ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

ΝΕΥΡΟΑΠΟΚΑΤΑΣΤΑΣΗ

Διευθυντής ΠΜΣ: Αναπλ. Καθηγητής ΕΥΘΥΜΙΟΣ ΔΑΡΔΙΩΤΗΣ

Μεταπτυχιακή Διπλωματική Εργασία

NONINVASIVE BRAIN STIMULATION IN PPA

ΚΩΝΣΤΑΝΤΙΝΟΣ ΠΑΠΑΝΙΚΟΛΑΟΥ
ΛΟΓΟΘΕΡΑΠΕΥΤΗΣ

Υπεβλήθη για την εκπλήρωση μέρους των απαιτήσεων για την απόκτηση του
Μεταπτυχιακού Διπλώματος Ειδίκευσης
«ΝΕΥΡΟΑΠΟΚΑΤΑΣΤΑΣΗ»

Λάρισα, Μάιος 2022

Βεβαιώνω ότι η παρούσα διπλωματική εργασία είναι αποτέλεσμα δικής μου δουλειάς και δεν αποτελεί προϊόν αντιγραφής. Στις δημοσιευμένες ή μη δημοσιευμένες πηγές έχω χρησιμοποιήσει εισαγωγικά όπου απαιτείται και έχω παραθέσει τις πηγές τους στο τμήμα της βιβλιογραφίας.

Υπογραφή: Κωνσταντίνος Παπανικολάου

ΚΩΝΣΤΑΝΤΙΝΟΣ ΠΑΠΑΝΙΚΟΛΑΟΥ

Πανεπιστήμιο Θεσσαλίας, Σχολή Επιστημών Υγείας, Τμήμα Ιατρικής, 2022

ΔΙΕΥΘΥΝΤΗΣ ΠΡΟΓΡΑΜΜΑΤΟΣ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

ΕΥΘΥΜΙΟΣ Γ. ΔΑΡΔΙΩΤΗΣ

ΑΝΑΠΛ. ΚΑΘΗΓΗΤΗΣ ΝΕΥΡΟΛΟΓΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟΥ ΘΕΣΣΑΛΙΑΣ

Επιβλέπων: Νάσιος Γρηγόριος, Αναπλ. Καθηγητής Λογοθεραπείας Π.Ι

Τριμελής Συμβουλευτική Επιτροπή:

1. Νάσιος Γρηγόριος, Αναπλ. Καθηγητής Λογοθεραπείας Π.Ι.
2. Δαρδιώτης Ευθύμιος, Αναπλ. Καθηγητής Νευρολογίας Π.Θ.
3. Πατρικέλης Παναγιώτης, Επικ. Καθηγητής Νευροψυχολογίας Α.Π.Θ.

Τίτλος εργασίας στα αγγλικά:

“NONINVASIVE BRAIN STIMULATION IN PPA”

ΕΥΧΑΡΙΣΤΙΕΣ

Θα ήθελα να ευχαριστήσω θερμά όλους αυτούς που συνέβαλαν για την πραγματοποίηση αυτής της διπλωματικής εργασίας. Αρχικά, τον καθηγητή Νάσιο Γρηγόριο, ο οποίος είναι και επόπτης αυτής της διπλωματικής, για την ανάθεση αυτού του πολύ ενδιαφέροντος θέματος καθώς και για την καθοριστική καθοδήγηση του καθ΄ όλη την διάρκεια της συγγραφής της εργασίας. Ξεχωριστά θα ήθελα να ευχαριστήσω τον διευθυντή του Νευρολογικού Ινστιτούτου Αθηνών, Καραγεωργίου Ελισσαίο του οποίου οι συμβουλές ήταν πολύτιμες. Τέλος (αλλά όχι τελευταίο) θέλω να ευχαριστήσω τον καθηγητή Παπανικολάου Ανδρέα, του οποίου η βοήθεια και η συνδρομή υπήρξε πολύτιμη και καταλυτική για την εκπόνηση της διπλωματικής εργασίας.

Abstract

Primary progressive aphasia (PPA) is a gradually progressive clinical syndrome in which the first and predominant symptoms involve language and/or speech production that interfere with daily activities. Transcranial magnetic stimulation is a non-invasive brain stimulation method based on electrophysiological principles. Its main purpose is to induce currents within neural networks through the application of a magnetic field that traverses the skull and reaches the cortex. Transcranial direct current stimulation (tDCS) is also a non-invasive brain stimulation method that induces electrical activity in the brain. It is painless and easy to use. The first application of tDCS was on animals but in the last few years it is used as a modulation tool for the human brain. The current review surveyed all studies of rTMS and tDCS involving PPA patients that were found in pubmed searches. A general observation for both types of stimulation, magnetic and electrical, is that the small number of studies, the small samples used, the small number of investigations and the reduction in the number of such publications following a period of growth in that number, are factors that should be taken seriously into account before drawing any definite conclusions about the effectiveness of neurostimulation in PPA. Nevertheless, it appears that both types of stimulation are promising especially if they involve, at the same time, behavioral therapy.

Key words: Noninvasive brain stimulation, rTMS, tDCS, Primary progressive aphasia, PPA, Speech therapy, Neurostimulation

ΠΕΡΙΕΧΟΜΕΝΑ

INTRODUCTION

A description of Primary Progressive Aphasia (PPA)

Primary progressive aphasia (PPA) is a gradually progressive clinical syndrome in which the first and predominant symptoms involve language and/or speech and production interfering with daily activities. [1,2]The most typical language and speech features affected in PPA are naming, grammar, semantic comprehension, and speech production. On this basis, three major variants of the disorder have been defined using current classification criteria: (a) non-fluent/agrammatic PPA (nfvPPA), (b) logopenic variant PPA (lvPPA), and (c) semantic variant primary progressive aphasia (svPPA).

PPA is a clinical syndrome with multiple neuropathologic causes. The main characteristic of the disease is cortical atrophy and neuron loss, which depends on underlying pathology. Current studies show us that most patients with PPA have been found to have tauopathy, ubiquitin/TDP43- positive frontotemporal lobar degeneration (FTLD) pathology [2–4]or Alzheimer disease pathology. [5,6]According to clinical studies, non-fluent progressive aphasia has been linked to tau-positive pathology[2,7,8] semantic variant of PPA to ubiquitin-positive, TDP43, positive pathology[3,8,9] and the logopenic variant of PPA to AD pathology[8] .

There are three diagnostic criteria of PPA. [10]

1) The progressive degeneration of the language network: Aphasia has to be the first and only symptom at the early stage of the disease. [10]

2) Linguistic symptoms must have a neurodegenerative nature. Neurological evaluation, which includes clinical history, tests of language functions and neuroimaging procedures, must indicate a neurodegenerative disorder, which leads to left hemisphere atrophy and affects the language network.[10]

3) Aphasia must affect everyday activities and the quality of life of the patients for at least 2 years. [10]

Once the PPA diagnosis is established, evaluation of several language domains (naming, grammar, praxis, sound errors) will determine the type of PPA. There are clinical criteria for each variant of PPA. The classification of PPA into one of the variants presupposes the existence of one of three diagnostic levels: clinical, imaging supported or definite pathology diagnosis. [11]

Nonfluent/agrammatic variant PPA (also known as progressive nonfluent aphasia): In that clinical syndrome the main characteristic is the fluency disorder. The core criteria are agrammatism in language production and effortful speech. At least one of those should be present. [10] Agrammatism is characterized by short and simple phrases with lack of functional

words. Effortful speech refers to slow and labored speech production. [11] Furthermore, another clinical symptom that exist at the initial stage of the disease is the apraxia of speech.[2,12] Also, speech sound errors such as distortions, deletions, substitutions, insertions, or transportations are often observed in the nonfluent variant of PPA. Prosody is disrupted also. [11] With respect to imaging, the existence of abnormalities in the left posterior fronto-insular region, the (inferior frontal gyrus, insula, premotor and the supplementary motor areas) are necessary to make a diagnosis based on imaging, supporting the nonfluent variant. [9] Progressive atrophy of the brain in PPA impacts negatively many aspects of language processing. Yet the extent of decrement in linguistic task performance, notably lexical retrieval, seems to be modulated by prior exposure to printed language such as reading newspapers and books.[13,14] The co-existence of these two sources of variability in patients' language performance renders assessment of the impact of atrophy alone difficult. In a recent study, Peristeri et al. (2021)[15] explored the extent to which atrophy and exposure to print affected picture naming and word reading in a sample of 14 Greek speaking individuals with the nonfluent variant of PPA reaffirming the importance of print exposure and explaining part of the variance in linguistic performance in patients equally impacted by tissue atrophy.

