Augmentation of spelling therapy with transcranial direct current stimulation in primary progressive aphasia: Preliminary results and challenges

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Background: Primary progressive aphasia (PPA) is a neurodegenerative disease that primarily affects language functions and often begins in the fifth or sixth decade of life. The devastating effects on work and family life call for the investigation of treatment alternatives. In this article, we present new data indicating that neuromodulatory treatment, using transcranial direct current stimulation (tDCS) combined with a spelling intervention, shows some promise for maintaining or even improving language, at least temporarily, in PPA.

Aims: The main aim of the present article is to determine whether tDCS plus spelling intervention is more effective than spelling intervention alone in treating written language in PPA. We also asked whether the effects of tDCS are sustained longer than the effects of spelling intervention alone.

Methods & Procedures: We present data from six PPA participants who underwent anodal tDCS or sham plus spelling intervention in a within-subject crossover design. Each stimulation condition lasted 3 weeks or a total of 15 sessions with a 2-month interval in between. Participants were evaluated on treatment tasks as well as on other language and cognitive tasks at 2-week and 2-month follow-up intervals after each stimulation condition.

Outcomes & Results: All participants showed improvement in spelling (with sham or tDCS). There was no difference in the treated items between the two conditions. There was, however, consistent and significant improvement for untrained items only in the tDCS plus spelling intervention condition. Furthermore, the improvement lasted longer in the tDCS plus spelling intervention condition compared to sham plus spelling intervention condition.

Conclusions: Neuromodulation with tDCS offers promise as a means of augmenting language therapy to improve written language function at least temporarily in PPA. The

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consistent finding of generalisation of treatment benefits to untreated items and the superior sustainability of treatment effects with tDCS justifies further investigations. However, the small sample size still requires caution in interpretation. Present interventions need to be optimised, and particular challenges, such as ways to account for the variable effect of degeneration in each individual, are discussed.

**Keywords:** PPA; tDCS; Intervention; Spelling; Writing; Language rehabilitation.

Primary progressive aphasia (PPA) is a clinical neurodegenerative syndrome that first and foremost affects language (Mesulam, 2001, 2008). There is no treatment for the neuropathology of affected individuals. However, there have been several reports of successful language treatment for PPA. Several research groups have recently focused great effort on the development of interventions to reduce the rate of decline. Spelling is often one of the earliest affected language skills (Faria et al., 2013; Mesulam, 2001; Sepelyak et al., 2011), and, given today’s extensive use of email and texting technologies, may cause particular concern. Language interventions targeting the main cognitive mechanisms recruited during spelling have been modest but encouraging in PPA (Rapp & Glucroft, 2009; Tsapkini & Hillis, 2013). The sustainability of treatment gains, however, has not been assessed over time. Transcranial direct current stimulation (tDCS) is a relatively new, safe, non-invasive, non-painful electrical stimulation of the brain; it has been shown to improve language and cognitive abilities in healthy controls and individuals with stroke and dementia when administered during language learning interventions (Baker, Rorden, & Fridriksson, 2010; Floel, Rosser, Michka, Knecht, & Breitenstein, 2008; Wassermann & Grafman, 2005). Here, we review the available neuromodulatory investigations of language functions in healthy controls and individuals with aphasia, with emphasis on interventions in neurodegenerative diseases. Then, we report early results of an ongoing study of tDCS treatment for individuals with PPA. To our knowledge, this is the first report of a tDCS treatment in PPA. Finally, we discuss the challenges of such a treatment approach in PPA.

