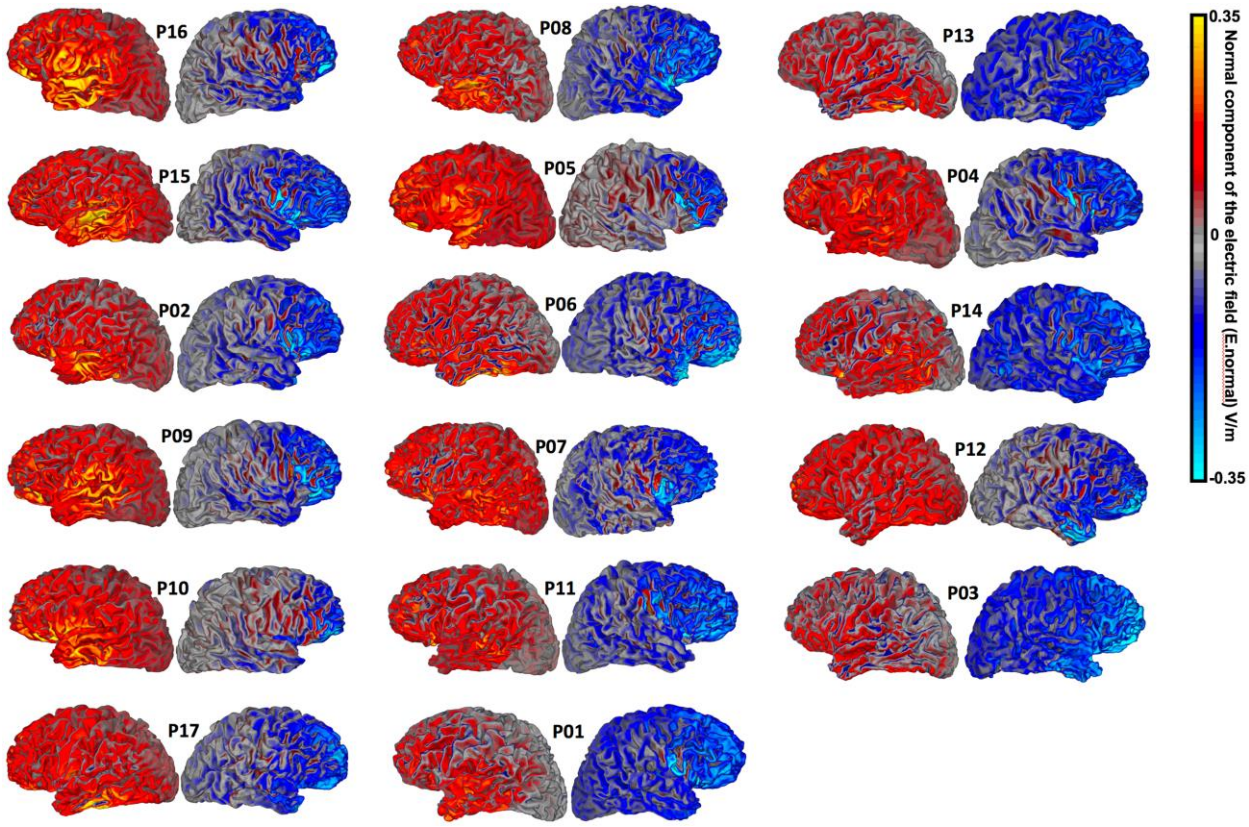

Figure 4. Normal component of the electric field (E.normal) for all patients (P1 to P17) in the native space, on a 3D reconstruction of each individual brain (left and right hemispheres). Patient models are presented in decreasing levels of maximum 'E.normal' values within the selected left temporal lobe ROI (presented from top to bottom and left to right in the figure). The color bar represents values of 'E.normal' in V/m. Warm colors (positive values) represent current that flows into the brain while cold colors (negative values) represent current that flows outwards.

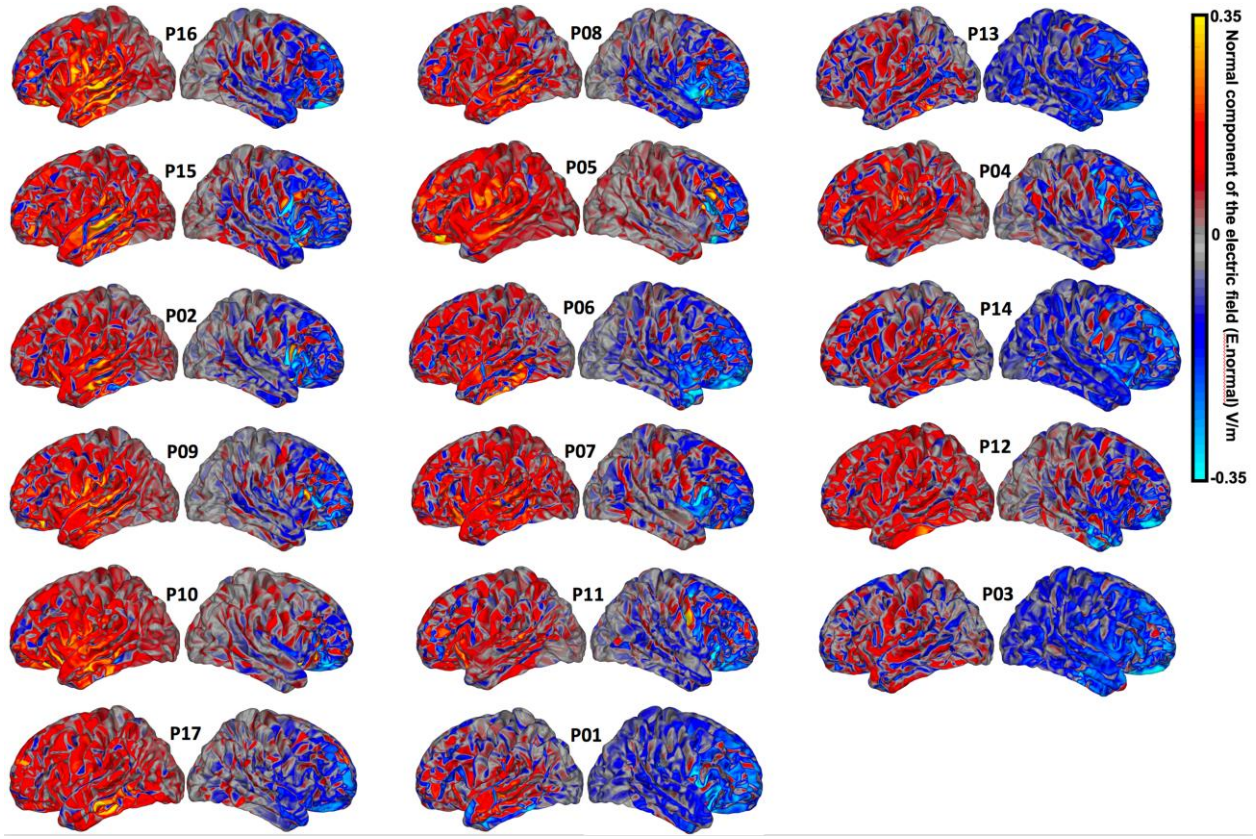

Figure 4 Alt. Normal component of the electric field (E.normal) for all patients (P1 to P17) in the 'fsaverage' normalized space provided by Freesurfer model on a 3D reconstruction of each individual brain (left and right hemispheres). Patient models are presented in decreasing levels of maximum 'E.normal' values at the ROI target (from top to bottom and left to right in the figure). The color bar represents values of 'E.normal' in V/m. Warm colors (positive values) represent current that flows into the brain while cold colors (negative values) represents current that flows outwards.

Peak values of the normal component of electric field showed a marginally significant positive correlation with cortical thickness in the temporal cortex (Figure 5A): $r = 0.485$, $p = 0.026$ (uncorrected), $p = 0.12$ (corrected). A marginally significant negative correlation was found between electric field strength and CSF volume in the temporal cortex (Figure5B): $r = -0.511$, $p = 0.024$ (uncorrected), $p = 0.091$ (corrected). However, no significant correlation was found between

electric field strength and scalp/skull thickness (Figure 5C): r = -0.422, p = 0.095 (uncorrected), p = 0.226 (corrected).

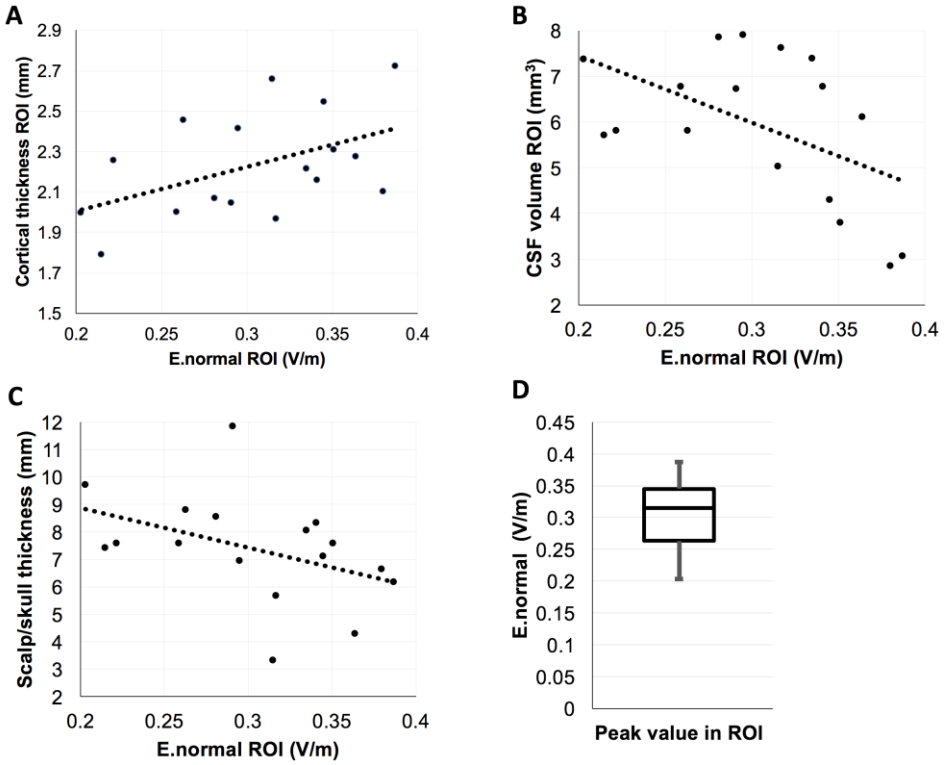

Figure 5. Correlations between values of the normal component of the electric field ('E.normal') in the targeted ROI for the three anatomical measures: cortical thickness, CSF volume and scalp/skull thickness. Three main outcomes are to be noted: (A) A positive correlation with cortical thickness in the ROI (B) A negative correlation with CSF volume in the ROI (C) Lack of any significant correlation with scalp/skull thickness. (D) Boxplot representing the variability of normal component of electric field peak values in the ROI (maximum, minimum and median); in general, the peak value in the ROI coincided with the peak value taking in account the whole brain.

Explanatory variables for patients' response for left anodal tDCS effects on semantic access

Since the 'normE' and 'E.normal' parameters associated to the electric field are highly correlated (r = 0.905, p<0.001), these cannot be introduced together in a multiple linear regression analysis. Assuming that the effect of stimulation is highest if the electric field is directed parallel to the fibers, and that gray matter pyramidal neurons lie perpendicular to the cortical surface, we

opted for using the 'E.normal' parameter in our model. The combination in a regression analysis of the factors 'E.normal' and baseline performance for the *Semantic association* task explained 48% of the variance of post-pre performance changes (R^2 = 0.48, F(2,14) = 6.473, p = 0.01). Both 'E.normal' and baseline performance added statistically significantly to the prediction of performance improvement ('E.normal': p = 0.023; baseline performances: p = 0.006). This demonstrates that explored features exerted a significant influence on patients' response to tDCS. In such context, the equation to predict performance improvements works as follows: performance improvement = -6.224 + (126.152 * 'E.normal') + (0.528* 'baseline performance').

Discussion

We here aimed to explore associations between individual anatomical features of sv-PPA patients extracted from patient's MRI datasets and simulations of anodal tDCS induced current values in a targeted left temporal cortex. We also aimed to explain variability in the post-pre tDCS performance outcomes in a *Semantic association* task on the basis of patients' baseline performance (i.e., informing on disease severity at the time of inclusion) and model-estimated electric field values. The electric field orthogonal to the cortical surface (represented by the so called normal component, 'E.nomal') is considered the main responsible factor for physiological effects such as facilitation (anodal, inward current, positive) or inhibition (cathodal, outward current, negative) of cortical activity (Antonenko et al., 2019; Bindman et al.,1964). The role of other field components is less clear, considering the isotropy of horizontally oriented neurons (Laakso et al., 2016). For these reasons we supplemented the study of the absolute value of the electric field (also known as electric field strength, 'normE') with that of its normal component ('E.normal').

Semantic PPA patients are characterized by a selective atrophy of the left ATL (Gorno-Tempini et al., 2004). Computational models have consistently predicted that cortical volume and thickness greatly influence the flow and distribution currents during tDCS (Bikson et al., 2012; Wagner et al., 2007) which should be even more noticed in neurodegenerative patients as compared to healthy control, due to their strong brain alterations. This is in part caused by pathological structural anisotropies adding to those already present naturally in the cortex, such as gyri or sulci (O'Brien et al. 2016; Wagner et al., 2007, Wagner et al., 2009). Most importantly however, the thinning of the cortex increases the volume of CSF cumulated in sulci and between the piamater and the duramater (Mahdavi et al., 2018), acting as a highly conductive media which tends to blur out the distribution of current making them less predictable (O'Brien et al. 2016; Wagner et al., 2009).

The MRI based individual biophysical models of current distribution we produced for each of our 17 sv-PPA patients showed, as we expected, that currents were dispersed across the whole left temporal cortex. Nonetheless, peak values of electric field strength ('normE') and the normal component ('E.normal') were not necessarily located in the targeted left ATL region, but rather in orbitofrontal regions between the left ATL anode and the right supraorbital cathode (for the normE) or more posteriorly in the temporal cortex (for the E.normal). When considering the whole left temporal cortex as ROI, our analyses showed that both peak values of 'normE' and 'E.normal' in this region correlated positively with cortical thickness in this region. These results suggest that atrophy of the temporal cortex has a negative impact on electric field measures.