Semantic variant PPA (also known as semantic dementia): Semantic comprehension is the main domain that is affected in that clinical syndrome. The core criteria are anomia and single word comprehension deficits. In the semantic variant of PPA, naming problems are severe, and the semantic comprehension problem is more pronounced for low frequency words. The comprehension deficit is linked to semantic memory. Dyslexia and dysgraphia are also common features of the semantic variant of PPA. Paragrammatism, sparing repetition, and motor speech, also occurs, although language production is grammatically correct. The atrophy in the semantic variant of PPA exist in the ventral and lateral portions of the anterior temporal lobes bilaterally although the damage is usually greater on the left. [12,16–19]

Logopenic variant PPA (also known as logopenic progressive aphasia): The language deficits in the logopenic variant of PPA are word retrieval and sentence repetition. Spontaneous speech is the main characteristic of that type of PPA which means that the patients have a slow rate with frequent pauses in their speech due to word-finding difficulties. There are numerous language domains that distinguish the logopenic variant PPA from the other two types. Those are prosody, agrammatism, phrase repetition and mostly phonological paraphasias that patients with lvPPA present with well articulation.[11] A diagnosis of logopenic variant of PPA also requires imaging abnormalities in the left temporo-parietal junction area, i.e., posterior temporal, supramarginal and angular gyri. [12]

Specific language deficits are detailed in **table 1**

Language Deficits	**Variant PPA**
Agrammatism	Nonfluent/agrammatic variant PPA
Apraxia of speech	Nonfluent/agrammatic variant PPA
Impaired comprehension of syntactically complex sentences	Nonfluent/agrammatic variant PPA
Spared single-word comprehension	Nonfluent/agrammatic variant PPA, Logopenic variant PPA
Spared object knowledge	Nonfluent/agrammatic variant PPA, Logopenic variant PPA
Impaired confrontation naming	Semantic variant PPA
Impaired single-word comprehension	Semantic variant PPA
Impaired object knowledge, particularly for low frequency or low-familiarity items	Semantic variant PPA
Surface dyslexia	Semantic variant PPA
Surface dysgraphia	Semantic variant PPA
Spared repetition	Semantic variant PPA
Spared speech production (grammar and motor speech)	Semantic variant PPA, Logopenic variant PPA
Impaired single-word retrieval in spontaneous speech naming	Logopenic variant PPA
Impaired repetition of sentences and phrases	Logopenic variant PPA
Speech phonological errors in spontaneous speech and naming	Logopenic variant PPA

Table 1 [11]

Speech and language therapy in Primary Progressive Aphasia

As pharmacotherapy is not effective in treating the disease or arresting progressive deterioration, behavioral language interventions aim to improve the quality of life of patients. Speech therapy is a reasonable choice for the maintenance and optimization of the communication skills of patients with PPA. Speech therapists use individualized treatment protocols aimed at treating aphasia, depending on the sub-type of PPA.

Rehabilitation therapies target specific language symptoms and aim for maximizing functional communication. The most common and earliest symptom of aphasia is word finding difficulty. Consequently, word retrieval strategies are especially common in many treatment plans and naming visually presented objects and engaging in the phonological, graphemic and semantic analysis of words, enhances performance of PPA patients. However, the literature is not yet clear as to the extent of the benefits and their persistence over time following therapy.

Another important linguistic symptom of PPA, especially of the nonfluent agrammatic variant, is the defective motor programming of speech and agrammatism. Word retrieval therapies are not effective in improving verbal dysfunction and agrammatism. Regarding the treatment of these symptoms, speech therapists report low effectiveness of treatments for verbal and oral dyspraxia used in patients with aphasia following stroke. Finally, another therapeutic approach that aims to improve spontaneous speech in the everyday environment is the procedure of repeating verbatim s story told by the therapist. In this therapeutic approach, the patients are aided visually with cards that urge them to initiate speaking and aid them to develop the requisite verbal production skills.

In addition to the classical therapeutic interventions, however, in the context of patient rehabilitation, some compensatory techniques are used. These techniques aim to enhance the support that the patient receives from his environment as well as to reduce any communication deficits caused by the disease in social interactions. The Augmentative and Alternative Communication (AAC) approach is considered the basic compensatory technique for communication of aphasic patients. The goal of this approach varies from simply expanding the vocabulary to achieving full communicating with an alternative medium. The media used in this case vary from the simple use of pen-and-paper to that of communication boards and communication booklets as well as advanced technological means such as tablets and computers that convert images or text into speech.

Finally, the role of speech therapy in helping patients with PPA is not limited to behavioral therapy but also in educating and supporting patients and their care-givers. Numerous studies have been conducted on the value of group education programs for both patients and their families. The benefits reported are reduced emotional and social isolation as well as a reduction in patients' emotional distress following diagnosis. [20]

Particularly important is the optimization and upgrading of the role of speech therapy in the recovery of aphasic patients. This, however, depends on the following factors: . First, the proper informing of all health professionals about the role and benefits of speech therapy. Second, training speech therapists through programs specifically designed to deal with PPA. Third, there should be clear and evidence-based guidelines for the management and evaluation of PPA patients. Fourth, raising the awareness of the public and private insurance companies of the need to cover speech therapy treatments. [21]

Repetitive transcranial magnetic (rTMS) and its uses

Transcranial magnetic stimulation is a non-invasive brain stimulation method based on electro-physical principles discovered by Faraday. Its main purpose is to activate currents within neural networks through the application of a magnetic field that traverses the skull and reaches the brain. A TMS device is made of one or two coils, positioned over a specific area of the brain, which noninvasively produces brief (100 to 400 μs) magnetic pulses to an estimated depth of 2-2.5 cm from the scalp surface. TMS is a relatively safe non-invasive method to study the brain, and it is very useful for mapping of brain cortex activity. During the last years is used for treatment in several neurologic conditions, especially rehabilitation. The hypothesis is that, low-frequency repetitive stimulation prolonged synaptic depression.[22]

Transcranial Magnetic Stimulation has been used to study the cortical plasticity in the human cortex. TMS is thought to promote functional reorganization of the human cortex. There are three different ways of using TMS to explore that reorganization.

Change the pattern of connectivity. Changes occur on mapping of cortical areas or their spinal projections.

Function improvement. TMS can promote functional changes as a result of plastic reorganization in a specific cortical area.

Immediate change in cortical function. The use of Repetitive Transcranial Magnetic Stimulation (rTMS) has been correlated with a short-term functional reorganization which it depends on several parameters of stimulation, such as intensity, frequency, duration of stimulation, pulse trains, number of trains and inter train interval.

Those actions, make rTMS a useful in different neurological conditions as investigation tool and as a therapeutic tool in several psychiatric and neurological disorders. [23]

Physiological mechanisms modulated by TMS

For each of the purposes for which TMS stimulation techniques are used is associated with a different working hypothesis as to how its effects are mediated. Frequency is the main parameter that is thought to affect brain plasticity through long-term potentiation (LTP) and long-term depression (LTD). Results from numerous studies have shown us that, low frequency (LF) stimulation has an inhibitory effect, and high frequency (HF) stimulation has an excitatory function. [23] Several studies have tried to assess the inhibitory and excitatory action of TMS. The result is controversial. Many factors and parameters of stimulation are related with inhibitory and excitatory type of stimulation.