**Neuromodulation of language functions in healthy controls and individuals with aphasia**

tDCS was first shown to enhance cortical excitability and function when anodal current was applied in healthy individuals (Floel et al., 2008; Fritsch et al., 2010; Stagg & Nitsche, 2011). There are several benefits of tDCS—it is inexpensive, non-invasive and safe; and these facilitate research on its use in PPA as a possible means to augment behavioural intervention effects and to reduce the rate of decline in language. So far, tDCS has been used in clinical populations to improve motor and language recovery mainly after stroke (Baker et al., 2010; Fiori et al., 2011; Fridriksson, Richardson, Baker, & Rorden, 2011; Hamilton, Chrysikou, & Coslett, 2011; Monti et al., 2008). Amid a plethora of reports on language recovery using tDCS after stroke, only a few studies have reported on its use in neurodegenerative diseases—three studies on Alzheimer’s disease (Boggio et al., 2008, 2011; Ferrucci et al., 2008) and one study on frontotemporal dementia (Huey et al., 2007). The tasks targeted were verbal and visual recognition memory in Alzheimer’s disease and in fronto-temporal dementia. In the latter study, Huey et al. (2007) did not find any
effect of tDCS in improving verbal fluency in fronto-temporal dementia. Some reasons for this null result may be that the tDCS effects were measured before and after one stimulation session of 40 min that was not coupled with any language therapy during the stimulation. We are aware of only three other neuromodulation studies in PPA using a different technique—repetitive transcranial magnetic stimulation (rTMS). All showed improvement with neuromodulation (Cotelli et al., 2012; Finocchiaro et al., 2006; Trebbastoni, Raccah, de Lena, Zangen, & Inghilleri, 2013). Of particular interest is Trebbastoni et al.’s (2013) case study, in which treatment comprised language therapy coupled with five consecutive TMS sessions followed by five sham sessions and then a further five TMS sessions over the dorsolateral prefrontal cortex and close to inferior frontal gyrus (IFG) and middle frontal gyrus. Following this regime, the PPA participant showed improvement in phonemic verbal fluency and written language (decrease in semantic and syntactic errors in sentences) only after real stimulation (not after sham). Despite the importance of written language as an alternative means of communication in aphasia, we are not aware of any other published studies of neuromodulation, including tDCS, coupled with language therapy in PPA and particularly, no written language intervention studies.

Nevertheless, there is research on neuromodulation in language rehabilitation more widely, with 15 reviews in the last few years. Most of these reviews include effects of neuromodulation in general, i.e., both through TMS or tDCS. In particular, Flöel (2012) reviewed tDCS studies on healthy adults; Medina et al. (2012) reviewed TMS studies in post-stroke aphasia rehabilitation and Holland and Crinion (2012) reviewed tDCS studies in post-stroke aphasia with emphasis on speech production. Hansen (2012) described the mechanisms of the effects of tDCS on memory in neurodegenerative diseases; three recent reviews (Boggio et al., 2011; Freitas, Mondragón-Llorca, & Pascual-Leone, 2011; Nardone et al., 2012) reported on the effects of tDCS and TMS in Alzheimer’s disease.

Long-term effects of tDCS have not been clearly identified; this is especially true for neurodegenerative disease (Hansen, 2012). In stroke, two studies showed that tDCS gains may be retained for a week (Baker et al., 2010) or even 3 weeks (Fridriksson et al., 2011). Two more studies (Fiori et al., 2011; Marangolo et al., 2011) evaluated tDCS effects in naming and syllable training up to 2 months. One study in Alzheimer’s disease showed improvement in naming even 1 month later (Boggio et al., 2012). In general, long-term effects—whenever shown—appeared after at least five consecutive days of stimulation. Knowing the duration of therapeutic effects is crucial, especially in neural degeneration, because it enables us to judge more accurately whether and when treatment should be repeated.

Spelling intervention studies

Intervention studies in PPA are, in general, difficult, given the degenerative nature of the disease, the variable rate of decline amongst individuals and the heterogeneity of each variant. Therefore, most intervention studies are case reports or include a small number of participants (for a review, see Croot, Nickels, Laurence, & Manning, 2009 and Graham, 2014). Behavioural studies have mostly investigated treatment of word retrieval in all PPA subtypes: (1) semantic variant PPA (svPPA) (Graham, Patterson, Pratt, & Hodges, 1999; Henry, Beeson, & Rapcsak, 2008; Jokel & Anderson, 2012; Jokel, Rochon, & Anderson, 2010; Jokel, Rochon,
Distinct cognitive mechanisms underlying spelling can be impaired in PPA—at least in the earlier stages of PPA—and can be individually targeted in treatment. Two “routes” for spelling a word have been proposed: (1) the lexical route that involves access to the stored orthographic lexical representation of the word and its meaning—used mostly for spelling of familiar words and (2) the sublexical route that involves using a phoneme-to-grapheme conversion (PGC) mechanism—used mostly for spelling of unfamiliar words (nonwords). Spelling of all familiar words and unfamiliar words/nonwords requires temporary storage of the sequence of letters in working memory—a storage system called the graphemic buffer—while the individual letters are being written or spelled out loud. These mechanisms have been described in a series of detailed case studies of focal brain lesions, resulting in selective deficits in each of these components of the cognitive architecture underlying spelling (Caramazza, 1997; Hillis & Caramazza, 1987; Rapcsak et al., 2009; Rapp & Caramazza, 1997). In PPA, any of the aforementioned mechanisms or combinations of mechanisms may be disrupted.