As indicated above, the CSF is the highest conductive medium present the brain, hence expected to be the most influential pathological factor affecting cortical structure that influences an accurate prediction of current fields and clinical outcomes. It is well-established that loss of

gray matter volume caused by cortical atrophy is associated with the broadening of CSF volume (Mahdavi et al., 2018). Either marginally significant or significant negative correlation reported in our datasets between CSF volume in the left temporal cortex and both electric field measures ('normE' and 'E.normal') suggest that a great atrophy of the temporal cortex, reflected by a higher CSF volume, dissipates the field and reduces its magnitude on the ROI around the specific target. We also addressed the influence of interindividual variability in scalp/skull thickness, which we measured as the Euclidean distance (shortest or most straight path-length) from the center of the anode to the CSF/bone interface in an imaginary line linking the former to the ATL cortical target. Both skin and bone are two layers the current has to go through before reaching the brain. This structural feature has been suggested to exert an influence on electric field measures (Datta et al., 2012; Opitz et al., 2015; Russell et al., 2013). However, surprisingly, our outcomes did not reveal an influence of this anatomical feature, neither on absolute electric field strength ('normE') or its normal component ('E.normal'). Nonetheless, this outcome can be explained. Indeed, Opitz et al. (2015) showed that electric field strength is influenced not only by skull thickness but also by its specific composition and particularly the thickness of spongy versus compact bone layers. In the same vein, the thickness and resistivity/conductivity properties of tissue layers overlying the bone, such as skin, fat and muscle, which according to differences in head shape could be very different across participants, may also influence electric field values (Miranda et al., 2013). Unfortunately, the faculty to segment either bone layers (e.g. the inner and outer *tables* and in between the *cancellous* bone layer known as *diploe*) or accurately estimate skin, fat and muscle layer thickness was hindered by the resolution of our clinical MRI and the limited ability to independently measure the thickness of these layers and sublayers. Hence, we cannot rule out that head-to-head interindividual differences in tissue types might have influenced our results.

Importantly, our regression model showed that patients' symptom severity at baseline (or said otherwise, patient performance skills at baseline) along with the electric field generated in the cortex is an important factor to predict performance benefits of stimulation. This result has precedence in the domain of non-invasive brain stimulation and neurodegenerative diseases. For example, Rutherford et al. (2015) showed that transcranial magnetic stimulation (TMS) improved performance in a word-picture association task in patients with Alzheimer's disease (AD) more strongly in early-stage than late-stage patients. Similarly, Zhao et al. (2017) found improvements in the Alzheimer's Disease Assessment Scale-cognitive subscale after TMS for mild but not moderate AD. Taken together, the observation that the pre-clinical or clinical success of neurostimulation (either with TMS or tDCS), might depend on acting in patients within a specific window of clinical severity has been gaining momentum. It could be explained by floor/ceiling effects and poor sensitivity of tasks used to assess outcomes; tied to poor levels of electric field strength unable to significantly shift resting membrane potentials, or excessive levels of cortical atrophy sparing insufficient resources to be neuromodulated by tDCS on the targeted area.

To avoid the labor-intensive process required for manual segmentation of patients' MRI (Huang et al., 2013), we here tested the automated segmentation performed by the 'headreco' function included in SimNIBS. Unfortunately, this procedure has not off-the-shelf support for injured brains (Saturnino et al., 2019). To this regard, an unpublished study demonstrated significantly different values for the predicted electric fields in post-stroke lesioned brains, when comparing the use of manual vs. automated segmentations tools (Datta, 2019). Moreover, in our study we used a hypothesis-based approach to select a limited set of structural outcome measures (cortical thickness, CSF volume and scalp/skull thickness) as the three fundamental variables used for further correlations. Nonetheless, we cannot rule out that many other macro- and

microstructural properties or physiological features, that we could not easily quantify or determine, may have also played a role. Future work needs to validate current results with manually corrected segmentation and expand the number of anatomical and physiological brain features considered in correlations or multivariate analyses.

A strength of the current work is the use of an MRI-based frameless neuronavigation system to accurately place the electrodes on the patients' scalp. Data saved by this system, and device with millimeter precision, allowed an accurate placement in MRI based models of tDCS electrodes in the exact same sites employed during real stimulation sessions. This is important as Opitz et al. (2018) recently reported that the predicted electric fields generated by transcranial electric stimulation, using bipolar montages with 25cm^2 round sponge electrodes, is compromised when the placement of the electrode *in silico* on FEM head model differ 1 cm or more from the actual electrode placement, used in vivo. The use of MRI based neuronavigation systems to place electrodes on the scalp becomes critical to increase model accuracy, and enhance intrasubject reproducibility in stimulation protocols and adequately reflect inter-subject variability in outcomes (Miranda et al., 2018). Moreover, post-hoc modeling studies allowing to estimate the site of local current maxima and distribution of the electric field during tDCS applications can be very useful to better understand behavioral outcomes and their variability (Miranda et al., 2018). More interesting however, once models are optimized and accurate, MRI based computer simulations calculated prior to a stimulation protocol, could be used to guide the customization of stimulation montages and parameters based on each patient characteristics.

Conclusion

We here used *in silico* computational approaches and provided quantitative estimates of electric field cortical magnitudes in sv-PPA patients by modeling, on their individual MRI datasets, the distribution of tDCS currents. We individually implemented electrode placement schemes, stimulation conditions and parameters which mimicked those employed in *in vivo* on our patients. We aimed to understand performance variability in a *Semantic association* task modulated by tDCS. We showed that individual anatomical parameters such as cortical thickness and CSF volume do play a major role on the magnitude of the electric field reaching the intended target region. We thus confirmed the criticality of these two factors, particularly for neurodegenerative diseases in which local or widespread atrophy will largely impact the distribution of tDCS electric fields and its clinical effects. Moreover, we showed that the amount of current reaching the cortex and the clinical severity of patients at baseline are responsible, among other unexplored factors, for performance variability. With the use of accurate MRI-based and biophysically-inspired computational models, the use of *pre-hoc* simulations able to predict current fields in individual brains will become the norm to individualize stimulation parameters.

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CHAPTER V

The future of clinical trials using tDCS on neurodegenerative patients – PHRC-STIM-SD

Testing the therapeutic effects of transcranial direct current stimulation (tDCS) in semantic dementia: A double blind, sham controlled, randomized clinical trial

The following article has been accepted for publication by Trials.

Résumé en français

La démence sémantique (DS) appartient au groupe des dégénérescences lobaires frontotemporales et entraîne une atteinte profonde des capacités langagières. La DS affecte plus particulièrement le système sémantique en endommageant les pôles temporaux avec une latéralisation hémisphérique gauche. Il s'agit d'une maladie à début précoce, souvent avant 65 ans, et il n'y a aucun traitement validé.

Toutefois, une nouvelle piste thérapeutique pourrait être celle de la stimulation transcrânienne en courant continu (STCC) qui a permis de fournir des résultats prometteurs dans les aphasies post-Accident Vasculaire Cérébrale. Les effets de la STCC sont basés sur un faible courant électrique (1-2 mA) véhiculé entre deux électrodes (un actif et un retour) placées à différents endroits du cuir chevelu, avec la possibilité de générer un gradient de polarisation à travers une grande zone corticale entre les deux électrodes, modulant ainsi l'excitabilité corticale à l'intérieur de ses limites. Deux modalités de la STCC sont couramment utilisées: la stimulation anodale (l'anode est placée sur la région cible) augmente le potentiel de repos membranaire dans les neurones, facilitant ainsi l'activité neuronale; la stimulation cathodale (la cathode est placée sur la région cible), qui entraîne généralement l'effet inverse: une diminution du potentiel membranaire, inhibant ou réduisant l'activité neuronale.

Plusieurs études ont ciblé des aires corticales du langage dans l'hémisphère gauche par une STCC anodale ou des aires homologues droites par une STCC cathodale. Cette approche est basée sur le principe d'inhibition interhémisphérique, et notamment l'influence inhibitrice de aires homologues droites sur les aires langagières gauches. De plus, des études dans l'aphasie post-AVC utilisant la STCC répétitive sur plusieurs jours ont montré des effets langagiers relativement durables, allant jusqu'à 3 mois, probablement par des mécanismes de neuroplasticité induite par

la STCC répétitive. Malgré ces résultats encourageants, la plupart des études n'ont pas ciblé les régions cérébrales spécifiques au langage et le petit nombre de patients a exclu la conception d'une étude contrebalancée. De plus, les deux types de STCC anodale-gauche / cathodale-droite ne sont pas systématiquement évalués pour révéler la stratégie la plus efficace pour l'aphasie d'origine dégénérative.

Notre étude propose l'application répétitive sur plusieurs jours de la STCC sur les pôles temporaux dans une large population de patients atteints de DS. Elle est bâtie sur une investigation pilote de notre équipe qui a utilisé trois séances de STCC dans une étude en double aveugle controlée par placebo dans la DS (N=12). La stimulation anodale du pôle temporal gauche et cathodale du pôle temporal droit (versus STCC placebo) ont permis d'obtenir une modulation hautement significative et transitoire des processus sémantiques. Cette investigation de 'preuve de concept' a fourni le rationnel pour l'étude actuelle qui utilisera la STCC répétitive sur 10 jours pour obtenir un effet thérapeutique par neuroplasticité.

L'objectif principal de cet essai clinique est d'évaluer l'efficacité thérapeutique d'un régime de STCC sur plusieurs jours sur les déficits du langage chez les patients atteints de DS. L'étude explore également l'évolution dans le temps des améliorations potentielles induites par la STCC et utilise des biomarqueurs d'imagerie qui pourraient refléter la neuroplasticité induite par la stimulation.

C'est une étude randomisée en double-aveugle contrôlée par placebo, appliquant la STCC quotidiennement pendant 10 jours et avec des évaluations langagières/sémantiques et des examens de neuroimagerie à 4 moments: ligne de base, 3 jours, 2 semaines et 4 mois après les 10 séances de stimulation. Les évaluations linguistiques/sémantiques seront appliquées aux 4 points dans le temps. Une tomographie par émission de positons au fluorodésoxyglucose (TEP-FDG), une imagerie par résonance magnétique fonctionnelle au repos (rs-fMRI), des images pondérées en T1 et une imagerie du tenseur de diffusion de la substance blanche (DTI) seront appliquées à la ligne de base et à la période de deux semaines post-stmulation. Selon le principe d'inhibition interhémisphérique entre les régions homotopiques gauches et droites, nous utiliserons deux modalités de stimulation: la STCC anodale gauche et cathodale droite sur les lobes temporaux antérieurs. En conséquence, la population de patients (N = 60) sera divisée en 3 sous-groupes: STCC anodale gauche (N = 20), STCC cathodale droite (N = 20) et STCC placebo (N = 20). La

durée de la stimulation sera maintenue pendant 20 minutes à une intensité de 1.59 mA. Les électrodes de stimulation rondes avec une superficie de 25 cm^2 (densité de courant de 0,06 mA/cm^2) seront placées sur les lobes temporaux antérieurs gauche et droit pour la stimulation anodale et cathodale, respectivement. Un groupe de sujets sains (N = 20) d'âge, de sexe et d'éducation similaires aux patients sera également recruté et testé pour fournir des valeurs normatives pour les tâches langagières/sémantiques et les mesures de neuroimagerie.

L'étude vise à évaluer l'efficacité de la STCC dans le traitement des troubles du langage et des troubles sémantiques liés à la DS et les méchanismes de neuroplasticité induits par la stimulation. Un traitement potentiel serait facilement applicable, peu coûteux et renouvelable lorsque les effets thérapeutiques disparaissent en raison de la progression de la maladie.

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Trials

STUDY PROTOCOL Open Access

Testing the therapeutic effects of transcranial direct current stimulation (tDCS) in semantic dementia: a double blind, sham controlled, randomized clinical trial

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Abstract

Background: Semantic dementia is a neurodegenerative disease that primarily affects the left anterior temporal lobe, resulting in a gradual loss of conceptual knowledge. There is currently no validated treatment. Transcranial stimulation has provided evidence for long-lasting language effects presumably linked to stimulation-induced neuroplasticity in post-stroke aphasia. However, studies evaluating its effects in neurodegenerative diseases such as semantic dementia are still rare and evidence from double-blind, prospective, therapeutic trials is required.

Objective: The primary objective of the present clinical trial (STIM-SD) is to evaluate the therapeutic efficacy of a multiday transcranial direct current stimulation (tDCS) regime on language impairment in patients with semantic dementia. The study also explores the time course of potential tDCS-driven improvements and uses imaging biomarkers that could reflect stimulation-induced neuroplasticity.

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Methods: This is a double-blind, sham-controlled, randomized study using transcranial Direct Current Stimulation (tDCS) applied daily for 10 days, and language/semantic and imaging assessments at four time points: baseline, 3 days, 2 weeks and 4 months after 10 stimulation sessions. Language/semantic assessments will be carried out at these same 4 time points. Fluorodeoxyglucose positron emission tomography (FDG-PET), resting-state functional magnetic resonance imaging (rs-fMRI), T1-weighted images and white matter diffusion tensor imaging (DTI) will be applied at baseline and at the 2-week time point. According to the principle of inter-hemispheric inhibition between left (language-related) and right homotopic regions we will use two stimulation modalities - left-anodal and right-cathodal tDCS over the anterior temporal lobes. Accordingly, the patient population ($n = 60$) will be subdivided into three subgroups: left-anodal tDCS ($n = 20$), right-cathodal tDCS ($n = 20$) and sham tDCS ($n = 20$). The stimulation will be sustained for 20 min at an intensity of 1.59 mA. It will be delivered through 25cm^2-round stimulation electrodes (current density of 0.06 mA/cm^2) placed over the left and right anterior temporal lobes for anodal and cathodal stimulation, respectively. A group of healthy participants ($n = 20$) matched by age, gender and education will also be recruited and tested to provide normative values for the language/semantic tasks and imaging measures.

Discussion: The aim of this study is to assess the efficacy of tDCS for language/semantic disorders in semantic dementia. A potential treatment would be easily applicable, inexpensive, and renewable when therapeutic effects disappear due to disease progression.

Trial registration: ClinicalTrials.gov NCT03481933. Registered on March 2018.

Keywords: Non-invasive brain stimulation, Transcranial direct current stimulation, Semantic dementia, Primary progressive aphasia, Language impairments, Neurodegenerative diseases, Neurology

Introduction

Semantic dementia (SD), also referred to as the semantic variant of primary progressive aphasia (sv-PPA) [1], is part of the spectrum of frontotemporal lobar degeneration and constitutes one of the major clinical variants of this disorder [2]. The onset age of SD is frequently before 65 years [3] and it severely affects the ability to communicate, which generates a major impact on the family and socio-professional life of patients.

SD is characterized by a gradual and severe loss of conceptual knowledge, resulting in anomia, impaired word comprehension and speech that is fluent but empty of content [2], leaving grammar and speech articulation preserved [4]. Although the most prominent deficits concern word meaning [1, 4], SD might eventually cause deterioration of knowledge for all kinds of semantic concepts [5, 6] impacting on face recognition [7], object feature attribution [8], sound-picture matching [9] and object-use [10]. The damage to multi-modal semantic representations, besides the verbal domain, gave birth to the concept of semantic dementia [11]. It therefore appears that sv-PPA is a purely linguistic variant of SD [12] and/or that SD results from the evolving disease course of sv-PPA [13, 14].

At the anatomical level SD affects the anterior temporal lobe (ATL) of both hemispheres, predominantly in left lateralized regions [1, 4]. Correlation has been identified between gray matter loss in the ATL and different semantic tasks like picture naming [15, 16] and word-picture association [17]. It is associated with disruptions of functional connectivity between a broad range of brain regions across the temporal, frontal, parietal and occipital lobes, including visual and auditory association cortices [18]. Alterations of structural connectivity such as a white matter volume reduction in the left temporal lobe, the periventricular white matter and the corpus callosum [19], and damage to white matter tracts such as the inferior longitudinal fasciculus (ILF) and the uncinate fasciculus (UF) have also been found in SD [20]. Signs of cortical hypometabolism, which are a useful neuroimaging hallmark for diagnosis have mainly been found in the ATL cortices, sometimes extending to the subgenual region and the right anterior cingulate cortex [21].