The physiological effects of TMS have been assessed in healthy subjects. The main process was motor evoked potential (MEP) changes in response to primary motor cortex (M1) stimulation. Therefore, the use of TMS in pathological conditions, outside motor cortical areas should be very cautious. [24] MEP measurements in healthy studies have shown as that rTMS stimulation with frequencies ≤1 HZ is considered as inhibitory and frequencies ≥5 Hz as excitatory. [23]However, both high frequency (HF) and low frequency (LF) rTMS stimulation may have mixed excitatory and inhibitory effects. [25] Thus, the evaluation of different studies in witch has been used different protocols of TMS with LF or HF TMS should be extremely cautiously interpreted. However, the use of TMS in multiple neurological conditions is rapidly expanding, and the results for rehabilitation are very promising. [26]

Numerous studies have shown that TMS has his own position in the field of rehabilitation. [27-30] Above all TMS is as a non-invasive stimulation, which may trigger neural plasticity. Many variables have to be taken into account for future studies in neurological disorders. [26] In the Primary Progressive Aphasia field there isn't a systematic review that assesses the efficacy for patients with Primary Progressive Aphasia. There are small studies with promising results that have showed significant results of improvement of patient suffering from PPA. [26]

Transcranial direct current stimulation and its uses.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation (NIVS) method that provokes electrical activity in brain cortex. It is painless and easy to use. TDCS first application was on animals but in the last few years tDCS is used as a modulation tool for the human brain. The main goal of that type of stimulation is to trigger neuroplasticity for therapeutic reasons in neuropsychiatric diseases.

The application of tDCS is by injecting low intensity electrical currents (typically 1-2 mA) via sponge electrodes attached to the scalp. The inhibitory or excitatory effect of the brain cortex correlates with the polarity of tDCS. More specifically, the anodal polarization induces excitation, and is called depolarization and the cathodal polarization induces inhibition and is called hyperpolarization. [31,32] Furthermore, tDCS is capable of modulating the resting membrane potentials of neurons in addition to TMS. [33]

tDCS also has a long-lasting after effect. This may be due to the fact that it modulates the resting membrane potential and the whole axons generally. [34] However it is essential for the therapeutic use of tDCS to consider the major influence that parameters of stimulation (such as intensity and duration) have on the results of therapeutic protocol. [32]

Regarding neurorehabilitation, there is another important effect of tDCS. This is the impact that tDCS has not only to neurons but on other types of tissues and cells, because these are also sensitive to electric fields.[35] Non-neuronal effect could be very promising for therapeutic uses in neuroinflammatory and neurodegenerative diseases (such as Multiple sclerosis and Alzheimer disease). More specifically, in Alzheimer disease, tDCS may have an impact on the course of the disease because of the changes in beta-amyloid and other pathological proteins that could occur when they are exposed to appropriate electric fields. [326] Furthermore another important factor for neurorehabilitation and functional recovery is that, current fields are correlated with axonal regeneration and neurite outgrowth. [37] Finally, beyond the neuronal excitability, tDCS could also cause changes in different pathological process in the central nervous system. [32]which makes tDCS a useful therapeutic tool for neurological conditions.

Over the years, several studies have indicated that tDCS is a potential therapeutic tool for neurodegenerative diseases. In the PPA there is not yet a systematic review to give guidelines for tDCS treatment for neurodegenerative aphasia.

In this review we try to gather useful information from studies and case reports, and also explain the lack of useful results, about neuromodulation on PPA patients.

NON INVASIVE BRAIN STIMULATION IN PPA

rTMS

A literature search (using pubmed) and the symbols PPA and rTMS as inclusion criteria, resulted in a group of five relevant studies. The first one, titled **"**A Case Study of Primary Progressive Aphasia: Improvement on Verbs After rTMS Treatment"[38] by Chiara Finocchiaro et al. (2007) used rTMS in order to examine the effectiveness of high-frequency stimulation in linguistic functions in one patient with PPA. For assessing the efficacy of stimulation the patient underwent an assessment of his linguistic and cognitive performance, before, during and after stimulation, with a specific time between sessions in order to avoid learning effects.

The linguistic-cognitive domains that were assessed were: Nouns, verbs and the memory span. The specific tasks were sentence completion for nouns and verbs and the memory span test with series of pseudo-words or numbers respectively. The patient was asked to repeat each sequence, as pronounced by the experimenter. The hypothesis was that the rTMS delivered to the targeted area should only affect the patient's performance on verb tasks—noun production was already at ceiling and memory should be unaffected by the treatment.

The procedure was the following: The patient underwent two separate sessions of experimental tasks before the beginning of the rTMS protocol, in order to avoid learning effects. Then, the experimental tasks were administered in six sessions after real rTMS: two sessions after sham rTMS and four sessions after the second real rTMS. The second author who tested the subject was blind to hypothesis. The experimental test battery was administered in each testing session, the first testing session of post real-rTMS and post sham-rTMS that was performed one or two days after treatment. The between session interval was 15 days.

The Inferior frontal gyrus on the left hemisphere was chosen as the target of stimulation. The reason for choosing this specific region was that the patient had a deficit for verb production and according to Shapiro et al. (2001) the inferior frontal gyrus is responsible for verb processing.

The following stimulation parameters were implemented: The intensity were at 90% of resting motor threshold (RMT) and for that patient specifically, it was 56% of the intensity of the device. The frequency was 20HZ (high frequency which has, presumably, an excitatory effect). The total number of trains was 10, each of them had 40 pulses and inter train interval was 30". The study designed for 5 consecutive days of stimulation. The order of stimulation treatments in that patient was as follows: real rTMS-sham rTMS- real rTMS. So they were 2 cycles with real

and 1 with sham rTMS. The time between each treatment cycle was 15 days. Finally, a sham condition stimulation was included in that protocol too. The parametres were the same that they used in real TMS, however the coil was angled 90°.

The authors reported a statistical improvement on performance of only the task involving verbs. That improvement was observed after the 2 real-TMS stimulations sessions. There was no difference on nouns and memory span tasks. The fact that there were not improvement on memory tasks and also the fact that there were no difference between baseline and sham-TMS condition treatment, suggests that the TMS effect was specific to verbs. However, the lack of functional MRI can't support the belief that that specific area had modulated. Another factor that strengthens the hypothesis of TMS effectiveness is the fact that there can't be improvement in neurodegenerative aphasias without any kind of intervention. However, Several factors cast doubt in the effectiveness of rTMS in this case study: first the fact that it is unclear if the improvement was sustained for long time. Small, spontaneous, and reversible variations in performance (including improvements) are known to occur in this condition. Therefore, the improvement noted could very well be independent of rTMS. The rationale of the study is suspect: the IFG is not a verb-specific mechanism, and the fact that someone says so it does not make so.

The second study (M.Cotelli et al.,2012) was titled "Prefrontal cortex rTMS enhances action naming in progressive non-fluent aphasia"[39]. It was aimed at assessing the efficacy of rTMS on dorsolateral prefrontal cortex of left and right hemisphere of people with non fluent agrammatic variant of PPA. Ten patients with non-fluent agrammatic variant of PPA were participate in it. They are also enrolled four patient with semantic dementia as a comparison group. All the patient assessed on cognitive skills and aphasia severity. Secondly, patients with nfvPPA separated to three groups. First group was stimulated on left hemisphere, the second on right hemisphere and the third group was the placebo stimulation group. The design was the follow: All three groups were exposed to 84 pictures, (42 actions, 42 objects). Patients had to name, as rapidly as they could as each of them was shown on the monitor. During that procedure a 500ms stimulation was applied at the onset of each picture. The answers were recorded, and the results were evaluated after that procedure.

In this study the targets chosen for rTMS were the dorsolateral prefrontal cortex of both right and left hemisphere. The pulse intensity was at 90% of Resting Motor Threshold (RMT) of each patient, the frequency was set at 20Hz and was delivered for 500ms from the onset of visual stimulus. The modulation was assumed to be excitatory. A sham stimulation condition was added using a 3cm thick piece of plywood was placed between the coil and the head so there wasn't any magnetic field reaching the cortex.

The results showed that action-naming performance during stimulation of the left and the right DLPFC was better than in the placebo stimulation but thepatients did not display anypost-stimulation effect. This study is rather problematic for the following reasons: No evidence was provided that the stimulation was indeed excitatory or that the DLPFC was in anyway modulated**.** The plywood used in the sham condition made it obvious that the sham trial did not involve stimulation, which vitiates the condition as one of placebo. It is possible that rTMS stimulation on the DLPFC improved the performance of action naming of nfvPPA patients. That is very important for the possibility of an effective intervention in neurorehabilitation of PPA. However, that study examined the naming performance during the neuromodulation. So we can't be sure if the results remained, and if so, for how long, and what was the impact of that intervention, if any, in daily life of patients. Also, the fact that there was stimulation of both the left and the right DLPFC and it was effective, raises some questions regarding the form of functional reorganization of the brain of PPA patients.