Recent studies have provided evidence from focal lesion studies, PPA and functional imaging for the neural networks underlying these cognitive mechanisms involved in spelling (Beeson et al., 2003; Philipose et al., 2007; Planton, Jucla, Roux, & Demonet, 2013; Purcell, Turkeltaub, Eden, & Rapp, 2011; Rapcsak et al., 2009; Sepelyak et al., 2011; see also Tsapkini & Hillis, 2014 for a review). These studies indicate that left IFG is essential for both direct lexical access and PGC mechanism; left supramarginal gyrus (SMG) is essential for the PGC mechanism and left fusiform gyrus for direct lexical access to the orthographic lexicon mechanism. Other important areas are the left anterior temporal lobe (ATL) for access to semantics (Adlam et al., 2006; Davies, Halliday, Xuereb, Kril, & Hodges, 2009; Lambon Ralph, Cipolotti, Manes, & Patterson, 2010; Patterson, Nestor, & Rogers, 2007; Schwartz et al., 2009; Tsapkini, Frangakis, & Hillis, 2011) and the superior temporal gyrus for phonological processing (Purcell et al., 2011) and PGC mechanism (Purcell et al., 2011; Sepelyak et al., 2011). Interestingly, lvPPA participants typically show atrophy in left parieto-temporal areas, whereas nfvPPA participants...
often show atrophy in left fronto-parietal areas and svPPA participants usually show atrophy in anterior temporal areas (Gorno-Tempini et al., 2011; Sepelyak et al., 2011). Correspondingly, we found that PGC mechanism impairments occur mostly in nfvPPA and lvPPA participants; svPPA participants rely on PGC mechanism to write words and thus produce mostly phonologically plausible errors, at least initially (Sepelyak et al., 2011). Later in the course of the disease, however, individuals with svPPA also begin to have trouble with spelling unfamiliar words using the PGC mechanism (Adlam et al., 2006; Patterson et al., 2007).

The current study

In the present study, we employed an intervention targeting the PGC mechanism, previously implemented in stroke (Hillis, 1992; Hillis-Trupe, 1986; Hillis & Caramazza, 1987) and recently in PPA (Tsapkini & Hillis, 2013) for participants with an impaired PGC mechanism. With tDCS, we targeted the left IFG, an area found to be involved in the PGC mechanism in numerous spelling studies including two recent meta-analyses (Planton et al., 2013; Purcell et al., 2011). We sought to evaluate the following hypotheses: (1) Improvement of performance in spelling (in treated and untreated items) will be greater in the tDCS + spelling interventions (labelled: “tDCS treatment condition”) than in the sham + spelling interventions (labelled: “sham treatment condition”). (2) Improvement will last longer after tDCS treatment than sham treatment conditions as measured at 2-week and 2-month follow-up intervals. (3) Improvement in other language tasks subserved by the area of stimulation will be greater after tDCS than after sham.

METHODS

Participants

Six individuals with PPA participated in our study in a crossover design. All were clinically diagnosed with PPA at Dr Hillis’ clinic, were right-handed, were native speakers of English, with at least college education, and had a spelling deficit. They were all premorbidly proficient spellers. Diagnosis was based on neuropsychological and language testing, MRI and clinical assessment. Two participants were characterised as nfvPPA and four as lvPPA. The study was approved by the Johns Hopkins Hospital Institutional Review Board. All participants and their spouses (for those with comprehension deficits) provided informed consent to participate. Table 1 summarises demographics and language and cognitive performance of the five participants at baseline.