There is currently no validated treatment for SD given that speech therapy protocols have not been validated and pharmacological trials did not demonstrate significant effects [22–24]. In this context, new approaches based on the use of non-invasive brain stimulation and neuro-modulation [25] might represent a promising therapeutic strategy. Two of the most common technologies for non-invasive brain stimulation are repetitive transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) [26]. Repetitive TMS involves the application of a series of magnetic pulses through a stimulating coil placed in contact with an area of the scalp. In a frequency-dependent and pattern-dependent manner, this stimulation technology induces an intracranial electric current that subsequently modulates (inhibits or facilitates) neuronal activity [26]. Repetitive TMS is characterized by its excellent spatial and temporal resolution and ability to make neurons

discharge, features that come at the cost of low portability, high financial cost and epileptic risk. The effects of tDCS are based on a weak electric current (1–2 mA) conveyed between two electrodes (an active and a return) placed on separate locations of the scalp, with the ability to generate a polarization gradient across a large cortical area between electrodes, hence modulating cortical excitability within its boundaries [27]. Two modalities of tDCS are commonly used: Anodal and Cathodal stimulation. Anodal stimulation (in which the anode is placed on the targeted region) shifts the membrane resting potential of local neurons bringing it closer to their firing threshold (i.e. making it more positive hence depolarizing local cells). This modality increases regional excitability and facilitates the activation of neurons hence the production of action potentials in response to physiological inputs (excitatory effects). Cathodal stimulation (in which the cathode is placed on the targeted region), shifts the resting membrane potential of nearby neurons away from their firing threshold (i.e., making it more negative, hence hyperpolarizing local cells). Consequently, this modality decreases regional excitability hindering the likelihood of such neurons to generate an action potential in response to a physiological input (inhibitory effects).

For several years a growing number of studies have explored the effects of non-invasive brain stimulation in patients with aphasia following left hemisphere strokes. These studies rely on the assumption that weak electrical currents can interact with neural networks subtending language and promote neural plasticity, allowing short-term modulations, and eventually clinical recovery. Within these language-related networks, left and right homotopic regions are connected via transcallosal connections [28, 29] which, according to the principle of inter-hemispheric inhibition, tend to convey mutual net inhibitory influences [30]. The use of non-invasive brain stimulation in left hemisphere stroke aphasia relies on three potential mechanisms or combinations thereof [31, 32]: (1) the use of left-excitatory (anodal tDCS or high-frequency TMS) stimulation on left hemisphere language systems to reactivate language processes implemented by peri-lesional regions; (2) the delivery of right-inhibitory (cathodal tDCS or low-frequency TMS) stimulation to reduce the inhibition that right hemisphere systems exert on the left dominant language network and (3) the delivery of right-excitatory stimulation to activate potential language contributions of right hemisphere networks. The most promising clinical outcomes on language disabilities have been achieved from studies adopting the first two approaches using either TMS (e.g., see [33–36]) or tDCS (e.g., see [37–39]). Beneficial effects have been shown either transiently with single-session applications, or as longer-lasting impacts (> 6 months) following periodical stimulation sessions across several days, probably related to stimulation-induced neuroplasticity [34, 40].

Non-invasive brain stimulation has also been used with relative efficacy in Alzheimer's disease by targeting the left and/or right dorsolateral prefrontal cortex [41, 42]. In PPA, including SD (or sv-PPA), two small-cohort studies have suggested encouraging results with both TMS and tDCS [43, 44]. However, the authors did not target language-specific brain regions and the small number of patients precluded a counterbalanced study design. In addition, left-excitatory versus right-inhibitory TMS or tDCS have not been systematically evaluated to reveal the most efficient strategy in aphasia of neurodegenerative origin.

The purpose of this article is to present a clinical protocol (PHRC "STIM-SD") implementing a multi-day tDCS regime in a large population of patients with SD ($n = 60$) specifically targeting the left ATL (with anodal stimulation) or the right ATL (with cathodal stimulation) to provide evidence for potential therapeutic effects and brain plasticity outlasting the duration of the treatment. This intervention builds on a previous pre-therapeutic double-blind, sham-controlled study by our team using a single tDCS session applied to the left and right ATL in patients with SD [45]. This approach allowed the comparison of left anodal (excitatory) to right cathodal (inhibitory) tDCS stimulation and showed that a single session of both left anodal and right cathodal tDCS resulted in transient but highly significant intra-semantic effects [45]. The goals of the present study include the evaluation of the potential therapeutic efficacy of periodical sessions of tDCS over the ATL during 10 days in language/semantic performance in patients with SD, the assessment of the time course of potential improvements, the exploration of potential effects on brain plasticity using functional connectivity measures (resting-state functional magnetic resonance imaging (fMRI)) and cortical metabolism (fluorodeoxyglucose positron emission tomography (FDG-PET)), the identification of the most efficient stimulation modality (left-anodal versus right-cathodal) and the identification of biomarkers such as ATL atrophy levels, which could be individually indicative of an efficient tDCS impact.

Methods

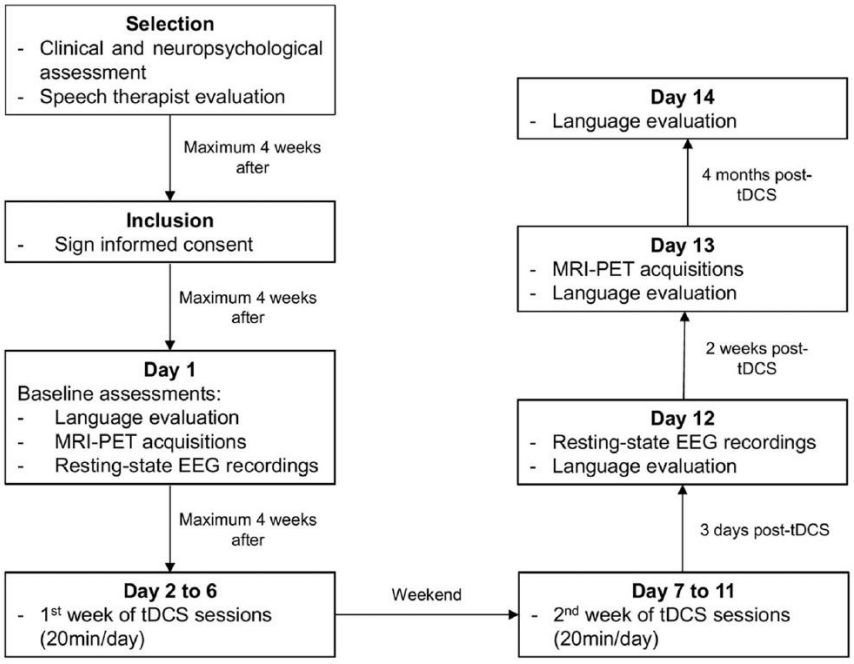
Study design

The *STIM-SD* protocol is a double-blind, sham-controlled, randomized study testing the efficiency of periodical tDCS sessions for 10 days (Monday to Friday for 2 weeks) using language/semantic assessments, and PET and MRI-based neuroimaging at four time points: baseline and 3 days, 2 weeks and 4 months after the end

of the tDCS sessions (Fig. 1a, b, and Additional file 1). The patient population ($n = 60$) is randomly assigned to three subgroups each receiving a different treatment over the ATL: left-anodal tDCS ($n = 20$), right-cathodal tDCS ($n = 20$) and sham tDCS ($n = 20$).

Language/semantic assessments are applied at the four time points by a set of computer-based tasks. For each task, we have developed two equivalent versions matched on various linguistic variables, which are used alternatively either at baseline or during follow-up

A



B

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	$-t_1$	0	W0	W1	W2	W3	W4	W20
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
tDCS sessions				X	X			
ASSESSMENTS:								
Experimental Language Tasks			X			X	X	X
PET-MRI			X				X	
EEG recordings			X			X		

Fig. 1 **a** Flow diagram from patients' selection to the end of their participation in the study. tDCS, transcranial direct current stimulation; MRI, magnetic resonance imaging; PET, positron emission tomography; EEG, electroencephalography. **b** Standard protocol items: recommendations for Interventional Trials (Additional file 1). Table defining the different evaluations or interventions (left column) that would be performed for each study period or time point (top rows)

evaluations, in a counterbalanced order across patient subgroups to avoid test/re-test confounds. Neuroimaging acquisitions (structural MRI, resting-state fMRI, FDG-PET) are performed at baseline and the 2-week time point. We also acquire resting-state electroencephalogram (EEG) recordings at baseline and after the end of tDCS sessions (3-day time point) given that patients with SD might have an altered pattern of resting state neuronal synchronizations [46].

To ensure double-blinding a first investigator (stimulator) performs and supervises the tDCS sessions, whereas a second investigator (evaluator) conducts the langue/semantic tasks, blinded to the stimulation condition (anodal, cathodal or sham). During sham stimulation, tDCS current is ramped up and down along 30 s respectively during the initial and final phases of the session, to emulate the transient skin-itching sensations characterizing active anodal or cathodal stimulation. Unnoticed by the patients, the stimulation unit is turned off during the 20-min sham tDCS session.

Stimulation sessions are applied daily for 10 days (Monday to Friday for 2 weeks). Each tDCS session lasts for 20 min. The direct current has an intensity of 1.59 mA (25cm^2-round electrodes, current density of 0.06 mA/cm^2). A group of 20 healthy subjects are also evaluated at baseline to provide normative values for language/semantic tasks and for imaging measures. Healthy participants do not undergo tDCS treatment and are only assessed once with the same language/semantic tasks and neuroimaging assessments performed by SD patients.

The primary endpoint of the *STIM-SD* protocol is to evaluate the potential therapeutic efficacy of multiday tDCS (10 days) on language/semantic performance in patients with SD (see the section "Language/semantic tasks" – the semantic association task). In addition, we will also (1) assess the time course of potential language/semantic improvement through the application of four follow-up time points; (2) assess neuroimaging biomarkers (PET and MRI) that could reflect stimulation-induced neuroplasticity and response to stimulation; (3) compare the effects of left-anodal and right-cathodal tDCS to define the most efficient stimulation modality; (4) identify biomarkers that could individually predict tDCS impact and (5) improve the understanding of the semantic roles of the left and right ATL and their potential structural connectivity, contributing to the definition of anatomic-functional models of semantics.

The protocol has been approved by the local Ethics Committee and is registered in ClinicalTrials.gov with the identifier NCT03481933 and the study title "'Evaluation of a Transcranial Stimulation with Direct Current on Language Disorders in Semantic Dementia (STIM-SD)". Written informed consent is obtained from all patients and healthy subjects before the onset of any of the study procedures. All research protocol visits take place at the same site, the Pitié-Salpêtrière Hospital. Two additional centers contribute to the protocol by recruiting patients with SD.

Participants

Patients with SD are recruited in the National Reference Center for Rare or Early Onset Dementias at the Pitié-Salpêtrière Hospital, at the Rothschild Ophthalmologic Foundation and at the Léopold Bellan Hospital in Paris. Patients are recruited based on the following inclusion criteria: (1) diagnosis of SD based on current research criteria [1] comprising progressive language impairment, single-word comprehension deficits and anomia, without sentence repetition impairment, agrammatism or motor speech disorders; (2) age > 18 years and (3) affiliation to a social security regime.

Non-inclusion criteria are the following: (1) psychiatric disorders or neurologic diseases other than SD; (2) contraindication for MRI, PET or tDCS such as presence of intracranial ferromagnetic devices, scalp or skull lesions or epilepsy; (3) MRI recordings revealing pathological processes other than those associated with SD; (4) severe aphasia (severity score < 3 in the Boston Diagnostic Aphasia Evaluation (BDAE) [47]); (5) Mini Mental State Examination (MMSE) [48] score < 15; (6) Frontal Assessment Battery (FAB) [49] score < 10; (7) Montgomery Asberg Depression Rating Scale [50] (MADRS) score ≥ 20, indicating a major depressive disorder; (8) not having the French language as a mother tongue; (9) being left-handed and (10) being under curatorship or tutorship. Prior to inclusion in the protocol all patients undergo a neuropsychological and speech therapist evaluation to check for inclusion/non-inclusion criteria, and to characterize global cognitive/language/semantic capacities on the basis of several published standard tests.

Healthy participants are recruited among hospital staff, caregivers and patients' relatives via announcements in the neurology department. They are matched with the patients with SD on sex, age, handedness and number of years of education. Non-inclusion criteria for healthy participants are the following: (1) neurological or psychiatric disorders or physical deficits that can interfere with cognitive function; (2) contraindications to MRI or PET and (3) not having French language as mother tongue.

Randomization

A computer-generated block randomization list has been prepared by the Clinical Research Unit of the Pitié-Salpêtrière - Charles Foix Hospital group. The randomization list is integrated into the electronic case report form (eCRF) and a randomization number assigning patients to one of the

three stimulation conditions (anodal, cathodal or sham tDCS) is attributed automatically upon completion of inclusion/non-inclusion criteria. The randomization is not stratified by center of inclusion because all stimulation sessions and time-point evaluations are performed at the Pitié Salpêtrière Hospital.

Stimulation administration

The stimulation procedure (electrode montage and stimulation parameters) is the same as the procedure used in our aforementioned pre-therapeutic study [45]. During the baseline visit patients undergo FDG-PET and MRI including anatomical 3D T1-weighted images. The T1-weighted images are registered in standardized Montreal Neurological Institute (MNI) space and the left and right ATL are identified and labeled with a 5-mm sphere centered on MNI coordinates (x = − 52, y = 2, z = − 28) and (x = 53, y = 4, z = − 32), respectively [51], using custom-made SPM8 (Statistical Parametric Mapping, Matlab Mathworks) procedure. Images are then denormalized in each patient's native space. The day of the stimulation a scalp inspection is performed to verify the absence of skin lesions. Before the placement of the tDCS electrodes the scalp is carefully cleaned using an abrasive paste to limit impedance losses between the skin and the electrodes. Two round sponge electrodes, one acting as the active electrode (anodal or cathode) and the other as return (Sponstim®, 5.65 cm diameter, 25cm^2 surface, NEuroelectrics, Barcelona, Spain) are placed under MRI guidance using a stereotactic neuronavigation system (Brainsight®, Rogue System®, Montreal, Canada). This procedure minimizes the distance between the labeled cortical target on a 3D reconstruction of each patient's MR image and its closest (shortest Euclidian path) scalp location (Fig. 2).

Stimulation is delivered using a wireless hybrid EEG/tDCS 8-channel neurostimulator (Starstim, NEuroelectrics, Barcelona, Spain). The active electrode is placed over the left ATL for left-anodal tDCS (between 10 and 20 EEG coordinates ~ FT7 and FT9), while the cathodal tDCS targets the right ATL (between ~ FT8 and FT10). In sham tDCS stimulation, the active electrode is placed over the same MNI coordinates as left-anodal tDCS. The return electrode is placed over the contralateral supra-orbital region with regards to the active electrode location (10–20 EEG coordinates AF8 for left anodal tDCS and AF7 for right cathodal tDCS). Additionally, six EEG scalp electrodes (NG Geltrode® Ag/AgCl, 1.0 cm^2) provided by the same tDCS device, which allow for continuous monitoring of brain activity during the session, are placed in 10–20 EEG system locations F4, F3, C4, C3 and P4, P3.