Trebbastoni et al. (2013) conducted this, third, study to be reviewed, titled "Repetitive Deep Transcranial Magnetic Stimulation Improves Verbal Fluency and Written Language in a Patient with Primary Progressive Aphasia-Logopenic Variant (LPPA)"[40], with the purpose of examining the efficacy of high-frequency rTMS stimulation, in a lvPPA patient, in improving the patient's cognitive and language functions.

Patient assessment took place six hours before the first session of each cycle, and 24 hours after last session of each cycle. Furthermore an evaluation performed 7 days after a cycle of session completed. Cognitive and linguistic domains (verbal and writing) were evaluated in each assessment. Specific, frontal functions, visuo-spatial functions and verbal fluency are assessed with a neuropsychological battery, phonemic verbal fluency was evaluated with Phonemic Verbal Fluency test (PLF test). A "creative writing" task (the patient had to write an episode of his own life) was used by the authors to estimated the patient's written language skills. The patient was not submitted to speech therapy.

Four cycles of intervention (two real rTMS and two sham rTMS) were performed in a 69 days protocol. Each cycle consisted by 5 consecutive sessions. The time interval between each cycle was 14 days. Cycles of intervention were performed alternately. The targeted region was approximately the middle (MFG) and inferior (IFG) frontal gyrus over the Broca's areas 44 Brodmann's area (BA) 44 and 45 respectively and it was stimulated Intensity was at 100% of resting motor threshold (RMT) of the patient, the frequency was set at 20Hz, the total number of pulses was 1500 and the duration of stimulation was 20 minutes**.**

The authors reported a highly significant but temporary improvement in phonemic verbal fluency, and a high reduction in grammatic and semantic errors in writing speech. Those results

were obtained only in the real rTMS condition. Improvement was eliminated 7 days after each intervention. The reported significant improvement of phonemic verbal fluency in lvPPA, suggest the efficacy of high-frequency excitatory rTMS to the MFG and IFG of the left hemisphere. The temporary effect of those results further suggests that there should be follow-up research.

A more recent study titled “Left Prefrontal Repetitive Transcranial Magnetic Stimulation in a Logopenic Variant of Primary Progressive Aphasia: A Case Report” [41](Matthieu Bereau et al., 2016) purported to investigate the effectiveness of rTMS in a logopenic aphasia patient and the persistence of these effects. Behavioral assessment of the patient took place at baseline, on month after treatment and three months after last session. The patient was evaluated on linguistic skills. Assessment consisted by oral language evaluation (Sentences comprehension assessment, Picture naming test (PNT80) word, non-word and sentence repetition and phonological and categorical fluency tests) , and cognitive functions (speed of processing and executive functions, verbal and visual memory). Patient submitted also to a SPECT examination. Regarding to linguistic skills, anomia, word finding difficulties, phonemic and semantic paraphasias and sentences comprehension were the main deficits of the patient. Patient did not submitted to a speech therapy.

The left dorsolateral prefrontal cortex (DLPC). of the patient was stimulated with the intensity set at 100% of RMT of the patient and the frequency at 10Hz. The patient was treated for 10 sessions over a week (two sessions per day) witheach session lasting 20 minutes . The duration of the pulse train was 5 sec and the inter train interval 25sec.

According to the authors, the patient showed a significant improvement in speed of processing in the Picture naming test. Also, three months after the last session, verbal fluency and paraphasias reduction still observed. However, We can not be sure about the stimulation effect because the patient was assessed using the same materials so maybe the improvements were due to learning. Also, there wasn’t an assessment immediately after the protocol, so we are not in a position to know the reduction of the improvement over time.

The final study of this set by Seth A. Margolis et al.(2019), titled “A pilot study of repetitive transcranial magnetic stimulation in primary progressive aphasia” [42] was conducted to examine the efficacy of stimulation with rTMS of the left dorsolateral prefrontal cortex or over the corresponding region on the right hemisphere. The six male patients who participated in that study had mild to moderate dementia. They submitted in an evaluation in baseline before any stimulation about cognitive skills (MOCA) and letter fluency (and 10 minutes post every session). Then subjects submitted to modulation with a sham followed by a real rTMS session. The tms condition was blind for the subjects but not for the examinators. Each participant

stimulated on both hemisphere. Also, during rTMS stimulation online task took place and the participants had to perform some linguistic tasks. More specifically, the tasks were the following: Action naming, object naming, stroop word reading, stroop ink naming. Those task evaluated for the comparison of real and sham rTMS stimulation.

The rTMS intensity was at 90% of resting motor threshold of each subject. Number of trains was 84, number of pulses in train was 20 and the inter train interval was 6,5 to 7,5 seconds. Neuromodulation was excitatory with a high frequency of 20Hz. There was also sham stimulation with the same parameters but with a specific sham coil. Total sessions were two. Each sessions was sham followed by a real stimulation.

According to the authors, significant improvement in action naming and general post session gains in global cognition led to the conclusion that left DPC rTMS stimulation may be more beneficial than right. The duration of the protocol and the total number of sessions are not sufficient to allow drawing of a proper conclusion about the effects of left DPC rTMS in patients with PPA. Such a conclusion would have important theoretical implications regarding the mechanism of improvement through rTMS. If, in fact stimulation of the language-dominant DPC is effective it would mean that rTMS enhances the function of the language -specific networks. If the opposite were the case, it would indicate that rTMS enhances reorganization of language in the non-dominant hemisphere.

These five studies raise several methodological questions. First, the application of rTMS does not take into account the lateral language dominance of each patient making it impossible to know why rTMS has the effects it does. The reasons provided for the choice of rTMS stimulation target are not coherent, nor is there a clear explanation as to whether the stimulation has excitatory or inhibitory effects, applied as it usually does, close to the premotor cortex, given that stimulation in motor regions is excitatory.

Authors	Publication Year	Country	N	Stimulation Parameters	Stimulation Target	Sham	Outcomes	Comment
Chiara Finocchiaro et al	2007	Italy	1	HF 20Hz, 90% of RMT	Left IFG	Yes	statistical improvement on performance of only the task involving verbs	The improvement noted could very well be independent of rTMS
M.Cotelli et al	2012	Italy	14	HF 20Hz, 90% of RMT	Left and Right DLPFC	Yes	Action-naming performance during stimulation of left and right DLPFC was better than the placebo stimulation	the fact that there was stimulation of both the left and the right DLPFC and it was effective raises some questions regarding the form of functional reorganization of the brain of PPA patients

Trebbastoni et al	2013	Italy	1	HF 20Hz,100% of RMT	Proximity of MFG and IFG	Yes	Highly but temporary significant improvement in phonemic verbal fluency, and a high reduction in grammatic and semantic errors in writing speech	Significant improvement of phonemic verbal fluency in lvPPA, suggest the efficacy of high-frequency excitatory rTMS to the MFG and IFG of the left hemisphere
Matthieu Bereau et al	2016	France	1	Hf 20Hz, 100% of RMT	Left DLPFC	No	Significant improvement in speed of processing in the Picture naming test	We are not sure about the stimulation effect because the patient was assessed by the same materials so maybe the improvements were due to learning

Seth A. Margolis et al	2019	USA	6	HF 20HZ, 90% of RMT	Left or Right DLPFC	Yes	Significant improvement in action naming	The duration of the protocol and the total number of sessions are insufficient to allow drawing of a proper about the effects of left DPFC rTMS in patients with PPA.

Table 2 : rTMS studies

tDCS

A literature search (using pubmed) and the symbols PPA and tDCS as inclusion criteria, resulted in a group of five relevant studies. The firsts study was titled "Effects of transcranial direct current stimulation on language improvement and cortical activation in nonfluent variant primary progressive aphasia"[43] by Wang et al, 2013. In it ,tDCS was used in order to examine the efficacy of transcranial direct current stimulation on improving linguistic skills of a nonfluent agrammatic patient (variant of PPA) as well as the cortical activation.

The treatment protocol consisted of two cycles of sessions. Each cycle consisted of 10 sessions of sham tDCS (2 daily sessions over 5 days) followed by 10 sessions of anodal tDCS (2 daily sessions over 5 days). The current was delivered over left Wernicke's area in the morning and left Broca's area in the afternoon. A constant anodal current of 1.2mA was applied and the duration of treatment was 20 minutes. There was sham stimulation too. The sham stimulation was delivered with the same parameters except that in the sham condition the current was turned off after 30".