Design

We used a within-subject crossover trial design, where each patient underwent two experimental conditions: “left IFG tDCS + behavioural (spelling) interventions” and “sham tDCS + behavioural interventions”. Each participant received either the tDCS treatment (in weeks 1–3) and then the sham treatment (in weeks 12–14), or vice versa. Evaluation took place before, immediately after, 2 weeks and 2 months post-intervention for each condition (see Table 2). There were two sets of materials: trained items, practiced at each stimulation session, either tDCS or sham, and untrained
| Test from the WAB | PZR (F) | TBT (M) | SKR (M) | JRD (M) | LRL (F) | BNR (F) |
|------------------|---------|---------|---------|---------|---------|---------|
| Time post-onset  | Non-fluent, agrammatic | Non-fluent, agrammatic | Logopenic | Logopenic | Logopenic | Logopenic |
| PPA variant      | 6 years | 3 years | 8 years | 4 years | 6 years | 10 years |
| Spontaneous speech total | 100 | 75 | 50 | 65 | 60 | 75 |
| Information content | 100 | 100 | 80 | 50 | 80 | 80 |
| Fluency, grammatical competence | 100 | 90 | 40 | 90 | 40 | 70 |
| Auditory verbal comprehension | 100 | 98 | 77 | 63 | 95 | 80 |
| Yes/no questions | 100 | 100 | 90 | 83 | 100 | 100 |
| Auditory word recognition | 100 | 100 | 90 | 97 | 100 | 100 |
| Sequential commands | 100 | 80 | 51 | 44 | 80 | 55 |
| Repetition total | 60 | 74 | 24 | 65 | 75 | 60 |
| Naming and word finding | | | | | | |
| Object naming | 100 | 100 | 67 | 67 | 80 | 70 |
| Word fluency | 80 percentile | 40 percentile | 10 percentile | 10 percentile | <10 percentile | 10 percentile |
| Sentence completion | 80 | 80 | 20 | 20 | 30 | 30 |
| Responsive speech | 100 | 100 | 40 | 40 | 40 | 60 |
| Pseudoword spelling | 82 | 53 | 15 | 72 | 0.03 | |
| Trail making | | | | | | |
| Part A | 30 s | 40 s | 73 s | 180 s | N/A | N/A |
| Part B | 90 s | 170 s | 390 s | Incomplete | N/A | N/A |
| Digit span | Forward | 5 | 7 | 3 | 3 | 3 | 2.5 |
|_backward | 4 | 6 | 1 | 2 | 2.5 | 2 |
| Word span | Forward | 4 | 4 | 2 | 3 | 3 | 0 |
| Backward | 3 | 4 | 1 | 2 | 2 | 0 |

The three-letter code corresponds to each participant, and “F” denotes female gender whereas “M” denotes male gender. The numbers reported correspond to per cent correct. N/A corresponds to “non-applicable” due to lack of data.
items, not practiced but only tested in the beginning and at follow-up intervals. Follow-up assessment probed both sets (trained and untrained) of phoneme-to-grapheme and phoneme-to-word correspondences and words to identify whether the participant retained knowledge of the trained items. We looked at generalisation effects (i.e., effects of training on untrained items) before and after the completion of each treatment condition. All evaluations were done by technicians blind to the treatment condition. The interventions and evaluations (two levels) are described below. Three participants (TBT-non-fluent agrammatic PPA, PZR-non-fluent agrammatic PPA, LRL-logopenic PPA) received both the first and the second level of treatment. One had sham first (PZR); the others had tDCS first. Amongst the three participants who were given only the first level of intervention, one (SKR-logopenic PPA) received sham first and the other two participants (JRD-logopenic PPA and BNR-logopenic) received tDCS first.

**Spelling intervention: Treatment of the PGC mechanism**

For the first level of treatment, 30 English sounds were selected representing the most common word-initial English phonemes and were divided into three sets using a counterbalanced design with respect to the frequency of the initial phoneme. A set of 30 English words starting with these sounds were then selected as prompts to help the patient relate each sound to a grapheme. The sequence of events in the therapy sessions was as follows: The participant was asked to write the letter or combination of letters corresponding to a particular phoneme, e.g., /f/. If the participant was correct, then s/he was reinforced. If the participant was incorrect or could write the correct letter from the sound provided, s/he was asked to think instead of a word that started with this sound and try to retrieve the whole word representation instead of the correspondence of a single sound to a letter. If unable to do so, the participant was provided with such a word-prompt (e.g., farm); then s/he was asked to write the word-prompt or the word-prompt was written by the experimenter; finally, the participant was explicitly instructed in PGC for all letter-sounds of the word and asked to associate that initial phoneme to the particular word and its initial grapheme. Each session consisted of teaching the same PGCs of 10 initial word phonemes using 10 common English words and practicing the PGCs of each word-prompt. Three participants (TBT, PZR, LRL) rapidly (four to five sessions) learned the initial PGCs (initial sound to letter) but were still unable to use this knowledge in the rest of the word and spell the whole word correctly, i.e., they still made phonologically implausible nonword errors, e.g., “talbk” instead of “table”. This is not

| Time | W1–3 | W6 | W12–14 | W17 | W23 |
|------|------|----|--------|-----|-----|
| Group 1: Control then sham then tDCS | 15 Sham | 15 Left IFG |
| Group 2: Control then tDCS then sham | 15 Left IFG | 15 Sham |
| Both groups | eval (b + a) | eval | eval (b + a) | eval | eval |