During anodal or cathodal tDCS, current intensity is linearly increased over 30 s to reach a maximum of 1.59 mA. This level of tDCS intensity has been chosen to ensure similar levels of current density (0.06 mA/cm^2) with our 25cm^2 electrodes as those applied in previous post-stroke aphasia or PPA studies with larger leads [37, 45, 52]. Current is kept at this intensity for 20 min before being ramped down along 30 s at the end of the tDCS session. During sham stimulation the tDCS current is ramped up and down along 30 s

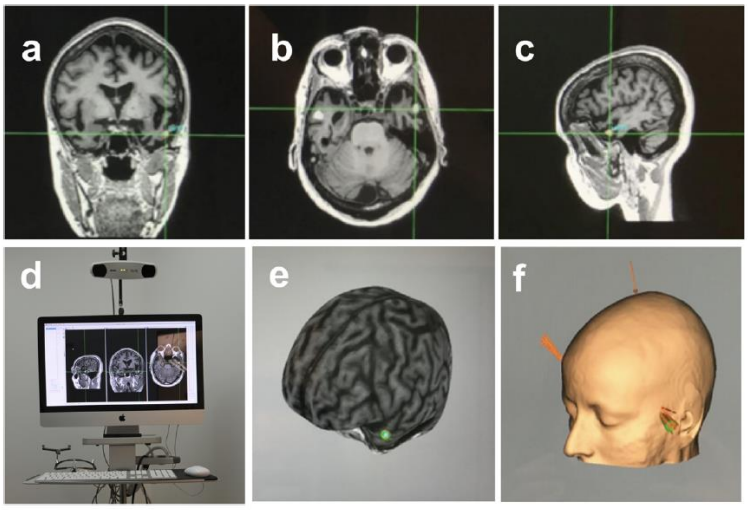


Fig. 2 The three upper panels show, respectively, **a** coronal, **b** axial and **c** sagittal sections from magnetic resonance imaging (MRI) in a representative patient with semantic dementia (SD). The crosshair signals the location of the stimulation target in the left Anterior Temporal Lobe (ATL). **d** MRI-based frameless stereotactic navigation system device (Brainsight) employed for accurate targeting of the left ATL in SD patients. 3D brain curvilinear **e** cortical and **f** skin reconstructions from the MRI of a patient, provided by the neuronavigation system with a sphere indicating the left ATL target aimed by the stimulation

at the initial and final phase of the session but is turned off during the 20 min session. This process makes active (anodal or cathodal) and sham stimulations similar (same somatosensory skin sensations) as required by a double-blind design. During each stimulation session, values of mean voltage (V), mean current intensity (uA) and mean impedance (Ohm), directly provided by the stimulation software, are recorded for means of tDCS verification intents. Treatment duration has been chosen based on previous studies showing beneficial tDCS effects with the same amount of time (e.g., [44, 45]). During tDCS sessions patients perform a language-neutral visuo-motor task on a laptop screen consisting of pressing the space bar on a computer keyboard every time a slowly moving dot contacts the edge of a surrounding rectangle. This task is intended to limit variability in neural activity states across sessions and patients (forcing patients to maintain vigilance) without interfering with language processes and tasks. At each session, performances (number of trials, number of successes and number of errors) in the visuo-motor task are recorded.

To ensure safety and comfort and to assess the tolerance of patients to stimulation, immediately after each tDCS session patients are asked to complete a tDCS adverse effects questionnaire [53] that measures, through a rating scale, patients' sensations in a set of the most frequent adverse effects reported in tDCS studies such as itching, tingling, burning sensations, skin redness or sleepiness.

Language/semantic tasks

A set of computer-based language/semantic tasks is used to assess the potential effectiveness of tDCS. These tasks are carried out by patients at four time points: pre-tDCS (baseline) and 3 days, 2 weeks and 4 months after the end of the 10-day tDCS regime. The five language/semantic tasks are the following:

- Semantic association task (SA)
- Picture naming task (NAME)
- Reading task (READ)
- Letter and category fluency task (FLU)
- Category judgment task (CJ)

Two additional tasks evaluating tDCS impacts on other cognitive functions are also applied:

- Executive function task (EXE)
- Recognition of famous faces - a subtest of the French *Batterie Imagerie-Perception* (BIP).

The tasks are computer-programmed using E-Prime software (E-Prime®, Psychology Software Tools, Sharpsburg, PA, USA). Participants are comfortably seated in front of a laptop computer screen (HP EliteBook 8770w, USA) and a response box that records responses. Performance accuracy, reaction times and voice records are automatically registered by the software. The sessions are carried out in the presence of an investigator immediately after familiarization/training blocks comprising five trials for each task.

Semantic association task (SA)

This task assesses semantic capacities and provides the primary endpoint criterion. It is based on the principle of the Pyramid Palm Trees Test [54]. The material includes 78 French words, which are grouped into 26 trials. Each trial includes three words, two of them are semantically related (the target item and test item), while the third word is a semantically unrelated distractor. The three words are displayed on the computer screen for 8 s and the participant has to decide, using two response buttons, if the target item (on top of the screen) is associated with the test item (on the bottom of the screen, either left or right) or the distractor item (on the bottom of the screen, either left or right, opposite to the test item). Thirteen test items appear on the left and 13 on the right. The lack of response during this 8-s time interval is recorded as an error. The task assesses two category dimensions using the contrast between trials containing only living items ($n = 13$) and trials containing only non-living items ($n = 13$). Two modalities of this task are applied: a verbal modality (described above) and a picture modality that uses pictures instead of words. The language stimuli (pictures or words) used in these two tasks for "living" and "non-living" trials are matched for (1) lexical frequency, (2) number of letters, (3) familiarity of words and pictures and (4) visual complexity of the pictures. Stimuli of version 1 and version 2 of the test are also matched for these four variables. Outcome measures will focus on performance (number of correct responses), and reaction times in milliseconds. Figure 3 illustrates different trials of the task.

Picture naming task (NAME)

This task evaluates lexical and semantic abilities. The material includes 40 pictures, derived from two picture-naming databases [55, 56]. Each picture is displayed on the computer screen for 8 s and participants are asked to name it aloud. Responses are voice-recorded and notified. The lack of a response during this time interval is recorded as an error. Stimuli of version 1 and version 2 of the test are matched for (1) lexical frequency of words, (2) familiarity of words and pictures and (3) visual complexity of the pictures. The task will allow for assessing (1) the number of correct responses, (2) the number of non-responses and (3) the number of

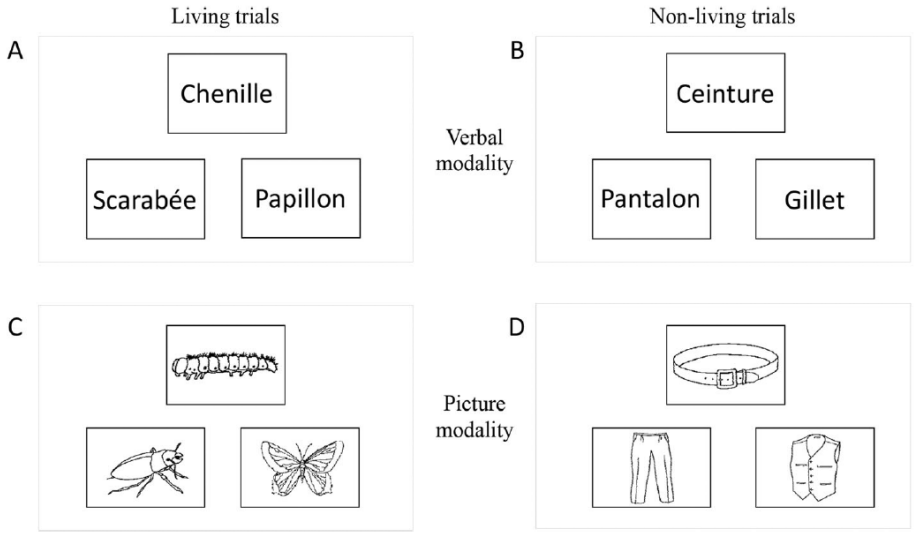


Fig. 3 Two trials of the semantic association (SA) test in their verbal and picture modalities. **a** Trial with living items for the verbal modality (*chenille* (caterpillar) - target item, *scarabée* (beetle) - distractor, papillon (butterfly) - test item). **b** Trial with living items for the picture modality using the same items in a picture format. **c** Trial with non-living items for the verbal modality (*ceinture* (belt) - target item, *pantalon* (trousers) - test item, *gilet* (vest) - distractor). **d** Trial with non-living items for the picture modality using the same items in a picture format. For each trial in each modality subjects have to decide, by pressing one of two buttons in the response box, which of the items presented on the bottom of the screen is associated with the target item, on the top of the screen

semantic paraphasias. The number of correct responses and non-responses are markers of lexico-semantic abilities, and the number of semantic paraphasias is an additional marker of semantic abilities.

Reading task (READ)

The task provides a semantic marker in written language. During reading the phonological pathway allows for mapping each letter (grapheme) to a phoneme while the lexical-semantic pathway allows for "whole word reading" that depends on knowledge of written words [57]. The lexical-semantic route is therefore critical for reading irregular words where the grapheme-phoneme correspondence is not transparent (e.g., bear). In contrast, the phonological route is essential to read unknown or non-words. Regular words can be read through both the lexical-semantic and the phonological route. It has been shown that patients with SD have difficulties reading irregular words linked to their semantic impairment (e.g., see [58]) and performance with such irregular items will therefore provide a semantic marker. The task contains 45 stimuli: 15 irregular words, 15 regular words and 15 non-words that are matched for the number of graphemes. Each word appears on the computer screen for 8 s and subjects are asked to read them aloud. Responses are voice-recorded and registered in written form by the evaluator. The lack of response during this interval is recorded as an error. Stimuli of version 1 and version 2 of the test are also matched for the number of graphemes.

Verbal fluency task (FLU)

This task assesses language fluidity and access to lexical-semantic representations of words. It has two modalities: (1) in the "letter fluency" subtask participants are asked to produce, during 1 min, a maximum of words beginning with a particular letter displayed in the center of the screen; (2) in the "category fluency" subtask participants are asked to produce, during 1 min, a maximum of words belonging to a given semantic category displayed in the center of the computer screen. For the "letter fluency" subtask, stimuli of version 1 and version 2 are matched for the number of existing words starting with the given letters and also their cumulative frequencies. For the "category fluency" subtask stimuli of version 1 and version 2 are matched for the number of existing items within that category. The measured variables are the number of items produced per minute in each of the two tasks. The subjects' responses are voice-recorded and quantified.

Category judgment task (CJ)

The task assesses semantic capacities in the verbal modality. The material includes 40 French words, 20 of which represent "living items" and 20 of which represent "non-living items". Words representing "living" and "non-living" items, and words of both versions of the task, are matched for lexical frequency, number of letters and number of phonemes. Each word stimulus is displayed in the center of a computer screen for 8 s. Subjects are asked to judge whether a given word item belongs to a "living" or to a

"non-living" semantic category and answer by pressing the corresponding buttons of the response box.

Executive function task (EXE)

This task is used as a control task to assess whether tDCS over anterior temporal regions has semantic-specific effects or whether it might impact on executive functioning, which may indirectly modulate semantic performance. Using a similar task design and procedure as in the SA task, the EXE task assesses executive/attention and decision-making abilities without the influence of semantics. As in the SA task, the task contains a verbal and a picture modality. For the verbal modality, the material includes 78 French words grouped into 26 trials. Each trial includes three words; two of them have the same initial and final letters (the target item and test item), while the third word is a distractor sharing only the initial or the final letter with the target item. The three words presented in each trial are semantically unrelated. The picture modality of the test uses drawn images instead of words. The pictures represent colored geometrical shapes. The material includes 78 pictures grouped into 26 trials. Each of the 26 trials includes three pictures, two of them representing the same geometrical shape or color (the target item and test item), while the third picture represents a distractor not sharing any of these features with the target item. The items of the verbal modality are matched for the number of letters with the word items of the SA task. Stimuli of version 1 and version 2 are matched for the number of letters. The three items are displayed on the computer screen for 8 s and subjects decide (using two response buttons) if the target item (on top of the screen) is related to the test item (on the bottom of the screen, either left or right) or the distractor item (on the bottom of the screen, either left or right, opposite to the test item). Thirteen test items appear at a left and 13 at a right bottom location. The lack of response during this 8-s time interval is recorded as an error. Figure 4 illustrates two trials of this test.

Recognition of famous faces subtest

This test is adapted from the French BIP [59]. It is used to detect eventual negative effects of tDCS, decreasing the activity of the right ATL, which has been shown to play an important role in the recognition of known faces [7]. The material includes 28 pictures of faces of famous people. Each picture is displayed on the computer screen for 8 s. Participants have to decide if the face corresponds to one of the four professional categories (politician, actor, singer or TV presenter) by pressing one of four associated keys in the response box. The lack of response during this time interval is recorded as an error.

Ecological evaluation

Additionally, a semi-quantitative daily life communication questionnaire - *Echelle de Communication Verbale de Bordeaux* [60], which assesses the effectiveness of communication of patients with aphasia in everyday situations, is applied at baseline and at the 2-week post stimulation time point. This questionnaire was included in the protocol to count with an ecological measure of potential language improvements after tDCS and to assess its impact in patients' day-to-day life.

PET-MRI neuroimaging and EEG recording

Neuroimaging data (PET, MRI) are collected before the tDCS sessions (baseline) and 2 weeks after the tDCS sessions. These acquisitions provide all the sequences underlying the following explorations: cortical metabolism, gray matter thickness measures, white matter fiber tracking and functional connectivity. The examination is performed on a hybrid PET-MRI scanner (Signa 3 T GE Healthcare, USA). The injection of FDG (Fluoro-Deoxy-Glucose 2-18F: MÉTATRACE®, half-life of 109,77 min, or GLUSCAN®, half-life of 110 min) is performed if the blood glucose checked prior to injection is ≤ 1.5 g/l. Participants lie in neurosensory rest in a quiet and unlit room for at least 30 min post-injection, prior to image acquisition.

The acquisition of brain images with PET is conducted in *list mode*. It begins 30–40 min after injection of the

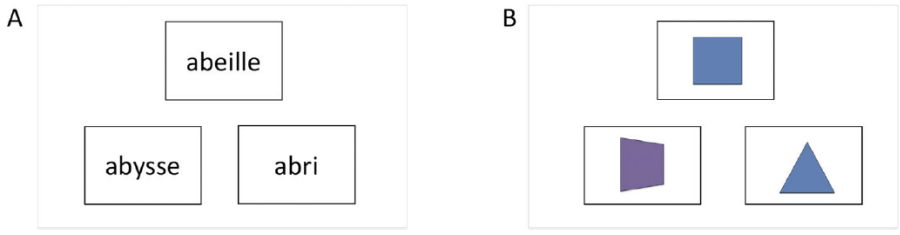


Fig. 4 Two illustrative trials of the executive function (EXE) task. **a** Trial in the verbal modality. For each trial participants have to decide which of the test items presented on the bottom of the screen begins *and* ends with the same letter as the target item (*abeille* (bee) - target item, *abysse* (abyss) - test item, *abri* (shelter) - distractor). **b** Trial in the picture modality. For each trial subjects have to decide which of the test items on the bottom of the screen has the same color *or* the same geometric form as the target item

radiopharmaceutical FDG tracer and lasts for 20 min (3 × 5 min). Images are reconstructed and corrected for physical phenomena. They are expressed in standard uptake value (SUV). Magnetic resonance images are acquired simultaneously and include two anatomical sequences (3D-T1, 3D-FLAIR), a functional imaging sequence (resting state fMRI) and a diffusion tensor imaging (DTI) sequence.