Two specific areas of the left hemisphere were stimulated in that protocol. A) posterior temporal region (known as a Wernicke's area) and frontotemporal region (Broca's area). The cathodal electrode was applied on the shoulder.

The experimental tasks that the subject was submitted were some subtests of psycholinguistic assessment from a Chinese aphasia test. The subtests were given with the following order: picture naming, auditory word identification, oral world reading and word repetition. The behavioral assessment was given before and after each treatment phase. Also an EEG recording was made in the beginning of protocol and after the two phases of real tDCS in order to measure changes in electrical brain activity. EEG recording occur in two conditions: a) eyes closed for about 5 minutes b) eyes closed during a three-syllable word repetition task.

According to the authors, there were significant improvement in the four subtests after first the treatment of anodal tDCS. The EEG results are difficult to evaluate because there was not straight clinical EEG interpretation bur a statistically derived measure the clinical value of which does not appear to have been established.

The tDCS was reported to have a positive effect in the specific patient but it is not certain if that was the result of stimulation of Broca's or Wernicke's area or of both. Moreover, there was no follow-up to determine whether the effect was long-lasting except for the report of the care

giver to the effect that the symptoms of the patient deteriorated. But the initial improvement suggests that repetition of the intervention might have had more permanent effects.

An interesting study, the second one by Cotelli et al 2013, titled "Treatment of Primary Progressive Aphasias by Transcranial Direct Current Stimulation Combined with Language Training"[44] tried to examine the efficacy of tDCS combined with speech therapy in non-fluent agrammatic variant of PPA patients.

Sixteen navPPA patients participated in the protocol. The patients were separated into two groups of 8: the real stimulation and the placebo group. Both groups were submitted to tDCS (real or sham) and received individual speech therapy with individualized computerized anomia training (ICAT) at the same time. An assessment took place at baseline, and two and twelve weeks after the end of the protocol. Total sessions were 10. (5 sessions per week for two weeks)

Anodal current of 2mA was given to the patients for a total duration of 25 minutes. There was sham stimulation too. In the sham stimulation the current was turned off 10 seconds after the beginning of the protocol and turned on again during the last 10 seconds, so patients had itching sensation under the electrodes. The target of stimulation was the left dorsolateral prefrontal cortex. The reference electrode was placed on the right arm.

Two specialists who were blinded to the stimulation condition, administrated the assessment in two sessions. Linguistic tasks were evaluated by the Aachener Aphasia test. (AAT). Communication and functional skills were tested using the stroke and aphasia quality of life scale (SAQOL-39). Moreover, they used the speech questionnaire and the communication assessment scale. The individual language therapy that patients were submitted included two lists of objects images. First was the evaluation list of objects and the second the therapy list of objects, which contained items for treatment. The accuracy of naming was tested at the end of the protocol and during follow up visits. The results showed that both groups experienced significant improvement in naming accuracy. However, the real tDCS group was significantly more improved than the sham stimulation-group.

These positive results in both patient groups support the notion that speech therapy alone is effective in agrammatic PPA. But the fact the stimulation resulted in greater improvement shows that the combination of the two therapeutic approaches is preferable. Even more encouraging was the fact that the improvements persisted for three months after the termination of the interventions and indicates that, likely, speech therapy may be responsible for the persistence of the effects since such persistence is normally absent in studies that do not use speech therapy in parallel with neurostimulation. Needless to say, the combined effectiveness of the two procedures should be explored in additional larger studies.

The third study that was reviewed was titled “Transcranial direct current stimulation for the treatment of primary progressive aphasia: An open-label pilot study” [45] by Gervits et,al., (2016). Its purpose was to examine the efficacy of tDCS in PPA patients.

Six patients participated in that protocol. Four had logopenic variant of PPA and the rest two had non-fluent variant of PPA Subjects were submitted to tDCS stimulation for 10 days, one session per day. Patients also were assessed at baseline, two, six and twelve weeks after the end of the protocol. During the stimulation each patient had to narrate a story from a wordless children book. A different book was used in every session.

Anodal current of 1.5mA was used for 20 minutes per session for total 10 sessions. There was not sham stimulation. The anode electrode was placed over the left fronto-temporal region(F7) of the brain and the cathode was placed over the left occipito-parietal region. (O1).

Regarding experimental tasks, the following cognitive and linguistic domains were included in the evaluation assessment. Speech production (Cookie theft task), Grammatical comprehension (L-TROG accuracy), Repetition (Sentences repetition) and Semantic processing. (Boston naming test, Pyramids and palm trees test, Category naming fluency). According to the authors there was significant improvement of speech production and grammatical comprehension that was maintained after 3 months.

The absence of sham condition and the fact that in the all-important spontaneous speech production was evaluated by the cookie theft test, raises the possibility that the persistence of the effect might have been due to learning effect. Nevertheless, this study also supports the hypothesis that neurostimulation does improve performance at least initially.

The following studies have many similarities. Tsapkini et al., (2014) and Tsapkini et al., (2018) conducted those studies with the following titles “Augmentation of spelling therapy with transcranial direct current stimulation in primary progressive aphasia: Preliminary results and challenges.”[46] and “Electrical brain stimulation in different variants of primary progressive aphasia: A randomized clinical trial”[47] respectively. The sixth study, which also is part of that specific group of studies by Fenner et al., (2019) was titled “Written Verb Naming Improves After tDCS Over the Left IFG in Primary Progressive Aphasia”[48]. The purpose of the above studies was to examine the efficacy of tDCS combined with a therapy for written language in PPA patients.

The target group was patients with PPA. More specifically, in Tsapkini et al. (2014) participated 6 patients with mixed nonfluent variant of PPA and logopenic variant of PPA; in Tsapkini et al. (2018) 36 patients(14 nfv PPA, 12 lvPPA, 10 svPPA) and in Amberlyn et al. (2019) 11 patients were enrolled. Moreover the design was the same because those studies were conducted by the same group of investigators. The design structure was the following. Firstly,

participants were submitted to a cycle of stimulation (real or sham), then there was a 2 month pause, and then they were submitted to the cycle of the other treatment condition. Each cycle consisted of 15 sessions (5 sessions per week for 3 weeks). Evaluation of the subjects occurred at baseline, immediately after and 2 weeks and two months after each treatment cycle. During the intervention, participants were submitted to spelling intervention.

The current used was anodal, 2mA in intensity. The duration of each session was 20 minutes, and there was sham stimulation too. A language intervention took place in each study. The point of stimulation was the left Inferior frontal gyrus, (IFG). The cathodal electrode was placed over the right cheek of each participant.

For experimental tasks fin Tsapkini et al., (2014), and Tsapkini et al., (2018) there were 2 lists of items: "trained" and "untrained". The trained list consisted of items that were practiced in each session. The untrained list consisted of items that were used for evaluation. The key measure was the accuracy in the trained and untrained items performance. In Fenner et al. (2019) an action picture was shown to participants, and they were asked to name it orally and to write it. If the patient could not name the verb orally or in writing), they were provided with the correct verb and then asked to write it in a spell-study-spell procedure.

The results of the Tsapkini et al. (2014) study showed improvement in written spelling that was maintained after two months; in the Tsapkini et al. (2018) study there were improvement in written spelling for both trained and untrained items, that were maintained for 2 months for nonfluent and logopenic variant of PPA patients No effect was found for semantic variant of PPA patients. In the. Fenner et al. (2019) study, the real stimulation condition showed significant results in the trained items. For untrained items written naming improved significantly more in tDCS than in the sham condition immediately after treatment. The two months tDCS profit was not significantly different between periods 1 and 2.

The above studies demonstrated that the effectiveness of combined speech therapy and neurostimulation in logopenic and agrammatic aphasia is clear but temporary . It is important to note the difference in the studies of Tsapkini et al. (2014) and the Amberlyn et al. (2019) study, in connection with the learned stimuli. In the former study there was no difference between true and sham stimulation but in the second there was a difference that indicates the volatility of the results. On the other hand in all three studies, it is important to note that combined behavioral and physiological intervention appears to result in more long lasting effects.

The second small group of studies tried to examine the efficacy of tDCS combined with an anomia treatment in logopenic variant of PPA patients. Studies number seven, eight and nine were titled "Inferior parietal transcranial direct current stimulation with training improves cognition in anomic Alzheimer's disease and frontotemporal dementia"[49] by Roncero et al.