W: week, left IFG: left inferior frontal gyrus, eval (b + a): evaluation before and after or evaluation only; 15: number of sessions.
unusual in patients with PGC deficits: some may learn the initial sound–letter correspondence, but because of additional problems they may have, such as short-term memory deficits, expressed in spelling as graphemic buffer deficits, they cannot write the whole word correctly. For these participants, we introduced a second level of PGC training in which they received more practice in using PGCs within a word: They were asked to write as many words as possible produced in 1 min starting from the same phoneme so that there would be more words in which to practice the PGCs with the experimenter and, thus, use the PGC rules in more contexts. Participants received five language therapy sessions per week, 30 min each, for both tDCS and sham treatments. The first two sets of 10 PGC were used in the first intervention session (sham or tDCS) as trained and untrained items. For the second intervention period, the untrained set of the first intervention was used as the trained set and the third set was used as the untrained set.

**tDCS intervention**

Participants took part in 15 consecutive training sessions for each stimulation condition (tDCS and sham, in randomly assigned order), three to five per week, depending on their availability. The two conditions were separated by 2 months (see Table 2). We used a Chattanooga Ionto device; stimulation was delivered at an intensity of 1–2 mA (estimated current density 0.04 mA/cm²; estimated total charge 0.048C/cm²) for a maximum of 20 min in the tDCS conditions and for a maximum of 30 s in the sham conditions. The stimulator was not connected to a mainline power source and could not produce an excess of 4 mA of current. We used non-metallic, conductive rubber electrodes covered by saline-soaked sponges to minimise the potential for chemical reactions at the interface of the scalp or skin and electrodes. For both types of intervention (tDCS and sham), the electrical current was increased in a ramp-like fashion at the onset of the stimulation, eliciting a transient tingling sensation on the scalp that usually disappeared over 30 s. Since the ramping process required the researcher’s input, the experimenter was not blind to the tDCS condition. These procedures have been shown to successfully blind participants as to whether they were members of experimental or control groups (Gandiga, Hummel, & Cohen, 2006). The sites of stimulation were left IFG (all cases). One case underwent an additional tDCS condition with left SMG stimulation. The stimulation site of left IFG was determined at F7 electrode, using the EEG 10–20 electrode position system (Homan, 1988); however, electrode patches were 2 inch × 2 inch, so the area stimulated covered more frontal tissue than the left IFG.

**Evaluation of treatment effects**

For relatively stable diseases, the assumption is that performance during the intervention period remains unchanged in the absence of treatment. For degenerative diseases, in the absence of treatment, performance is expected to deteriorate (although it could remain stable or even improve due to general practice effects). Showing the effectiveness of treatment would, thus, require showing the benefit relative to the possible deterioration that might otherwise have occurred without that treatment during the same time period. In our statistical analysis, we examined first a model allowing for period and carry-over effects. By “period effect”, we refer to the effect of time, i.e., of having tDCS or sham as the later treatment. By “carry-
over effect”, we refer to the effects of either tDCS + spelling therapy or spelling therapy only that may have survived beyond the 2-month follow-up and influence the next period of stimulation. The rationale for this analysis is to determine whether participants benefit only when tDCS occurs first or whether they benefit from having any therapy (even spelling therapy without tDCS; i.e., with sham) first. Follow-up assessment probed the sets of trained and untrained phoneme-to-grapheme and phoneme-to-word correspondences to identify whether the patient retained knowledge of the trained items and whether this knowledge generalised to untrained items. We employed a within-subject crossover design in which all participants took part in both stimulation conditions. For those who received the first level of treatment, outcome measures were: (1) the number of correct phoneme-to-grapheme correspondences and (2) the number of correctly spelled word-prompt items associated with each phoneme. For these patients, we calculated the accuracy on both the initial phoneme/grapheme of each word-prompt and the word-prompt as a whole. For those who received the second level of treatment, the outcome measure was the number of words spelled correctly.