Additionally, prior to and following stimulation, the tDCS device (Startsim, NEuroelectrics, Barcelona) automatically records brain activity through EEG scalp electrodes (sampling at 1500 Hz, low-pass high-pass filter 4–40 Hz). Resting-state EEG recordings are obtained from 10 to 20 EEG system locations F4, F3, C4, C3, P4, P3 and T8, T7.

Computational models of tDCS current magnitude and distribution

There is evidence that the thickness of the skull, the volume of the cerebrospinal fluid in the subdural space and the distance from the targeted region in the brain to the tDCS anode or cathode account for up to 50% of the spatial variation of the electric field strength [61–63]. Kim et al. [64] found that performance improvement in a working memory task correlated with the simulated current magnitude, suggesting that inconsistent behavioral outcomes of tDCS might be partly due to individual anatomical differences.

A computational approach of modeling should allow for defining if and how tDCS current magnitude and distribution in the heads of individuals can differ and how these differences will affect clinical outcomes. Individual computational models will be produced using the open-source tool ROAST [65] to simulate tDCS current magnitude and distribution using the anatomical 3D T1-weighted MRI images of each patient (Fig. 5). Then, correlation will be tested between model-estimated data for current magnitude values and clinical data, specifically the changes in scores in the SA task from baseline to post-stimulation. A region of interest (ROI) will be defined and the mean of the 5% highest electric field values in this region will be obtained for each patient. More specifically, we will define the left anterior/middle temporal lobe as our ROI, because this region is primarily damaged in SD and it is the region targeted during the stimulation. Finally, measures of thickness of the different tissue layers (skin, skull, cerebrospinal fluid volume, gray matter and white matter) and distances between the stimulation target (ATL) and the stimulating electrode will be obtained and regression models will be computed to identify specific features that most influence changes in current magnitudes. This will allow us to identify the characteristics that might influence patients' responses to tDCS and help predict if an individual patient might benefit from tDCS treatment.

Data management

Data are collected via the eCRF that was developed at the outset of the study. All clinical and language/

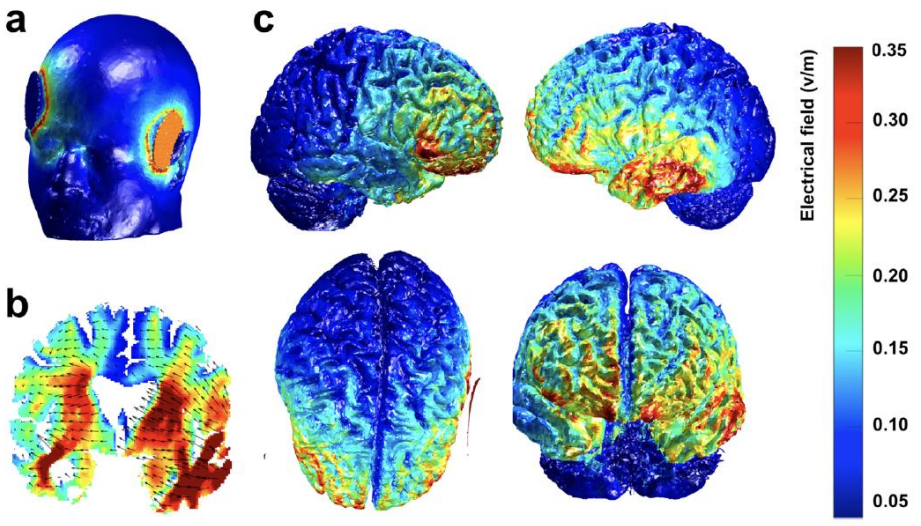


Fig. 5 Example of a computational model produced with the open-source tool ROAST for the simulation of transcranial direct current stimulation (tDCS) current magnitude and distribution using a 3D T1-weighted image from a representative SD patient. **a** Illustration of the montage for the left-anodal stimulation. The round blue patch represents the cathode, placed over the right supra-orbital region [10–20 electroencephalography (EEG) coordinates AF8], and the red round patch represents the anode, placed over the left Anterior Temporal Lobe (ATL) (Montreal Neurological Institute (MNI) coordinates: x = − 52, y = 2, z = − 28). **b** Coronal slice view of the electric field with current flow direction represented by the black arrows. **c** Electric field distribution on the cortical surface - right hemisphere view, left hemisphere view, upper view and frontal view. The colorbar represents the magnitude of the electric field, in Volts per meter, in different regions of the brain (for panels **b** and **c**)

semantic task information required by the protocol is entered into the eCRF. The data are collected as and when they are obtained, and any missing data are clearly coded. Every investigator participating in the protocol has access to the eCRF via a web-based password-protected data collection system. All data are collected in the same center, the Pitié-Salpêtrière Hospital. Investigators have been given instructions for using this tool prior to the beginning of the protocol. Regular monitoring by the promoter of the study (APHP. Assistace Publique-Hôpitaux de Paris) will ensure the accuracy and quality of all the data and detect and address any issues related to the implementation.

All data collected on participants are anonymized through a specific number attributed to the participant at inclusion and his/her respective last and first name initials. Data collected in this study include both quantitative (neuropsychological and language standard tests scores, study task scores) and qualitative data (clinical history, neurological information). A print-out, authenticated by the principal investigator of the protocol, will be requested at the end of the research by the promoter of the study and the investigator will archive a copy of the authenticated document that was issued to the promoter. Given the high volume and complexity of the pre-processing and analyses of PET-MRI and EEG data, the outcome measures cannot be added to the eCRF and will be handled by the expert investigators.

Data analyses

We will accept a significance level of 5% ($p < 0.05$) corrected for multiple comparisons when needed. To assess our primary endpoint criterion, i.e., performance changes on the SA task, outcomes at baseline and at the 2-week time point will be compared using two-way analysis of variance with "time" (baseline, 2 weeks post-stimulation) and "group" (anodal, cathodal, sham) as factors. Since two comparisons will be made (sham versus left-anodal and sham versus right-cathodal tDCS) Dunnett's two-tailed t test will be used to handle multiple comparisons. In the case that the data do not meet the normal distribution assumption, the non-parametric Mann-Whitney test will be used to compare performance improvements between the sham versus left-anodal and between the sham versus right-cathodal groups.

To assess the time course of potential improvements and test if such differ between the treatment groups, linear mixed models will be used with "time" (the four time points), "group" (anodal, cathodal and sham) and group-by-time interactions as fixed effects. The Benjamini and Hochberg method will be used for controlling for false discovery rate.

To identify imaging bio-markers of stimulation-induced neuroplasticity, we will analyze cortical metabolism and resting-state functional connectivity. PET images will be used for cortical metabolism, to analyze tissue metabolic activity and regional glucose uptake in the brain. A voxel-based analysis, using the Statistical Parametric Mapping (SPM) software [66], will be implemented to highlight regional differences in metabolism between the images obtained at baseline and post-stimulation. The resting-state fMRI sequence will be explored to study the status of functional connectivity within the language/semantic networks and possible alterations within it between baseline and post-stimulation images. Quantification of functional connectivity will be based on integration measures in specific networks established from the known anatomy, on indices derived from the graph theory or information theory. Cortical regions of interest will be obtained automatically using SPM toolboxes. More specifically, the language/semantic network will include the middle and anterior portions of the lateral ATL, the inferior frontal gyrus, the dorsomedial and ventromedial prefrontal cortex and the inferior parietal lobe. To study the neurophysiological impact of tDCS on specific brain networks, resting-state EEG datasets obtained at baseline and 3 days after the end of the 10 tDCS sessions will be also analyzed. Data will be filtered (4–40 Hz) and power distribution and local synchrony calculated across frequency bands and compared. Functional connectivity maps across the electrodes will be estimated by calculating the phase-lockimg value between the eight EEG leads and have them compared across in pairs.

To identify biomarkers that could individually predict an efficient tDCS impact, 3D-T1 and DTI sequences will be explored and individual computational models of tDCS current will be produced. Structural 3D-T1 MRI data will be studied using surface-based cortical thickness analysis. An ROI will be defined in the ATL and cortical thickness values at baseline between a group of eventual "responders" (mean improvement of 15% in correct responses in the SA test) and "non-responders" to the stimulation will be compared using a general linear model. Diffusion MRI data will be studied using ROI analysis of DTI metrics. Fractional anisotropy (FA) and mean diffusivity (MD) maps will be calculated and the integrity of a set of anatomical white matter tracts will be assessed (FA and MD measures in each tract). The tracts analyzed will include bilaterally the inferior longitudinal fasciculus, the uncinate fasciculus, the superior longitudinal fasciculus, the inferior frontal-occipital fasciculus and different corpus callosum tracts connecting the left and right temporal lobes. This will allow a detailed anatomical analysis of white matter fiber tracts and compare their status between a possible group of responders and non-responders. The individual computational models of tDCS current magnitude will be used to identify which anatomical characteristics influence the amount of current reaching the target in the brain and if

such measure can help predict the response to stimulation. Finally, the analyses of DTI data will also allow us to explore connectivity between the left and right ATL to improve the understanding of the semantic roles of each of these regions while contributing to the definition of anatomic-functional models of semantics.

Sample size

The primary evaluation criterion is the change over 2 weeks in performance on the SA task. Performance is measured by the percentage of correct responses. The trial will be considered as positive if performances after left-anodal or right-cathodal tDCS are shown to be significantly superior to sham stimulation. The sample size is based on the results of a preliminary study comparing sham stimulation to left-anodal and right-cathodal stimulation in 12 patients [45]. In our pre-therapeutic study, the mean difference in performance improvement between sham and both anodal and cathodal stimulation was about 15% with a standard deviation of 16% and an effect size of 1.464. The difference in mean change between sham stimulation and each of the two other groups is then expected to be 15% of correct responses. The inclusion of 20 patients in each group will provide statistical power of 80%.

Discussion

Language disorders in frontotemporal lobar degeneration, and particularly in SD, are a disabling feature representing an important medical problem. They are also a relevant issue for public health because most patients have symptoms prior to retirement causing substantial health costs. Given this context our project bears major importance because it could potentially provide evidence for the validity of a novel therapy strategy improving language/semantic capacities while diminishing the functional handicap and, eventually, healthcare expenditure.

The STIM-SD protocol proposes the first large-scale exploration of tDCS as a potential therapy for language/semantic impairment in SD for which no treatment is currently available. Contrary to most of the studies using transcranial brain stimulation in neurodegenerative diseases affecting language [43, 44, 67, 68], our study targets sites that have been selected based on the localization of anatomical damage and related contralateral regions to optimize language and semantic recovery.

We apply a double-blind, sham-controlled design in which the investigators and the patients are blinded to the type of stimulation used, reducing any source of potential bias. This design will also enable a comparison between two different stimulation approaches (left-anodal versus right-cathodal) and will contribute to identifying the most beneficial strategy. To our knowledge, not a single study applying tDCS to improve cognitive deficits in neurodegenerative diseases has employed supportive neuroimaging (PET, fMRI), and only one study has used neurophysiological measures (EEG) [69] to explore stimulation impact on relevant brain networks or demonstrate neuroplasticity effects. In the present study, we will generate both language/semantic data and a set of neuroimaging and resting-state EEG measures, which will allow us to study the impact of tDCS on language networks and neuroplasticity, to understand if this potential impact also subtends language/semantic improvements, and to better understand tDCS mechanisms.

In addition, baseline structural data (3D-T1 cortical thickness, DTI fiber tract analyses) and individualized models of tDCS current magnitude and distribution will be fundamental in understanding which anatomical features of our cohort most influence treatment efficacy, how the amount and spreading of electric current in the brain will impact individual clinical outcomes and possibly define a profile of patients that in the future would most benefit from tDCS.

Within neurodegenerative diseases specifically affecting language, SD is the most frequent variant of primary progressive aphasia [2], which contributes to the feasibility of the project in terms of patient recruitment. In the same vein, our National Reference Center for Rare or Early Onset Dementias provides a unique opportunity to recruit a large and homogeneous cohort of patients with SD. The active patient files on patients with early-stage SD in the three recruiting centers contained more than 20 patients with SD per year in 2013, 2014 and 2015. This shows that the total number of 60 patients with SD can be reached in the current project.

A potential tDCS treatment would be easily applicable, inexpensive and renewable when therapeutic effects disappear due to disease evolution. Significant effects of repetitive tDCS on language/semantics would also open an avenue for future tDCS trials targeting language non-related cortical regions such as areas subtending episodic memory, which is damaged, for example, in Alzheimer's disease. More generally, the protocol might improve the understanding of neuroplasticity and its modulation through inhibitory and/or excitatory tDCS-driven cortical impact, while providing a rationale for appropriate stimulation modalities and for identifying brain regions likely to demonstrate relevant plasticity. Such insights could prove important for both tDCS and TMS trials, and their combination with behavioral language rehabilitation strategies, which might further enhance plasticity-related modulation.

Conclusions

The aim of the STIM-SD protocol is to implement a novel therapeutic tDCS approach to language/semantic deficits in patients with SD for whom no treatment is available. If

found to be efficient, this strategy could be regularly implemented, as it is easily applicable and low-cost. Moreover, larger trials could be extended to other neurodegenerative diseases to check for efficiency in language and other cognitive functions.

Trial status

The protocol version number is P160937J first published in ClinicalTrials.gov on 29 March 2018. Patient recruitment began in June 2018. Sixteen patients have been screened for participation between June 2018 and March 2019. Of these, 13 patients were included in the study and randomized. Seven of those patients have already completed their participation in the study with 4-month follow up. Among the three patients screened but not included, two patients did not meet all the inclusion criteria while another was not able to undergo the planned neuroimaging examinations. Five healthy participants were also included in the protocol. Recruitment is expected to be completed by June 2021.

Additional file

Additional file 1: Standard protocol items: recommendation for interventional trials (SPIRIT) 2013 checklist: recommended items to address in a clinical trial protocol and related documents. (DOC 122 kb)

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Authors' contributions

MT and AV-C provided the idea, designed the protocol and will coordinate organizational and scientific aspects of the clinical trial, with an emphasis on data interpretation and a main role in manuscript writing. RL, SB, LVG, BD and MT will be in charge of patient clinical characterization, screening and recruitment. CS and AV-C will be responsible for carrying our tDCS stimulation, stimulation coupled EEG procedures and biophysical modeling of current distribution. MOH, SS, AuK, CS, AnK, NP and RM will be responsible for imaging acquisition. MOH, LM, NP and SS will define the neuroimaging analysis strategies with input from MT and AV-C. CS, AnK, RM, NP and MOH will be responsible for imaging analyses. AnK, CS and MT will be responsible for the evaluation and interpretation of language outcomes. CS, AB and MT elaborated language and executive evaluation tasks for this study. AV-C and CS were in charge of defining the tDCS stimulation and EEG recording strategies CS, MOH, SS, NP and RM have been in charge of designing and optimizing and will provide quality checks for neuroimaging sequences and datasets. CS, AV-C and MT were responsible for the preparation of the current manuscript. AV-C and MT were directly responsible for Institutional Review Board (IRB) protocol writing. All authors have read and approved the final version of the manuscript.