(2017); “Semantic Feature Training in Combination with Transcranial Direct Current Stimulation (tDCS) for Progressive Anomia.”[50] By Hung et al. (2017) and “Maximizing the Treatment Benefit of tDCS in Neurodegenerative Anomia”[51] by Roncero et al. (2019).

Ten patients participated in the protocol of Roncero et al. (2017). Five participants were given 10 sessions of anodal stimulation and 10 sessions of stimulation 2 months later. The other five were administrated the reverse procedure. They were first given 10 sham stimulation sessions and 10 real stimulations sessions after two months. All participants were blind to the condition.

Also, in the Roncero et al., (2019) study 12 patients with PPA mixed (nfvPPA lvPPA and sv of PPA) participated in the protocol. The protocol included three cycles of stimulation (parietal-temporal, DLPFC and sham). Each cycle consisted of an evaluation followed by 10 sessions of stimulation in a period of 3 weeks. As in the previous study of Roncero et al. (2017), subjects were administrated lists of items in order to name it. The evaluations occurred at baseline, 2 weeks and 2 months after each cycle treatment. Last in the Hung et al. (2017) study five participants with lvPPA and svPPA participated in the protocol. The treatments consisted of ten days of tDCS stimulation combined with behavioral therapy for two weeks. Participants were evaluated pre and post treatment (immediately after, 2 weeks and 6 months later). During the stimulation (which was 30minutes in duration) semantic feature analysis was administrated to the patients in order to treat anomia.

Anodal current of 2mA Roncero et al. (2017) and Roncero et al. (2019), and of 1,5mA Hunget al. (2017) was delivered to the participants for a 20 minutes duration. The duration of tDCS sessions was 30 minutes each for Roncero 2017 and Roncero 2019. There was sham stimulation too. For both sham and real stimulation participants felt a prickling sensation. The target of stimulation was the left Inferior pariental lobe (Roncero 2017) due to the presumed connection to semantic processes. The additional electrode was placed at right the orbitofrontal area. For roncero et al., 2019 the targets of stimulation were the left inferior parietotemporal region (P3) and the reference electrode was placed over at right orbitofrontal region or the left dorsolateral prefrontal cortex(F3) with the cathodal electrode was placed over the right deltoid muscle. For Hung et al., 2017 the target of stimulation was the temporoparietal region and the cathodal electrode was placed over the forehead.

Experimental tasks that were used in those studies were the following. Roncero et al**. (**2017)**:** For the naming task there were 3 lists of 60 images from the Snodgrass and Vanderward image test that they were matched for familiarity and frequency. In each round of stimulation, one list of items would be used for daily training session, whereas another naming list was left untrained. In the first round of the experiment, naming list 1 of items was trained and naming list 2 was left

untrained, whereas for round 3, naming list 2 was trained and naming list 3 was left untrained. This allowed authors to assess changes in naming pre- and post-tDCS, for both "trained" and "untrained" picture items. Similar procedures were also used in Roncero et al. (2019).

Moreover, in that study, authors evaluated cognition when DLPFC was stimulated. In the Hung et al. (2017) study**,** semantic feature analysis was the anomia treatment that was combined with tDCS. 21 items were given to the subjects each day and repeated twice through the 10 sessions. There was also a list with untrained items that was used in each evaluation period.

According to the authors (Roncero et al., 2017) there was improvement in picture naming for trained items and a less significant improvement for untrained items lasting at least for 2 weeks. And in the Roncero et al. (2019) study there was improvement in picture naming for trained items after both types of stimulation (DLPFC and Left inferior parientotemporal stimulation) This result lasted 2 weeks only for the parietotemporal stimulation; for untrained items the improvement lasted 2 weeks. Hung et al. (2017) showed that an improvement in the semantic features tasks for trained items only. Two conclusions seem to follow from the above studies: first that temporoparietal stimulation may also result in improvement as does frontal stimulation in logopenic aphasia patients and second that the behavioral training may consolidate the gains from the neurostimulation in this specific language domain. The final study in this set was conducted by Teichmann et al. (2016) titled "Direct current stimulation over the anterior temporal areas boosts semantic processing in primary progressive aphasia"[52]. Its purpose was to examine the effectiveness of tDCS treatment in patients with semantic variant of PPA. Twelve semantic variant of PPA participated to that study which employed a double blind sham-controlled crossover design. There were three conditions. Anodal current (excitatory stimulation), cathodal current (inhibitory stimulation) and sham stimulation.

The order of those conditions were counterbalanced and separated by one week. The task that was used in the protocol was a semantic matching task. That test was. split into two lists for pre and post-performance. Moreover, there was a linguistic evaluation which consisted in a test for aphasia severity (Boston Diagnostic Aphasia Evaluation 28), a picture naming test (D080 43), a single-word comprehension (Boston Diagnostic Aphasia Evaluation), a verbal fluency, a sentence repetition (Boston Diagnostic Aphasia Evaluation) and a semantic matching task in a visual and a verbal version (Pyramids and Palm Trees Test). Also, the cognitive assessment included the Mini-Mental State Examination and the Frontal Assessment Battery.

An anodal or cathodal current of maximum 1.59mA was given to the subjects. There was sham stimulation too, in which the electrodes were placed in the same place as anodal stimulation, and the current was changed up and down for 30 seconds at the beginning and ending of stimulation, so patients had the same itching sensation as in real stimulation condition.

The duration of each condition was 20 minutes. Two targets of stimulation were involved in that study: the Left and right temporal lobe. The reference electrode was placed over the contralateral supra-orbital region.

The positive result in that study was the improvement in the semantic task immediately after the stimulation treatment in both the excitatory and the inhibitory condition. Also, inhibitory tDCS improved processing speed. There were six conditions in this study. (two stimulation sites and tree stimulation conditions—anodal, cathodal and sham. Moreover, there was a variety of dependent measures. By mere chance alone one would expect that some measures under some conditions would show some significant effects. In a situation like this it is very difficult to interpret the reported improvement especially the interesting result that improvement occurred by excitatory stimulation of the left and inhibitory stimulation of the right temporal lobe.

Authors	Publication Year	Country	N	Stimulation Parameters	Stimulation Target	Sham	Outcomes	Comment
Jie Wang et al	2013	China	1	Anodal, 1.2mA	PTR and Broca's area	Yes	Significant improvement in four subtests after first treatment of anodal tDCS	tDCS was reported to have a positive effect in the specific patient but it is not certain if that was the result of stimulation of Broca's or Wernicke's are or of both
Maria cotelli et al	2013	Italy	16	Anodal, 2mA	Left DLPFC	Yes	Both groups showed significant improvement in naming accuracy, however the real tDCS group was significantly more improved than the sham stimulation-group	The fact the stimulation resulted in greater improvement shows that the combination of the two therapeutic(tDCS and SLT) approaches is preferable

Felix Gervits et,al	2016	USA	6	Anodal, 1.5mA	Left FTR	Yes	Significant improvement of speech production and grammatical comprehension that was maintained after 3 months	This study also supports the hypothesis that neurostimulation does improve performance at least initially
Kyrana Tsapkini et al	2014	USA	6	Anodal, 2mA	Left IFG	Yes	There were improvement in written spelling that was maintained after two months	effectiveness of combined speech therapy and neurostimulation in logopenic and agrammatic aphasia is clear but temporary

Kyrana Tsapkini et al	2018	USA	36	Anodal, 2mA	Left IFG	Yes	There were improvement in written spelling for both trained and untrained items, that were maintained for 2 months for nf and lv PPA. No effect was found for sv PPA patients	effectiveness of combined speech therapy and neurostimulation in logopenic and agrammatic aphasia is clear but temporary
Amberly n S. Fenner et al	2019	USA	11	Anodal, 2mA	Left IFG	Yes	The real stimulation condition showed significant results in the trained items	effectiveness of combined speech therapy and neurostimulation in logopenic and agrammatic aphasia is clear but temporary

Carlos Roncero et al	2017	Canada	10	Anodal, 2mA	Left IPL	Yes	Improvement in picture naming for trained items and a less significant improvement for untrained items lasting at least for 2 weeks	behavioral may consolidate the gains from the neurostimulation in this specific language domain
Jinyi Hung et al	2017	USA	5	Anodal, 1.5mA	Left temporoparietal region	Yes	Improvement in semantic features tasks for trained items only	Temporo-parietal stimulation may also result in improvement as does frontal stimulation
Carlos Roncero et al	2019	Canada	12	Anodal, 2mA	Left IPTL	Yes	Improvement in picture naming for trained items after both types of stimulation	behavioral may consolidate the gains from the neurostimulation in this specific language domain

Marc Teichmann et al	2016	France	12	Anodal and Cathodal, 2mA	Left and Rifgt Temporal lobe	Yes	Improvement in the semantic task immediately after the stimulation treatment in both excitatory and inhibitory condition	there were six conditions in this study. In a situation like this it is very difficult to interpret the reported improvement

Table 3: tDCS studies

DISCUSSION

The aim of this literature review was to highlight the effectiveness of neurostimulation in individual patients or in groups, with progressive aphasia, alone or in conjunction with speech therapy. The effectiveness of the rTMS and tDCS neurostimulation techniques was suggested by measurable benefits to patients' language symptoms in the stimulation, as compared to sham stimulation conditions.