Statistical analyses

(1) Within-subject analyses. For each participant in each treatment condition (tDCS or sham), we compared the correct responses before and after treatment on each stimulus type (trained or untrained) with McNemar’s test for correlated responses. We, thus, determined whether there was any gain from either treatment at the individual subject level for each stimulus type (see Table 3). McNemar’s test is an appropriate test for a predetermined set of responses as was the case for participants who completed the first level of intervention. We also used it to compare intervention gains for the second level of intervention, despite the fact that in that condition there were more possibilities for a correct response that may not have been in a predetermined set, as participants were trained in PGC mechanism in correct words that they produced in 1 min. We justify its use, given previous studies showing that in Alzheimer’s disease and fronto-temporal dementia with aphasia (the usual pathological causes of PPA), the actual possibilities are not really limitless: patients tend to produce fewer words than normal controls and these words are usually the same due to reduced lexical search capacities (Huey et al., 2007; Trebbastoni et al., 2013). Our data also confirm both findings: Participants produced fewer than normal words and these were the same throughout the sessions. The above analysis, however, may be confounded by the possible effects of the order of treatment and carry-over effects from tDCS to sham. To address these issues, we proceeded to the second level of analyses across subjects between treatments.

(2) Across subjects between treatments. For this analysis, all types of responses for all participants were transformed onto the same scale (0–100), and the following notation is used. Each patient $i$ was treated either with tDCS (T) in the first period and sham (S) in the second period (in which case, we say order$_i = TS$) or with sham in the first period and tDCS in the second period (in which case, we say order$_i = ST$). For each patient $i$, we measured the change in spelling performance immediately after minus before sham and denoted it by $\delta Y_{i,\text{sham}}$.
| Participant | Order of intervention |  |  |  |  |  |  |  |  |  |  |  |
|-------------|-----------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|             |                       | tDCS | Sham | tDCS | Sham | tDCS | Sham | tDCS | Sham | tDCS | Sham | tDCS | Sham |
| PZR         | Sham, tDCS            | <0.001 | 0.016 | <0.001 | 0.031 | <0.001 | na | <0.001 | na | 0.001 | Na | 0.001 | na |
| SKR         | Sham, tDCS            | 0.008 | 0.031 | 0.031 | 0.500 | 0.031 | 0.500 | 0.008 | 1.000 | 0.125 | 1.000 | 0.125 | 0.500* |
| TBT         | tDCS, sham            | <0.001 | <0.001 | <0.001 | 1.000 | <0.001 | 0.500 | <0.001 | 0.250 | <0.001 | <0.001* | <0.001 | 0.001* |
| JRD         | tDCS, sham            | 0.004 | 0.031 | 0.016 | 0.125 | 0.008 | 0.063 | 0.016 | 0.500 | 0.500 | 0.125 | 1.000 | 0.500* |
| LRL         | tDCS, sham            | <0.001 | 0.500 | <0.001 | 0.500 | <0.001 | 0.250 | <0.001 | 0.500 | 0.008 | 1.000 | 0.002 | 1.000* |
| BNR         | tDCS, sham            | 0.031 | 0.500 | 0.016 | 1.000 | 0.016 | 0.250* | 0.250 | 1.000* | 0.004 | 0.500 | 0.063 | 0.250 |

Shade: for significant improvement vs. just before treatment; *indicates deterioration, na is for data not completed.
and measured the change in spelling performance immediately after minus before tDCS and denoted it by $\delta Y_{i,tDCS}$. To evaluate the research hypothesis that the changes in spelling performance under tDCS will on average be larger than the changes in spelling performance under sham, we analysed the data (order, $\delta Y_{i,\text{sham}}$, $\delta Y_{i,tDCS}$), for patients $i = 1, \ldots, n$ to estimate the parameters of the standard crossover formulation (Jones & Kenward, 2003). This formulation decomposes the expected values of the changes under sham and under tDCS into parameters for a treatment effect, a period effect and a treatment-by-period interaction, as follows:

\[
E(\delta Y_{i,\text{sham}} | \text{order}_i) = \delta_S + (\text{order}_i = \text{TS}) \times (\pi_2 + \delta_{(S \text{after } T)})
\]