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Availability of data and materials

Not applicable. No data is available at this point because authors are still in the process of gathering such.

Ethics approval and consent to participate

The protocol has been approved by the local Ethics Committee - Comité de Protection de Personnes (CPP) Ile de France IV, Hôpital Saint-Louis. All patients and healthy subjects will be required to provide written informed consent.

Consent for publication

MRI datasets, images or any other clinical details of the participants will not compromise their anonymity.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

CHAPTER VI

General discussion

VI.1. Summary of the main results

This thesis pursued three main goals: (1) to better understand how word access is organized in the brain; (2) to characterize how several neurodegenerative diseases might differently impair language abilities in general and word access in particular; and (3) to explore if impaired language abilities could be transiently modulated by single sessions of non-invasive brain stimulation techniques in view of future multi-day therapeutic regimes. We used neurodegenerative lesion models, namely patients with Primary Progressive Aphasia (PPA), to study the behavioral mechanisms of word access and processing via language tasks specifically designed to attain the goals of each study. We then recruited groups of patients with different neurodegenerative diseases, specifically Progressive Supranuclear Palsy (PSP), behavioral variant of Frontotemporal Dementia (bv-FTD) and logopenic and semantic variants of Primary Progressive Aphasia (lv-PPA and sv-PPA), to characterize their impact on language abilities and to what extend deficits could be modulated with non-invasive brain stimulation. For the latter studies, transcranial Direct Current Stimulation (tDCS) was employed to stimulate on each patient group specific cortical regions, mostly affected by each disease process. In all studies, patients underwent three independent stimulation sessions spaced at least for a week: anodal tDCS over a left hemisphere target region; cathodal tDCS over a right homotopic region of the former; sham tDCS. Before and immediately after each stimulation session patients performed a set of language tasks, designed to evaluate the most prominent language impairments in each pathology. Changes (improvements) in task performance or reaction times comparing pre- and post- stimulation assessments were used as markers of tDCS effectiveness.

In *Chapter II* we present two studies developing fundamental research on language. The first study analyzed if information relative to the 3 components of the mental lexicon, *semantic*, *syntactic* and *word-form* components, could be accessed independently of each other. Our main findings provide clear evidence in favor of distinct semantic, syntactic and word-form

representations, which can be individually accessed despite damage to the other components, thus demonstrating a threefold segregation of the mental lexicon (Sanches et al., 2018). Our results substantiate previous single-case and small-cohort studies which only revealed "one versus one component" dissociations such as syntactic vs. word-form representations (Caramazza and Miozzo, 1997), or syntactic vs. semantic representations (Biran and Friedmann, 2012; Kavé and Levy, 2003).

The second study presented in *Chapter II* challenged the two major models of written language, namely connectionist and symbolic models, by investigating whether sv-PPA affects the lexicon in addition to the semantic system, and whether semantic or lexical deficits cause surface dyslexia/dysgraphia, impairing the reading of irregular words. Our findings, based on reading/writing scores with irregular words, on lexical and semantic markers, and on correlation and item-by-item consistency analyses, and a multiple regression model showed that: i) sv-PPA affects the mental lexicon; ii) lexical but not semantic impairments correlate with markers of surface dyslexia/dysgraphia; iii) lexical failure on a given irregular item reliably predicts reading/writing errors on that item; iv) lexical markers but not semantic markers predict reading/writing errors with irregular items (Teichmann, Sanches et al., 2019). Such results are in line with symbolic models, such as Dual Route Cascaded (DRC) accounts, proposing the existence of a mental lexicon, which contains whole word forms, in addition to semantic, phonological and orthographical representations, and its major role in reading/writing deficits with irregular words (Coltheart et al., 2010).

In *Chapter III*, we present 3 studies addressing the impact of neurodegenerative diseases on different aspects of language performance and evaluating the efficiency of tDCS to ameliorate language impairments. To this end, we applied a common sham-controlled double-blind crossover design delivering tDCS over the dorsolateral prefrontal cortex (DLPFC) in cohorts of PSP patients (n=12) and bv-FTD patients (n=12) and tDCS over the temporoparietal junction (TPJ) in a cohort of lv-PPA patients (n=12).

In the PSP cohort, a condition characterized by basal ganglia, midbrain, cerebellar and also a slight bilateral prefrontal atrophy, our results revealed impairments on both a *Category judgment* and a *Letter fluency* task at baseline, compared to healthy controls. These outcomes suggest that PSP patients present both semantic difficulties and compromised lexical access mechanisms. A comparison of post-stimulation vs pre-stimulation performance yielded language improvement in

the *Category judgment* task following a single session of right-prefrontal cathodal tDCS and in the *Letter fluency* task following left-prefrontal anodal tDCS (Valero-Cabré, Sanches et al., 2019).

In bv-FTD patients, a condition characterized by bilateral prefrontal atrophy, we confirmed a breakdown of language initiation/activation and research mechanisms in the mental lexicon, as shown by significantly lower performance in the *Picture naming* and the *Letter fluency* tasks, compared to healthy controls. As expected, these patients also presented executive impairments, showed by lower performance in the *Spatial sequence generation* task, a paradigm designed to assess executive control/attentional abilities. Unexpectedly, none of the single sessions of active tDCS conditions yielded evidence of language improvement in any of these three tasks (Sanches et al., in preparation).

Finally, in lv-PPA, a condition characterized by left posterior temporal-and inferior parietal atrophy around the temporo-parietal junction (TPJ), our results revealed impaired performance in a *Semantic association* task, a *Picture naming* task and a *Letter fluency* task. These outcomes support prior reports suggesting that in addition to impairments in the phonological/orthographic code, semantic representations are also impaired in lv-PPA (Rogalski et al., 2008; Teichmann et al., 2013). Any of the active tDCS conditions, delivered in single sessions over the TPJ (both left-TPJ anodal tDCS, or right-TPJ cathodal tDCS), produced language improvements in lv-PPA patients (Sanches et al., in preparation).

In *Chapter IV*, we analyzed data from an extended cohort of sv-PPA patients (n=17), characterized by predominant left anterior temporal lobe (ATL) atrophy, who received a single anodal tDCS session over the left ATL to evaluate modulatory effects on a *Semantic association* task. In this study, we aimed to relate selected anatomical features of each sv-PPA patient (scalp-to-cortex distance, CSF volume and cortical thickness), derived from MRI acquisitions, to electric field estimates from areas of left temporal lobe encompassing the ATL, provided by MRI-based biophysical computational models of current distribution and magnitude. We also tried to explain the variability in the behavioral outcomes in the *Semantic association* task based on patients' disease severity as well as on electric field values in the cortex. Our results showed that the electric field strength and its normal component correlated positively with cortical thickness and negatively with CSF volume in the left temporal cortex. This outcome suggests that greater levels of atrophy in the left temporal region has a negative impact on electric field estimates. Using a

regression model, we also showed that baseline severity of sematic access and electric field cortical estimates are essential factors to predict clinical stimulation outcomes.

Finally, *Chapter V* reports the design of a pre-registered ongoing clinical trial in which we aim to assess therapeutic outcomes of a multiday regime of tDCS on sv-PPA patients. This trial is based on previously reported impacts of a neurostimulation pre-therapeutic study very similar to those reported in Chapter III (Teichmann et al., 2016). In the original study in a small cohort of sv-PPA patients (n=12), a single session of both left-anodal and right-cathodal tDCS over the ATL significantly improved outcomes in a *Semantic association* task. On that basis, we designed a double-blind randomized clinical trial to study the long-term effects of 10 sessions (2 weeks) of tDCS in a large cohort (n=60) of sv-PPA patients with a 4-month follow-up on language tasks. Patients are randomly assigned to three treatment groups: anodal stimulation over the left ATL (n=20), cathodal stimulation over the right ATL (n=20) or sham stimulation (n=20). The study also aims to better understand the mechanisms of action of tDCS, by coupling language evaluations with neuroimaging assessments (PET-MRI), which could reveal stimulation-induced neuroplasticity, and help identify biomarkers predictive of baseline clinical severity or clinical response to tDCS (Sanches et al., 2019).

VI.2. Contributions of our works to models of mental lexicon and word processing

Research coming from several fields as psychology, neuroscience and linguistics provided an outline of studies on how words are represented, stored and accessed in the brain. It is now widely accepted that concepts in the human mind are cognitive units, each linked to associated information of different kind and that these connections represent a complex cognitive system known as the mental lexicon (Aitchison, 2012). Many theories have attempted to establish what information is represented in the lexicon and how this information is accessed. A revision of all the theories and models is out of the scope of this thesis. However, in our studies, we intended to contribute to the field by challenging models that claim a dependent or sequential access to different information stored in the mental lexicon - as the two-stage process for lexical access (Levelt 1992) and connectionist accounts of word processing such as the *Parallel Distributed Processing* (Plaut et al., 1996) – against those that privilege an independent access to information - as the Caramazza and Miozzo (1997) propositions of independent access to semantic, syntactic

and word-form representations and symbolic models of word processing such as the Dual Route Cascaded model (DRC) (Coltheart et al., 2001).

In agreement with the generally accepted view that there are three components associated to lexical items: *semantic*, *syntactic* and *phonological/orthographic* (Jackendoff, 2002), we studied the functional organization of the mental lexicon with language explicit tasks (requiring directed attention) and implicit tasks based on priming paradigms (requiring automatic processing) tapping into these three types of information. We recruited a cohort of patients diagnosed with the semantic and logopenic variants of PPA, along with healthy controls. Patient from these two PPA populations were chosen since their conditions are characterized by a progressive loss of language abilities, caused by progressive damage to the left lateral temporal cortical areas (from the most anterior to the most posterior regions) (Gorno-Tempini et al., 2011), an area of the brain suggested to be critical for lexical processing.

First, our results in healthy controls support the storage of semantic, syntactic and phonological/orthographic information in the mental lexicon, since priming effects in a *Lexical decision* task were elicited in the 3 implicit priming tasks, in which target words were preceded by unrelated or semantic/syntactic/phonological-orthographic related primes. Our PPA cohort showed impairments in accessing all types of lexical information. Nonetheless, we were able to show dissociations at the group and the individual patient level, with patients showing difficulties accessing one type of information while access to the other two was spared. This finding strengthens reports by other studies supporting cognitive models postulating an independent access to these different types of stored information (Biran and Friedmann, 2012; Caramazza and Miozzo, 1997; Kavé and Levy, 2003).

The outcomes of our second study, carried out in a cohort of sv-PPA patients, was also in line with models that privilege a more independent access to this information, specifically with symbolic accounts of word processing. We studied sv-PPA patients presenting with dyslexia/dysgraphia and we analyzed how they process irregular words by making them perform a reading and writing task with regular, irregular and non-words. Contrary to what is usually accepted, we were able to show that errors produced by these patients on irregular words were most often related to lexical disorders, as shown by poor performance in a *Lexical decision* task, than to semantic impairments, tested through mistakes in a *Category decision* task (e.g. Binney et al., 2016; Brambati et al., 2009; Patterson and Hodges, 1992). Moreover, to confirm impairment

in lexical access, we correlated performance in the *Lexical decision* task with the *Category decision* task, a semantic marker, and we did not find a statistically significant association. Thus, by showing that errors in irregular words are subtended by lexical damage and that there is a lack of significant correlation between performances in the *Category decision* and *Lexical decision* tasks, our results suggest that there is indeed a component of the lexicon that stores words as a whole, and that these representations can be accessed independently of semantic information.

Evidencing the notion that different kinds of information stored in the mental lexicon can be accessed independently holds implications for patients with impaired language abilities, such as lv-PPA and sv-PPA patients. These patients might be unable to access some information, like semantic representations, while being able instead to retrieve other kind of information, such as phonological/orthographic representations. These features should be implemented to guide effective rehabilitation programs, like speech therapy, by focusing not only on the impaired processes but developing novel strategies to reinforce lesion-spared (or less impaired) functions and systems, preventing such from further degradation and find strategies to bring communication abilities closest to normal.

VI.3. Impact of neurodegenerative diseases on language abilities

Detecting and characterizing language impairments has an important role in the identification and diagnosis of many neurodegenerative diseases (Boschi et al., 2017). However, the detection of such deficits is not always straightforward, due to the presentation of impairments in other cognitive or non-cognitive domains or the use of standard tasks that are not always sensitive to more discrete language deficits. In our studies, we used tasks specifically designed for each one of them, which allowed us to identify language impairments specific to each neurodegenerative disease studied. Our work also contributes to understand the role of some brain regions on different aspects of language processing, specifically the DLPFC and the temporal cortex, as well as the connections between these and other cortical sites.

Regarding PPA, we confirmed established evidence that sv-PPA patients present impairments in semantic access abilities (Gorno-Tempini et al., 2011; Mesulam et al., 2013, 2014) and that lv-PPA patients show impairments in the phonological/orthographic code, mainly influencing lexical representations (Gorno-Tempini et al., 2011). However, we went beyond these classical views and we showed that language deficits in both PPA variants are more extensive. Our

results from the 1st study in Chapter II, using a sensitive priming paradigm to analyze the three components of the mental lexicon - semantic, syntactic and phonological/orthographic - showed impairment of all three lexical components in both sv-PPA and lv-PPA patients, suggesting that priming tasks might allow for identifying even slight lexical damage in PPA. Our results from the second study in Chapter II and the third study in Chapter III, on sv-PPA and lv-PPA patients, respectively, reinforce the notion of extended language deficits on these populations. We showed that sv-PPA affects performance on a *Lexical decision* task, and that there is a negative correlation between word frequency and response reaction times, suggesting a breakdown of lexical access mechanisms, which adds to the breakdown of semantic access mechanisms, showed by poor performance on the *Category decision* task. Our cohort of lv-PPA patients displayed low performances in a *Picture naming* task, a marker for both lexical and semantic access and in a *Semantic association* task, requiring intact semantic access abilities. These data refines our current understanding of lexical deficits in PPA and is in line with evidence that already extended impairments in sv-PPA (Boukadi et al., 2016; Mesulam et al., 2013; Wilson et al., 2014; 2017) and lv-PPA (Rogalski et al., 2008; Teichmann et al., 2013). The identification of additional language deficits is important for disease characterization and allows a more targeted therapeutic intervention for each language symptom.

The brain regions implementing the processing of lexical and semantic information have been thoroughly investigated. Findings involved various temporal, parietal and frontal regions (e.g. Grossman et al., 2004; Lau et al., 2013; Pillay et al., 2014), yet they remain controversial (Migliaccio et al., 2016). Taken together, our results suggest that the temporal cortex is critical for both semantic and lexical access. Voxel-based morphometry analysis performed on PPA cohorts showed cortical atrophy encompassing regions of the left anterior, middle and posterior temporal cortex, slightly extending to the left inferior parietal cortex. The latter results, concomitantly with behavioral outcomes showing impairments in both lexical and semantic representations, strongly suggest the crucial implication of lateral temporal cortices in the processing or storage of lexical and semantic information. Our findings converge with studies indicating that lexical/semantic word processing is implemented across an anterior-posterior axis in the lateral-temporal cortices (Migliaccio et al., 2016).