Regarding the rTMS technique, it appeared that stimulation of the left hemisphere, targeting areas related to speech production appeared to have a positive effect in improving symptoms in individual linguistic capacities, such as improving verb production, reducing agrammatism and improving performance in naming and semantic tasks.

In addition, neuronal stimulation with electrical transcranial stimulation, with 1.5-2mA aniodal currents and targeting and nodal areas of speech networks in the left hemisphere, improved linguistic performance of aphasic patients in both oral and written speech production, verbal recall and the semantic word tasks. In addition, the effectiveness of tDCS in most studies reviewed, was enhanced by simultaneous speech therapy intervention.

In view of the lack of effectiveness of pharmacotherapy, the measurable positive results obtained in the studies reviewed are a promising as possible therapeutic modalities. The neurostimulation techniques that have been adopted in the field of neurorehabilitation, in recent years, seem to have their place in the treatment of PPA symptoms especially as adjunct to behavioral language therapies.

The neuromodulation of the cortex in PPA patients seems to result in reversible improvements in their linguistic skills. However, there are some factors that should make us cautious in evaluating these results. First, the number of rTMS studies that report positive results is very small and it is not known how many studies were performed that did not have positive results and they were not published.

Second, all studies involved excitatory stimulation (high frequency pulses) especially in the left hemisphere but there is an absence of studies of inhibitory, low frequency stimulation in the opposite hemisphere, where several studies have shown positive results on aphasics with left hemisphere stroke.

Third, many of the studies reviewed did not include in their protocol speech therapy which might have helped in consolidating the improvements over long time periods.

Finally, the lack of a standard instrument of assessing the severity of the neurodegeneration and the quality of life of the patients following interventions makes impossible to ascertain that

patients are actually helped not only in their language and cognitive skills but also in their daily lives, which is, after all, the goal of therapeutic interventions.

From the above it is concluded that what is needed is the design and execution of large scale studies which will take into account a) the reorganization of the language circuits, as it is known to occur in vascular aphasias, b) the use of a diagnostic instrument that will measure objectively linguistic performance but also account for progressive deterioration which is the hall-mark of the disorder, c) simultaneous use of speech therapy and d) assessment of quality of life and functionality of the patients in their natural environment. All these are required before deciding whether or not rTMS is an effective therapeutic approach that delays the rate of deterioration of linguistic performance in PPA.

Electrical stimulation (tDCS) appears to have some positive effects and is well tolerated by the patients. These improvements are statistically significant and involve specific aspects of linguistic performance. Moreover, there are indications that simultaneous speech therapy may consolidate the patients gains. This last feature differentiates them from rTMS were the absence of speech therapy was conspicuous. But in these studies, also, it is unclear first, if the statistically significant results are an artifact since from a variety of dependent variables used in the evaluation of the effectiveness of intervention only some showed significance and since the number of reported studies is most likely, once again, a subset of studies conducted with negative results. Moreover, as in the case of rTMS studies it is not clear if the reported statistically significant improvement is also clinically significant in terms of the quality of life of the patients.

A general observation for both types of stimulation, magnetic and electrical, is that the small number of studies, the small samples used, the small number of investigations that account for most of the reported studies and the reduction in the number of such publications following a period of growth in that number, are factors that we should take into account seriously before drawing any definite conclusions about the utility of neurostimulation in PPA.

REFERENCES

1. Mesulam MM. Primary Progressive Aphasia and the Left Hemisphere Language Network. *Dementia and Neurocognitive Disorders*. 2016;15(4):93. doi:10.12779/dnd.2016.15.4.93
2. Josephs KA, Duffy JR, Strand EA, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain*. 2006;129(6):1385-1398. doi:10.1093/brain/awl078
3. Hodges JR, Davies RR, Xuereb JH, et al. Clinicopathological correlates in frontotemporal dementia. *Ann Neurol*. 2004;56(3):399-406. doi:10.1002/ana.20203
4. Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. *Brain*. 2005;128(Pt 9):1996-2005. doi:10.1093/brain/awh598
5. Mesulam MM, Grossman M, Hillis A, Kertesz A, Weintraub S. The core and halo of primary progressive aphasia and semantic dementia. *Ann Neurol*. 2003;54 Suppl 5:S11-4. doi:10.1002/ana.10569
6. Forman MS, Farmer J, Johnson JK, et al. Frontotemporal dementia: Clinicopathological correlations. *Annals of Neurology*. 2006;59(6):952-962. doi:10.1002/ana.20873
7. Knibb JA, Xuereb JH, Patterson K, Hodges JR. Clinical and pathological characterization of progressive aphasia. *Ann Neurol*. 2006;59(1):156-165. doi:10.1002/ana.20700
8. Mesulam M, Wicklund A, Johnson N, et al. Alzheimer and frontotemporal pathology in subsets of primary progressive aphasia. *Annals of Neurology*. 2008;63(6):709-719. doi:10.1002/ana.21388
9. Nestor PJ, Balan K, Cheow HK, et al. Nuclear imaging can predict pathologic diagnosis in progressive nonfluent aphasia. *Neurology*. 2007;68(3):238-239. doi:10.1212/01.wnl.0000251309.54320.9f
10. Mesulam MM. Primary progressive aphasia. *Ann Neurol*. 2001;49(4):425-432.
11. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. *Classification of Primary Progressive Aphasia and Its Variants*.; 2011. www.neurology.org.
12. Luisa Gorno-Tempini M, Dronkers NF, Rankin KP, et al. *Cognition and Anatomy in Three Variants of Primary Progressive Aphasia*.
13. Chateau D, Jared D. Exposure to print and word recognition processes. *Memory and Cognition*. 2000;28(1):143-153. doi:10.3758/BF03211582

14. Lowder MW, Gordon PC. Print exposure modulates the effects of repetition priming during sentence reading. *Psychonomic Bulletin and Review*. 2017;24(6):1935-1942. doi:10.3758/s13423-017-1248-1
15. Peristeri E, Messinis L, Kosmidis MH, et al. The Impact of Primary Progressive Aphasia on Picture Naming and General Language Ability. *Cognitive and Behavioral Neurology*. 2021;34(3):188-199. doi:10.1097/WNN.0000000000000275
16. Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RS, Hodges JR. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. *Ann Neurol*. 2000;47(1):36-45.
17. Mesulam M, Wieneke C, Rogalski E, Cobia D, Thompson C, Weintraub S. Quantitative template for subtyping primary progressive aphasia. *Archives of Neurology*. 2009;66(12):1545-1551. doi:10.1001/archneurol.2009.288
18. Galton CJ, Patterson K, Graham K, et al. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology*. 2001;57(2):216-225. doi:10.1212/wnl.57.2.216
19. Rosen HJ, Kramer JH, Gorno-Tempini ML, Schuff N, Weiner M, Miller BL. Patterns of cerebral atrophy in primary progressive aphasia. *Am J Geriatr Psychiatry*. 10(1):89-97.
20. Taylor-Rubin C, Croot K, Nickels L. Speech and language therapy in primary progressive aphasia: a critical review of current practice. *Expert Review of Neurotherapeutics*. 2021;21(4):419-430. doi:10.1080/14737175.2021.1897253
21. Girirajan S, Campbell C, Eichler E. 乳鼠心肌提取 HHS Public Access. *Physiol Behav*. 2011;176(5):139-148. doi:10.1136/practneurol-2018-001921.Speech
22. Iglesias AH. Transcranial Magnetic Stimulation as Treatment in Multiple Neurologic Conditions. *Current Neurology and Neuroscience Reports*. 2020;20(1). doi:10.1007/s11910-020-1021-0
23. Siebner HR, Rothwell J. Transcranial magnetic stimulation: New insights into representational cortical plasticity. *Experimental Brain Research*. 2003;148(1):1-16. doi:10.1007/s00221-002-1234-2
24. Pascual-Leone A, Cohen LG, Shotland LI, et al. No evidence of hearing loss in humans due to transcranial magnetic stimulation. *Neurology*. 1992;42(3 Pt 1):647-651. doi:10.1212/wnl.42.3.647
25. Houdayer E, Degardin A, Cassim F, Bocquillon P, Derambure P, Devanne H. The effects of low- and high-frequency repetitive TMS on the input/output properties of the human corticospinal pathway. *Exp Brain Res*. 2008;187(2):207-217. doi:10.1007/s00221-008-1294-z