\[
E(\delta Y_{i,tDCS} | \text{order}_i) = \delta_S + \delta_{(T \text{ vs. } S)} + (\text{order}_i = \text{ST}) \times \pi_2
\]

where $E()$ means population average, and both the correlation between $\delta Y_{i,\text{sham}}$ and $\delta Y_{i,tDCS}$ and their variances are allowed to be arbitrary. The parameter of main interest here is $\delta_{(T \text{ vs. } S)}$, and it is the effect of tDCS vs. sham during the first period. The interpretation of each of the above parameters ($\delta_S$, $\pi_2$, $\delta_{(T \text{ after } S)}$) is given in Table 4.

The above research hypothesis can be assessed by evaluating the hypothesis that the effect $\delta_{(T \text{ vs. } S)}$ is positive, where this effect and the other parameters are estimated by the generalised estimating equation approach with robust estimation of the variance of the estimates (Liang & Zeger, 1986).

In order to limit complexity, for each follow-up time, we evaluated the predictive accuracy of each of three models: the model with only the tDCS vs. sham effect; the model that adds also the period effect and the model that adds also the interaction (carry-over effect); we compared among the three models using the leave-one-out cross-validated $R^2$, which is an essentially unbiased way of comparing among such models (Hastie, Tibshirani, & Friedman, 2008). Then, we estimated the tDCS vs. sham effect $\delta_{(T \text{ vs. } S)}$ using the model that explained the data best (highest $R^2$).

The same approach was followed for measuring changes at 2 weeks and 2 months to evaluate the hypothesis that the beneficial effect of combined tDCS with spelling treatment would be better sustained at 2 weeks and 2 months post-treatment when compared to spelling treatment alone (sham).

| Order of treatment | First period | Second period |
|--------------------|--------------|--------------|
|                    | Average of after–before change in outcome | Average of after–before change in outcome |
| Sham (first) then tDCS (second) | $\delta_S$ | $\delta_S + \delta_{(T \text{ vs. } S)} + \pi_2$ |
| tDCS (first) then Sham (second) | $\delta_S + \delta_{(T \text{ vs. } S)}$ | $\delta_S + \pi_2 + \delta_{(S \text{ after } T)}$ |

$\delta_S$ is the average gain under sham (behavioural spelling alone); $\delta_{(T \text{ vs. } S)}$ is the extra average gain under tDCS; $\pi_2$ is the effect of period 2 vs. period 1 under tDCS and $\pi_2 + \delta_{(S \text{ after } T)}$ is the effect of period 2 vs. period 1 under sham, so that $\delta_{(S \text{ after } T)}$ is the carry-over effect of tDCS on sham.
RESULTS

(1) *Within-subjects within-treatments results.* As shown in Table 3, both sham and tDCS treatments were effective for trained items, but only spelling intervention coupled with tDCS produced significant changes for untrained items for 6/6 patients immediately after stimulation and at most follow-up conditions (in 5/6 patients after 2 weeks and in 4/6 patients after 2 months). Conversely, sham produced significant changes for untrained items only in 1/6 patients immediately after treatment and in 1/6 patients after 2 months. For trained items, both tDCS and sham improved performance immediately after stimulation, although tDCS was beneficial for more patients than sham (in 6/6 patients after tDCS and 4/6 after sham). At 2 weeks post-stimulation, performance on trained items remained improved only in the tDCS condition in 6/6 patients but only in 1/6 patients in the sham condition. Finally, at 2 months post-stimulation, performance on trained items remained improved in 4/6 patients in the tDCS condition but only in 1/6 patients in the sham condition. Therefore, therapeutic gains generalised only in the tDCS condition and lasted longer than sham.

(2) *Across subjects between treatments.* Figure 1 summarises the preliminary data across the six patients. Patient PZR did not complete the 2-week and 2-month follow-up testing after sham, so these data are missing. For trained items, the average of the post-minus pre-treatment change in performance was 35% under tDCS and 16% under sham. Figure 1 also shows the treatment effects in each individual participant.