The behavioral variant of Frontotemporal Dementia damages the prefrontal cortex bilaterally (Rosen et al., 2002; Seeley et al., 2008; Whitwell et al., 2009) whereas Progressive

Supranuclear Palsy, although most known to affect subcortical structures, has been shown to also impact the DLPFC bilaterally (Cordato et al., 2005; Giordano et al., 2013; Paviour et al., 2006). This region has been shown to subtend executive functions and contribute to the control of behavior (Cummings, 1993; Peters et al., 2006). Accordingly, the symptoms of bv-FTD patients are characterized by a gradual deterioration of behavior resulting in apathy, impaired social convenience, impulsivity and disinhibition (Rascovsky et al., 2011), whereas PSP patients show deficits in executive functions (Brown et al., 2010; Grafman et al., 1995). However, some studies have also suggested that both diseases also impair language initiation and research mechanisms in the mental lexicon (e.g. Hardy et al., 2016; Paviour et al., 2006). In line with such studies our cohorts of PSP patients and bv-FTD patients showed impairments in a *Letter fluency* and a *Picture naming* task, hence displaying deficits on language initiation and on lexical research mechanisms. Moreover, PSP patients also presented with deficits in a *Category judgment* task, supporting the presence of semantic deficits in this population.

Taken together, these results do not only contribute to the characterization of language impairments but highlight the importance of prefrontal cortical regions in language initiation and retrieval. Indeed, despite the fact that the DLPFC does not host *per se* lexical or semantic representations, we suggest that it contributes to the activation of search/retrieval processes of representations implemented in interconnected distant cortical areas of the left hemisphere, such as the ATL for semantic information (Rice et al., 2015) or the temporoparietal region for lexical representations (Migliaccio et al., 2016). Indeed, prefrontal regions are connected to the ATL via the uncinate fasciculus and to temporoparietal regions via the arcuate fasciculus (Catani and Thiebaut de Schotten, 2008). The fact that language abilities are impaired in patients with DLPFC atrophy but spared temporal regions suggests that the prefrontal cortex, even though not directly implicated in language representations, remains crucial for language abilities. Furthermore, response selection mechanism impairments in PSP can be caused by fronto-striatal dysfunctions (Rosser and Hodge, 1994) which, in turn, impact verbal fluency.

VI.4. Modulation of language networks with non-invasive brain stimulation

The value of non-invasive brain stimulation techniques, as tDCS, to the treatment of post-stroke aphasia developed during the last decade, set the basis for the current growing body of work

in neurodegenerative language impairments (Norise and Hamilton, 2017), a field we expect to contribute to with the works presented in this dissertation. On this regard, the pursued goal of our studies were two-fold: (1) to evaluate uses of tDCS as a therapeutic tool for language impairments on several neurodegenerative diseases and, at the same time, (2) to understand the cognitive mechanisms and anatomical interactions driving behavioral change (Polanía et al., 2018). The pre-clinical outcomes achieved by stimulation in our work proved inconsistent across pathologies and language processes. On the one hand, in PSP patients tDCS led to significant improvement on *Letter fluency* and *Category decision* tasks. However, similar interventions failed to influence language abilities in bv-FTD and lv-PPA patients. We will first discuss the implication of the former to then analyze some possible reasons for the lack of effects in our other two cohorts.

Transient proof of language modulation in PSP was successfully achieved with both anodal stimulation over the left DLPFC and cathodal stimulation over the right DLPFC. Improvement in the *Letter fluency* task with left prefrontal anodal tDCS could reflect an activation of search/retrieval processes and a facilitation of language initiation, in which the left DLPFC was already known to be implicated (Jefferies, 2013; Klaus and Schutter, 2018). In spite of the limited spatial resolution of tDCS, this outcome also supports a causal role of the left DLPFC in such processes, among other potential effects, likely by increasing the excitability of underlying pre-frontal neurons. An fMRI study (Pereira et al., 2013) showing that anodal left prefrontal tDCS during a verbal fluency task increased functional connectivity between frontal and inferior parietal regions, implementing lexical representations (Migliaccio et al., 2016), suggests that indirect activation of inferior parietal brain sites could be a potential action mechanism. Whether our results came from a direct activation of the left DLPFC, from an indirect activation of language-specific regions linked with the former or a combination of both would need to be further clarified using neuroimaging or neurophysiological approaches. The basal ganglia and cortico-subcortical loops involving thalamic nuclei, the basal ganglia and DLPFC regions have also been shown to play a role in word-generation (Barbas et al., 2013; Crosson et al., 2003). The basal ganglia are one of the most affected structures in PSP patients (Paviour et al., 2006), hence we cannot exclude a network modulatory effect of stimulation on such loops as the mechanism explaining language improvement in our patients.

The observed improvement in the *Semantic association* task after right DLPFC cathodal stimulation in PSP patients is compatible with the notion that, in situations of left hemisphere

damage, the excess of right hemisphere activity might be deleterious to language function (e.g. Rosen et al., 2000). In such situations, decreasing the suppressive drive of right homotopic regions onto left language-dominant sites might prove beneficial for language processing. Moreover, since applying cathodal stimulation to the right DLPFC improved language abilities and it is unlikely that this strategy will indirectly activate left non-homotopic language-related regions, we suggest that our result reinforces the increased activation of the left DLPFC and hence its critical role on language. However, some studies in stroke patients have also shown a facilitatory role of right hemisphere regions on language, after damage to left hemisphere regions resulting in aphasia (Tukerltaub et al., 2011). It should be noted that, to date, the non-invasive transcranial stimulation paradigms currently used to address language impairments in neurodegenerative diseases are based on observations from stroke aphasic patients. Hence, the use of right hemisphere suppression paradigms in neurodegenerative diseases remain to be carefully characterized by means of structural and functional neuroimaging and/or neurophysiological techniques suited to pinpoint their net impact and mechanisms of action.

Contrary to our predictions, neither bv-FTD nor lv-PPA patients displayed beneficial effects on language performance following a single tDCS session. In the light of the stimulation conditions that yielded beneficial effects in prior studies, two main causes could be argued as potential explanations for the failure. First, it is well known that state-dependent effects of brain stimulation have shown that ongoing activity operating on the targeted region during stimulation may influence the direction and/or magnitude of modulatory effects (Silvanto and Muggleton, 2008). To this regard, prior studies of tDCS effects on language impairments affecting lv-PPA patient, reported clinical benefits by combining stimulation with concurrent language-related rehabilitation (e.g. Ficek et al., 2018; Gervits et al., 2016).

Second, disease severity at baseline is another factor known to eventually compromise modulatory responses. To this regard, our bv-FTD patients were more impaired in the *Letter fluency* task than for example a cohort of tDCS-treated Parkinson's disease patients who responded positively to a similar task (Pereira et al. 2013). Furthermore, whereas bv-FTD patients are characterized by signs of atrophy mainly in prefrontal regions, Parkinson's disease and PSP patients (the latter, our first cohort of patients that showed improvements in the *Letter fluency* task) suffer damage on subcortical structures such as the basal ganglia, and only secondarily and less critically on prefrontal areas. As verified in computational models simulating tDCS current fields,

the thinning (i.e. atrophy) of the cortical regions targeted by stimulation increases the cumulated volume of CSF, a highly conductive media that tends to dissipate and weaken current fields making them less effective (Wagner et al., 2007; Wagner et al., 2009; O'Brien et al., 2016). This explanation is also in line with our results from computational models simulating current magnitudes and distribution based on individual MRIs in sv-PPA patients. In this study, we report that cortical thinning influences negatively the strength of electric field reaching the targeted region within the left temporal lobe (encompassing the ATL). Moreover, based on a linear regression model, we also found out that baseline disease severity (estimated according to language performance levels) influences stimulation outcomes.

VI.5. Improving non-invasive brain stimulation in neurodegenerative diseases

The field of brain stimulation research has shown during the last decade an outstanding degree of dynamism and innovation. Basic science, pre-therapeutic and therapeutic TMS and tDCS studies have expanded our knowledge on how non-invasive brain stimulation (NIBS) operate and opened new avenues for the characterization and development of cognitive rehabilitation treatments in neurology. Nonetheless, an effective use of NIBS requires the neurostimulation community to move beyond classical approaches and fully integrate growing neurophysiological and neuroanatomical evidence subtending cognitive function and dysfunction. To this regard, we have identified some practical issues to be considered to improve the quality of pre-therapeutic and therapeutic NIBS trials in neurodegenerative diseases, which apply to tDCS applications as the ones presented in this dissertation. Thoroughly considering them should maximize chances of effective outcomes and help the field make progress towards successful therapies.

Disease specific selection of cortical targets for stimulation is paramount. Small or large, cortical target regions to be influenced by transcranial stimulation must be chosen considering structural and functional changes operating in injured brains, and their functional (and/or dysfunctional) contributions to the cognitive domain in which neuromodulation is intended (Tatti et al., 2016). More specifically, the localization and extent of damaged areas and their associated networks, contributing to cognitive deficits or to their potential compensation, should be carefully weighted in order to choose the most effective stimulation site. It is also imperative to adapt the stimulation technology (TMS vs tDCS) and stimulation strategies to each specific pathology, guiding such choice by prior knowledge on mechanistic neurophysiological aspects underlying

each disease. Likewise, spatial resolution optimally adapted to the cortical extent of damage requires to choose the most adequate stimulation approach and/or to adjust electrode montages (in tDCS) or coil shape and size (in TMS), all essential to achieve effective stimulation and drive cognitive improvements. The use of MRI-based neuronavigation to precisely determine the scalp region most closely overlying a cortical target (with the shortest straight path) and correctly place tDCS electrodes will also improve stimulation outcomes. Despite the fact that high-focality might not always be an advantage, particularly when treating cortically widespread pathologies or largely represented cognitive processes, a correct tDCS electrode placement is paramount. To this regard, Opitz et al. (2018) recently reported that the prediction of the electric fields generated by transcranial electric stimulation is compromised when the placement of the electrode in head models differs by only 1 centimeter (or more) from the actual electrode placement. This means that even for poorly focal techniques such as tDCS, precise electrode placement is crucial to maximize our chances to influence an intended brain area. Additionally, current intensity influences the radial spread and focality of the cortical impact. Generally, the higher the intensity the larger the radial spread of the induced electric field and the lower the spatial specificity of the effect. Hence a delicate tradeoff between field intensity and focality needs to be considered.

Multiple variables (e.g. cortical thickness, CSF volume, scalp-to-brain distance, skull shape, sulcal patterns and gyral geometries) determine the electric field strength reaching a targeted cortical region. In absence of direct physiological evidence, computational Finite Element Models can be employed to estimate the spread and intensity of current fields based on individual structural MRI. The systematic use of MRI-based computational models and simulations of current distribution (including peak electric field values at a specific target) should help in the selection of patients for a specific protocol and guide individualization of stimulation parameters based on the anatomical features characterizing the head and brain of each patient.

Besides behavioral or clinical evidence, complementary mapping tools (e.g. structural MRI and resting state/task activated fMRI, ^{18}[F]-Fluorodeoxyglucose Positron Emission Tomography [^{18}FDG-PET], spectroscopy, or EEG and MEG) can be essential to capture the short- and long-term impact of tDCS in local and distributed brain networks. Coupling NIBS with neuroimaging and neurophysiological recordings could then provide insights on whether and how brain networks are influenced by transcranial stimulation (Santarnecchi et al., 2015). This kind of measures can also reveal structural and functional biomarkers subtending cognitive alterations. Such evidence

allows a better understanding of the underlying pathology, informs on how NIBS might have interacted across a treatment with pathological brain areas and may be helpful to program more sophisticated and accurate computational models simulating current fields. In therapeutic trials, these same measures recorded before, during and at the end of the stimulation regime might serve to characterize plasticity processes, eventually explaining enduring recovery. High spatial resolution neuroimaging techniques are cumbersome and often stressful for patients. In contrast, electrophysiological technologies (such as EEG recordings, which is often built-in in commercially available tDCS devices) allow a more direct and high temporal resolution of NIBS impact on brain activity and the follow-up of its physiological impact after single stimulation sessions and throughout a multiday stimulation regime.

Another issue very likely to influence the outcomes of NIBS studies is the selection of cognitive/clinical tests to assess stimulation efficacy in terms of behavioral change. Tasks, scales or scores need to be clinically relevant and also feasible, sensitive and specific. Importantly, for pre-clinical studies assessing off-line effects of single tDCS stimulation sessions (as the ones featured in this dissertation), one should consider the fast decay of local stimulation impact, hence implement evaluation tasks that allow reliable estimations of behavioral changes in very short time. Paradigms that allow individual performance titration and several versions of the same task equated in difficulty are also important to limit interindividual variability and test-retest learning effects.

An influential finding in the NIBS field to be taken into account, and that has been mentioned already, is that the direction and magnitude of neuromodulatory effects is strongly determined by ongoing activity operating on the targeted region at the time of stimulation (Silvanto and Muggleton, 2008; Silvanto et al., 2008; Silvanto and Pascual-Leone, 2008 for a review). To this regard, it has been shown that when a TMS/tDCS pattern targets a cortical region hosting cellular subpopulations processing different functions or features, this tends to differentially influence neuronal resources as a function of their ongoing excitability levels. Based on this state-dependency principle, some NIBS studies aiming to improve cognition in neurodegenerative diseases have applied stimulation concurrently with cognitive exercises or tasks in Alzheimer's Disease (Brem et al., 2013; Cotelli et al., 2014a) or PPA patients (Cotelli et al., 2014b; 2016; Gervits et al., 2016; McConathey et al., 2017; Roncero et al., 2017; Tsapkini et al., 2014). Most of these attempts showed significant improvements compared to pre-stimulation performance (Brem

at al., 2013; Cotelli et al., 2014b; 2016; Gervits et al., 2016; McConathey et al., 2017; Tsapkini et al., 2014). However, none of them compared the former intervention to an active stimulation condition not implementing a concurrent task, a control that is necessary to highlight the specific benefits of combining task and brain stimulation. Interactions between transcranial stimulation and behavioral tasks used to activate targeted systems may prove complex and not always synergistic. For these reasons, in case of doubt (unless a previously tested facilitatory paradigm can be employed) a good strategy is to implement a simple task non-related to the cognitive function in study, ensuring that all patients will remain in a homogeneous brain state during stimulation.

Additionally, behavioral approaches such as task adaptation (i.e., sustained exposure to an invariant sensory pattern which decreases neuronal activity of the neuronal population processing a specific feature) could be employed prior, during or following stimulation to maximize the effects driven by excitatory stimulation patterns. Similarly, sensory, motor or cognitive tasks could be used to increase ongoing levels of activity, to facilitate the suppressive effect of inhibitory TMS/tDCS patterns and render such populations less sensitive to stimulation (e.g. see an example in visuospatial attention in Chanes et al., 2012). In neurodegenerative patients, one of the main sources of brain state modulations is the impact and progression over time of cortical damage and atrophy, which needs to be accounted for. Therapeutically, a well-suited manipulation of the activity state may allow clinicians to shape the direction, selectivity and magnitude of the neurostimulation on regions hosting mixed neuronal populations with a diversity of contributions and overcome limitations in TMS/tDCS spatial resolution.