26. Iglesias AH. Transcranial Magnetic Stimulation as Treatment in Multiple Neurologic Conditions. *Current Neurology and Neuroscience Reports*. 2020;20(1). doi:10.1007/s11910-020-1021-0

27. Aloizou AM, Pateraki G, Anargyros K, Siokas V, Bakirtzis C, Liampas I, Nousia A, Nasios G, Sgantzos M, Peristeri E, Dardiotis E. Transcranial magnetic stimulation (TMS) and repetitive TMS in multiple sclerosis. *Rev Neurosci*. 2021;32(7):723-36. doi: 10.1515/revneuro-2020-0140.

28. Aloizou AM, Pateraki G, Anargyros K, Siokas V, Bakirtzis C, Sgantzos M, Messinis L, Nasios G, Peristeri E, Bogdanos DP, Doskas TK, Tzeferakos G, Dardiotis E. Repetitive Transcranial Magnetic Stimulation in the Treatment of Alzheimer's Disease and Other Dementias. *Healthcare (Basel)*. 2021;9(8). doi: 10.3390/healthcare9080949.

29. Pateraki G, Anargyros K, Aloizou AM, Siokas V, Bakirtzis C, Liampas I, Tsouris Z, Ziogka P, Sgantzos M, Folia V, Peristeri E, Dardiotis E. Therapeutic application of rTMS in neurodegenerative and movement disorders: A review. *J Electromyogr Kinesiol*. 2022;62:102622. doi: 10.1016/j.jelekin.2021.102622.

30. Petsani C, Aloizou AM, Siokas V, Messinis L, Peristeri E, Bakirtzis C, Nasios G, Dardiotis E. Therapeutic Application of rTMS in Atypical Parkinsonian Disorders. *Behav Neurol*. 2021;2021:3419907. doi: 10.1155/2021/3419907.

31. Sebastian R, Tsapkini K, Tippett DC. Transcranial direct current stimulation in post stroke aphasia and primary progressive aphasia: Current knowledge and future clinical applications. *NeuroRehabilitation*. 2016;39(1):141-152. doi:10.3233/NRE-161346

32. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*. 2017;128(1):56-92. doi:10.1016/j.clinph.2016.10.087

33. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*. 2000;527(3):633-639. doi:10.1111/j.1469-7793.2000.t01-1-00633.x

34. Ardolino G, Bossi B, Barbieri S, Priori A. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. *Journal of Physiology*. 2005;568(2):653-663. doi:10.1113/jphysiol.2005.088310

35. Ruohonen J, Karhu J. tDCS possibly stimulates glial cells. *Clin Neurophysiol*. 2012;123(10):2006-2009. doi:10.1016/j.clinph.2012.02.082

36. Toschi F, Lugli F, Biscarini F, Zerbetto F. Effects of electric field stress on a beta-amyloid peptide. *J Phys Chem B*. 2009;113(1):369-376. doi:10.1021/jp807896g

37. Fehlings MG, Tator CH. The effect of direct current field polarity on recovery after acute experimental spinal cord injury. *Brain Res*. 1992;579(1):32-42. doi:10.1016/0006-8993(92)90738-u
38. Finocchiaro C, Maimone M, Brighina F, Piccoli T, Giglia G, Fierro B. A case study of primary progressive aphasia: Improvement on verbs after rTMS treatment. *Neurocase*. 2006;12(6):317-321. doi:10.1080/13554790601126203
39. Cotelli M, Manenti R, Alberici A, et al. Prefrontal cortex rTMS enhances action naming in progressive non-fluent aphasia. *European Journal of Neurology*. 2012;19(11):1404-1412. doi:10.1111/j.1468-1331.2012.03699.x
40. Trebbastoni A, Raccah R, de Lena C, Zangen A, Inghilleri M. Repetitive deep transcranial magnetic stimulation improves verbal fluency and written language in a patient with primary progressive aphasia-logopenic variant (LPPA). *Brain Stimulation*. 2013;6(4):545-553. doi:10.1016/j.brs.2012.09.014
41. Bereau M, Magnin E, Nicolier M, et al. Left Prefrontal Repetitive Transcranial Magnetic Stimulation in a Logopenic Variant of Primary Progressive Aphasia: A Case Report. *European Neurology*. 2016;76(1-2):12-18. doi:10.1159/000447399
42. Margolis SA, Festa EK, Papandonatos GD, et al. A pilot study of repetitive transcranial magnetic stimulation in primary progressive aphasia. *Brain Stimulation*. 2019;12(5):1340-1342. doi:10.1016/j.brs.2019.06.001
43. Wang J, Wu D, Chen Y, Yuan Y, Zhang M. Effects of transcranial direct current stimulation on language improvement and cortical activation in nonfluent variant primary progressive aphasia. *Neuroscience Letters*. 2013;549:29-33. doi:10.1016/j.neulet.2013.06.019
44. Cotelli M, Manenti R, Petesi M, et al. Treatment of primary progressive aphasias by transcranial direct current stimulation combined with language training. *Journal of Alzheimer's Disease*. 2014;39(4):799-808. doi:10.3233/JAD-131427
45. Gervits F, Ash S, Coslett HB, Rascovsky K, Grossman M, Hamilton R. Transcranial direct current stimulation for the treatment of primary progressive aphasia: An open-label pilot study. *Brain and Language*. 2016;162:35-41. doi:10.1016/j.bandl.2016.05.007
46. Tsapkini K, Frangakis C, Gomez Y, Davis C, Hillis AE. Augmentation of spelling therapy with transcranial direct current stimulation in primary progressive aphasia: Preliminary results and challenges. *Aphasiology*. 2014;28(8-9):1112-1130. doi:10.1080/02687038.2014.930410
47. Tsapkini K, Webster KT, Ficek BN, et al. Electrical brain stimulation in different variants of primary progressive aphasia: A randomized clinical trial. *Alzheimer's and Dementia:*

Translational Research and Clinical Interventions. 2018;4:461-472. doi:10.1016/j.trci.2018.08.002

48. Fenner AS, Webster KT, Ficek BN, Frangakis CE, Tsapkini K. Written verb naming improves after tDCS over the left IFG in primary progressive aphasia. *Frontiers in Psychology*. 2019;10(JUN). doi:10.3389/fpsyg.2019.01396
49. Roncero C, Kniefel H, Service E, Thiel A, Probst S, Chertkow H. Inferior parietal transcranial direct current stimulation with training improves cognition in anomic Alzheimer's disease and frontotemporal dementia. *Alzheimer's and Dementia: Translational Research and Clinical Interventions*. 2017;3(2):247-253. doi:10.1016/j.trci.2017.03.003
50. Hung J, Bauer A, Grossman M, Hamilton RH, Coslett HB, Reilly J. Semantic feature training in combination with transcranial direct current stimulation (tDCS) for progressive anomia. *Frontiers in Human Neuroscience*. 2017;11. doi:10.3389/fnhum.2017.00253
51. Roncero C, Service E, de Caro M, et al. Maximizing the Treatment Benefit of tDCS in Neurodegenerative Anomia. *Frontiers in Neuroscience*. 2019;13. doi:10.3389/fnins.2019.01231
52. Teichmann M, Lesoil C, Godard J, et al. Direct current stimulation over the anterior temporal areas boosts semantic processing in primary progressive aphasia. *Annals of Neurology*. 2016;80(5):693-707. doi:10.1002/ana.24766