To this same regard, a growing number of studies have shown effects on cognition trough the association of a cognitive rehabilitation program and NIBS. A combination of adapted cognitive training and NIBS targeting different brain regions (right and left DLPFC, right and left posterior parietal cortex associative areas, and Broca and Wernicke language areas) in Alzheimer's disease and related dementia patients showed promising results (e.g. Bentwich et al., 2011; Lee et al., 2016; Rabey et al., 2013). The reported benefits result from an overall modulation of intrinsic, homeostatic and synaptic plasticity, leading to normalization of neural network activity. It is possible that by matching NIBS and cognitive rehabilitation to the best, the latter may facilitate and further maintain the benefits derived from the brain stimulation and vice-versa. Coupling cerebral and cognitive stimulation should promote activity of specific cerebral areas and/or a specific neural circuit implicated in a given function; and/or should favor efficient interactions

between the specific brain systems to rehabilitate and spared areas/circuits, which may in turn contribute or eventually compete. In the latter case, the interaction between cognitive rehabilitation and NIBS can be synergistic or designed to eliminate detrimental antagonisms.

VI.6. Future directions for neurostimulation in neurodegenerative diseases

One of the goals of the studies presented in this dissertation was to provide proof-of-concept for uses of NIBS approaches to improve language deficits in patients with neurodegenerative diseases. More specifically, we aimed to assess pre-clinical applications with single tDCS sessions prior to considering large-scale clinical trials accruing regimes of several days of stimulation in three patient populations, PSP, bv-FTD and lv-PPA. Research in these three types of neurodegenerative patient suffers the burden of complex administrative and organizational aspects of working in sensitive and eventually rare clinical populations. Moreover, strict recruitment criteria hinder even further the feasibility of enrolling a large number of individuals. Nonetheless, in all our tDCS studies we did our best to overcome these hurdles and privileged the recruitment of small but well-diagnosed homogeneous cohorts. To this end, we opted for assessing and comparing short-term effects of several tDCS conditions in single sessions in the same population of patients for each disease. With this decision, we gave away immediate therapeutic value, but we limited the risks associated to interindividual variability in randomized independent group studies and reduced the need for large-scale recruitments, which tend to compromise feasibility.

We left many questions open or unanswered. Furthermore, on the basis of our findings, we pointed out to a number of challenges that the field of NIBS and neurodegenerative diseases will have to face in a fast-approaching future. Particularly important, is the fact that we explored the use of tDCS with a simple bipolar (with electrodes placed over non-symmetrical brain regions) bilateral montage. Nonetheless, in an attempt to overcome the limitations posed by canonical uses of TMS and tDCS techniques, the domain of non-invasive brain stimulation is engaged in developing novel stimulation approaches for human clinical settings. The complexity of the interactions between tDCS stimulation parameters, and the clinical and anatomical features of each individual patient was dealt with in a study using off-the-shelve computational models, which shed light on intricate factors that could influence clinical outcomes. Unfortunately, time constrains did

not allow the exploration, during the duration of this PhD, of longer-term effects of a multiday stimulation regime able to engage plasticity on language deficits. Nonetheless, the development of a long-term therapeutic protocol in sv-PPA should, in the years to come, provide clinically relevant evidence about neuroplasticity mechanisms subtending long-term tDCS-induced behavioral changes on semantic access abilities.

VI.6.1. Towards new families of brain stimulation technologies

The recent finding of the ability of frequency-specific rhythmic TMS bursts or sinusoidal tDCS patterns to either enhance and/or impose oscillatory activity involving cyclic fluctuations of activity in local clusters of cortical neurons (see Gross et al., 2011; Thut and Miniussi, 2009) will influence the use of NIBS and its application in clinical protocols. Additionally, locally entrained rhythms can also be conveyed to distant regions, enhancing temporally correlated activity or interregional synchrony. Research in this area has also shown that single TMS pulses have also the ability to phase-reset and align local oscillators in a given cortical region and induce transiently boosting of power at the so called "natural frequency" at which such oscillators are most likely to operate (see pioneering evidence by Paus et al., 2001; Rosanova et al., 2009).

These effects are relevant because cortical oscillations have emerged as an essential mechanism underlying specific cognitive operations and behaviors (Buzsáki and Draguhn, 2004). Accordingly, local and/or interregional entrainment of rhythmic TMS patterns have been shown to facilitate cognitive processes. For example, relevant for neurodegenerative diseases, the lasting echo of rhythmic beta TMS patterns (beyond burst duration) has shown to induce impairments of memory consolidation in inferior prefrontal frontal regions (Hanslmayr et al., 2014). This result suggests that the effects of rhythmic entrainment on cognition could be potentially relevant for modulating behavior in the healthy but also for treating neurological conditions. Moreover, effects proved site-, phase- and frequency-dependent, and showed that for some cortical regions and cognitive processes (e.g. attentional orienting), it is the episodic desynchronization of ongoing rhythmic activity during specific time-windows that can also result in cognitive enhancements (Thut et al., 2017). Similarly, transcranial Alternating Current Stimulation (tACS) has also shown the ability to entrain cyclic activity (Helfrich et al., 2014a, 2014b; Herrmann et al., 2016) and when delivered occipitally at 10 Hz, for example, co-cycles with alpha occipital activity and facilitates phase-dependent visual perception (Thut et al., 2011). Moreover, tACS makes possible the use of

complex patterns based on “nested” high-frequencies (gamma band) on top of slower underlying theta rhythms, which delivered pre-frontally have shown recently to enhance working memory capacity (Alekseichuk et al., 2016).

Alterations of oscillatory brain activity and neural synchrony emerged some years ago as novel potential biomarkers of cognitive neurological deficits following focal stroke lesions such as visuospatial neglect (Rastelli et al., 2013; Yordanova et al., 2017). Similarly, such alterations are also being now reported for neurodegenerative diseases (see Meder and Siebner, 2018 for a review). Although mechanistic causes and consequences remain unclear, Alzheimer’s disease patients exhibit for example relative power increases for slow oscillations (delta and theta rhythms) and in contrast decreases for fast rhythms (alpha, beta and gamma rhythms) (see Vecchio et al., 2013 for a review). Alterations of oscillatory activity and local or interregional synchrony have also been found more recently in other neurodegenerative diseases (Andersson et al., 2008; Ponsen et al., 2013; Ranasinghe et al., 2017).

A MEG study comparing Parkinson’s disease patients with or without dementia found differences in oscillatory power between these two groups, the former showing lower power in the alpha and beta bands in occipito-parieto-temporal and frontal areas compared to the latter, but stronger activation in the delta and theta bands in parieto-occipital and fronto-parietal areas (Ponsen et al., 2013). Patients with Dementia with Lewy Bodies have also displayed increased delta and theta activity and decreases of alpha and beta rhythms compared to healthy participants and to Alzheimer’s disease patients (Andersson et al., 2008). Most interestingly, Ranasinghe and colleagues (2017) reported MEG evidence of dysfunctional patterns of alpha and beta neural synchronization in PPA patients. Recordings revealed PPA-variant specific patterns of hypo- and hyper-synchrony. These alterations remained significant even after correcting for gray matter volume, hence supporting the idea that such alterations (known as oscillopathies) reflect genuine functional alterations of neural activity and cannot be solely explained by cortical atrophy (Ranasinghe et al., 2017).

In a similar vein a recent MEG study assessed, in five different neurodegenerative conditions, direct coherence measures and calculated nodal local efficiency, a proxy of how well connected a node is with its network neighbors, hence how resilient it can be to neural damage. Using a data driven whole-brain connectivity analytic approach on resting state MEG data, authors searched for characteristic neurophysiological signatures, likely distinctive in spatial and

frequency profiles for Alzheimer's disease, Posterior Cortical Atrophy, bv-FTD, PSP and non-fluent PPA patients. The study was able to cluster clinical syndromes sharing a similar underlying network pathology (referred to as "circuitopathy") and reported for example decreases in network efficiency in the gamma band for Alzheimer's disease and Posterior Cortical Atrophy, whereas alterations in bv-FTD, PSP and non-fluent PPA impacted lower frequencies (delta, alpha and low gamma) (Sami et al., 2018).

Finally, a very recent study in bv-FTD used a hypothesis driven single network analyses of MEG data during the generation and inhibition of responses with a Go-NoGo motor task and explored alterations of cross-frequency coupling phenomena (Hugues et al., 2018). Authors concluded a reduction of event related beta-band desynchronization -scaling with behavioral disinhibition- and also deficient beta rebound re-synchronization. Further analyses also revealed a general reduction of within and cross-frequency coupling between three key regions for inhibitory control such as the Inferior Frontal Gyrus, the pre-supplementary motor area and the primary motor cortex (Hugues et al., 2018). As the former study, this report emphasizes the notion of network- and band- specific alterations of oscillatory activity caused by cortical damage and/or the ensuing functional reorganization, and their role subtending the behavioral phenotypes of neurodegenerative diseases (Hugues et al., 2018; Meder and Siebner, 2018; Sami et al., 2018).

In sum, electrophysiological evidence suggests a disorganization of functional circuits and alterations of neural synchrony at early stages of neurodegenerative diseases, preceding structural atrophy changes (Ahnaou et al., 2017; Bonakdarpour et al., 2017). Moreover, spatiotemporal synchrony abnormalities reflect a breakdown of cytoarchitectural network properties and/or their struggle to compensate damage, hence accounting for brain resilience. Most important, spatiotemporal correlates of network dysfunction have a consequence on symptoms suffered by patients, hence can be used to tease apart disease variants (Ranasinghe et al., 2017; Sami et al., 2018) or specific neurodegenerative phenotypes (Hughes et al., 2018; Sami et al., 2018). The ability of some NIBS techniques, notably rhythmic TMS and tACS, to modulate oscillatory activity and interregional synchrony, will provide new opportunities to intervene on specific neurodegenerative diseases, with the aim to re-instate oscillatory normality across altered networks and, in turn, slow-down the progression of cognitive decline. The use of oscillation-based rhythmic neuromodulation principles in the rehabilitation of cognitive deficits in neurodegenerative patients remains to be developed. Nonetheless, successful application of anti-phasic tACS, individually

tailored for tremor in Parkinson's disease patients, signals a worth-following path for clinical translation (Brittain et al., 2013). Indeed, as the role of local and widespread oscillatory/synchrony activity in cognitive coding is being associated to many aspects of high-level cognition, the development of rhythmic stimulation is emerging as a promising therapeutic domain.

A great limitation of tDCS is the fact that it only allows the use of weak current intensities (up to 4 mA in humans) for patient safety and comfort, and a large amount of this current does not reach the cortical surface, failing to influence the resting membrane potential of neuronal populations. Particularly noteworthy for the field of novel transcranial brain stimulation technologies has been the search for devices capable of delivering higher intensities, in a more focal and 'steerable' manner, if possible directly into subcortical brain structures without having to influence all layers of non-neural and neural tissue before reaching a deep target. Some of such novel technologies have developed new uses of transcranial electrical currents by using extremely short pulses of direct electrical current with a rotating electrical gradient between an array of multiple pairs of tDCS electrodes, converging on a single cortical location. This approach, termed intersectional short pulse (ISP) stimulation taking advantage of a slow temporal summation in neuronal bodies, allows the injection of high currents into a brain location (>0.7-1 mV/mm), while keeping charge density low and scalp skin sensations bearable (Vöröslakos et al., 2018). Finally, Grossmann et al. (2017) have recently reported in rodents the ability to generate a deep, focal, and stable deep temporal interference stimulation (TIS). Effects are generated by merging within a superficial or deep spatial gradient around a brain target two high-frequency oscillating transcranial electric fields (equivalent to tACS) slightly shifted in frequency (Grossmann et al., 2017).

All in all, current research and therapeutic applications of neuromodulation in humans keep relaying in rTMS and tDCS approaches, and very particularly on tDCS for locally or more generally wide-spread conditions, as those presented in this dissertation. There is however little doubt that alternative currently-developing techniques will expand the array of neuromodulation technologies at the service of neurology.

VI.6.2. New strategies for patients' selection for therapeutic neurostimulation studies

In neurodegenerative diseases, symptomatology tends to appear many years after the onset of detectable brain atrophy, when the damage is already very intense and widespread. Recent failures of potential disease-modifying drugs, in particular for Alzheimer's disease, most probably reflect the fact that subjects enrolled in clinical trials are already pathologically too advanced to derive an impacting clinical benefit. Likewise, in our computational modeling study in sv-PPA, we showed that disease severity could affect current fields, hence effectiveness of a response to stimulation and that the degree of atrophy will greatly impact the current that reaches the brain. With this in mind, a major aim is to identify patients long before they develop symptoms or at very early stages of the disease.

The single or combinatorial use of different biomarkers has demonstrated a high potential to diagnose and track the progression of neurodegenerative diseases. Additionally, the identification of biomarkers of pre-clinical detection is essential for therapeutic advancement. For example, several biomarkers are available for Alzheimer's disease: positive amyloid or tau tracer retention on PET imaging; low CSF concentrations of the amyloid-β 1-42 peptide, high CSF concentrations in total tau and phospho-tau; mesial temporal lobe atrophy on MRI, and/or temporoparietal/precuneus hypometabolism or hypoperfusion on PET (for a review see Weiner et al., 2015). Many of these biomarkers have also been tested on cohorts of healthy individuals to detect early signs of Alzheimer's disease (Weiner et al., 2015). Current main goals are on the one hand to identify new easy-to-test biomarkers (e.g. plasma, retinal biomarkers) as soon as possible. On the other hand, we prompt moving from the identification of early phases of the disease to the characterization of individuals 'at high risk'. In the simplest cases, when the risk is genetic, as for individuals with genetically determined dementias, the early diagnosis is possible in the pre-clinical state (Balendra and Isaacs, 2018; DeJesus-Hernandez et al., 2011). In the other cases, it is important to identify potential high-risk factors, such as becoming old and being a homozygous carrier of the Apolipoprotein E4 allele, which increases the risk of getting Alzheimer's disease (Liu et al., 2013). Within this general framework, NIBS will definitely become more useful and effective as earlier it will be applied and more specific systems will be targeted.

VI.7. Final remarks and conclusions

In a context characterized by increasing population aging and the lack of effective treatments for age-associated neurological conditions, the search for novel therapeutic approaches

beyond pharmacology and cognitive rehabilitation is gaining momentum. The evidence reviewed in the introduction and presented in this dissertation suggests that language abilities are impaired in several neurodegenerative diseases presenting damage at different anatomical regions. Transcranial DCS is conferred the ability to drive improvements in such impairments. Yet, the value of tDCS approaches in neurodegenerative diseases remains to be consistently evaluated and verified using larger homogeneous cohorts of well-characterized patients, and sensitive behavioral and clinical assessments in combination with neuroimaging and neurophysiological evidence. To this end, determining the stimulation settings, strategies and parameters most likely to result in effective behavioral outputs and the use of comparable and reproducible evaluation methodology is paramount. Moreover, a further understanding of structural and physiological variables influencing the interaction of tDCS electric currents with head/brain tissue layers, via computational Finite Element biophysical head-brain-models of current distribution, is also relevant to tailor target location, stimulation patterns and dosing and to improve the choice of patients that will most benefit from such therapies. It is important to consider the new stimulation techniques that are rising and to apply them in the view of the new neurophysiological biomarkers specific to each pathology.

Our work set the stage for a new clinical trial exploring some of the questions opened by previous works, namely the impact of multi-day stimulation regimes that should hopefully allow for a long-term effect of stimulation and most important the combination of neuroimaging and neurophysiological measures to understand stimulation mechanisms and to disease characterization. We believe that the understanding of such mechanisms is critical for the future development of NIBS techniques in clinical settings and for the adequate use of the new techniques being developed.

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