To test the hypothesis that tDCS is more beneficial than spelling intervention alone, we allowed for an effect of the period at which a treatment was given as well as for carry-over effects from the previous intervention, using the crossover model and analysis defined in Table 4. Table 5 shows, for each follow-up time, the predictive accuracy measured by the cross-validated $R^2$ for (1) the model with only the tDCS vs. sham effect; (2) the model that allows also for a period effect and (3) the model that also allows a carry-over effect. In no circumstance did the carry-over effect improve accuracy. Moreover, for untrained items, the simplest model was best (there was no additional effect of period on model fit). For trained items, the model with period added had a better fit for the 2-week and 2-month follow-up assessment points. Table 6 shows, for each follow-up time, the estimates of the tDCS vs. sham effect based on the corresponding best-fitting model. The results are consistent with the hypotheses that tDCS + spelling intervention is more beneficial than spelling intervention alone immediately after as well as in the 2-week follow-up for trained items, and in all follow-up times for untrained items.

DISCUSSION

In this article, we reported perhaps the first tDCS intervention for spelling in PPA, a neurodegenerative disease affecting mainly language for which there is no treatment. We reported results from six participants who completed both tDCS and sham conditions. We also evaluated the effects of tDCS vs. sham at two follow-up intervals—2 weeks and 2 months. We provided consistent data from six participants in
Figure 1. Summary of performance (per cent correct scores) on trained (upper panels) and untrained (low panels) items for all participants. Each participant is represented with one line. Solid lines depict the performance on the period when tDCS was given and dotted depict the performance on the period when sham was given. Period 1 and Period 2 represent the first and second time periods, respectively.

TABLE 5

Model assessments by cross-validated $R^2$ for: the model with effect of tDCS vs. sham only; the model that estimates also a period effect (+period) and the model that also estimates a carry-over effect (+carry-over)

| Time since intervention | Trained items | Untrained items |
|-------------------------|---------------|-----------------|
|                         | $t$DCS vs. sham | +Period | +Carry-over | $t$DCS vs. sham | +Period | +Carry-over |
| Immediately after       | $\hat{\beta}_{(T vs. S)}$ | $\pi_2$ | $\delta_{(\text{after T})}$ | $\hat{\beta}_{(T vs. S)}$ | $\pi_2$ | $\delta_{(\text{after T})}$ |
| 2 Weeks after           | 34% | 23% | 0% | 66% | 64% | 55% |
| 2 Months after          | 52% | 56% | 49% | 67% | 37% | 53% |
|                         | 22% | 24% | 17% | 70% | 64% | 62% |

For each time, the best of the three models has underlined $R^2$. 
support of our hypotheses that tDCS coupled with spelling therapy is more effective than spelling therapy alone for (1) improving PGC mechanism in PPA for untrained items and (2) sustaining results in 2-week and 2-month follow-ups (although, one participant showed improvement under sham at the 2-month follow-up only). All six participants showed generalisation of treatment to untrained items when spelling therapy was augmented with tDCS and one showed it in sham as well.

To the best of our knowledge, this is the first study that has looked at maintenance effects over this time period with tDCS interventions, although maintenance effects up to 1 month have been shown with no less than five consecutive stimulations. A possible reason for the robust effects we obtained is the duration and intensity of our interventions (15 consecutive sessions, 5 per week). This long-term stimulation may have induced late long-term potentiation of neurons that may have lowered the threshold of neuronal excitability and subsequent synaptic connectivity in the areas applied (Baker et al., 2010; Wassermann & Grafman, 2005); however, further studies of neuronal connectivity are needed to shed light on the neuronal effects of tDCS. It is also notable that we found improvement in the sham condition for the trained items for all our participants. This result also shows the beneficial effect of behavioural language treatment as other previous studies have shown in PPA (Beeson et al., 2011; Graham et al., 1999; Henry et al., 2008; Jokel et al., 2010, 2006; Marcotte & Ansaldo, 2010; McNeil et al., 1995; Newhart et al., 2009; Rapp & Glueroft, 2009; Schneider et al., 1996; Tsapkini & Hillis, 2013) but underlines the possibility of significantly augmenting the duration and generalisation of these effects by the implementation of tDCS in neural degeneration. Overall, our results are preliminary but highlight the therapeutic potential of tDCS to augment language therapy in PPA. These results establish the feasibility of implementing tDCS in PPA to treat language deficits and show promise for confirming our hypotheses in a bigger sample of participants.

It is notable that we found improvement in the sham condition for the trained items for all our participants. Most studies in other populations do not find any positive effect in sham conditions (Boggio et al., 2011, 2012; Hansen, 2012; Nardone et al., 2012). A possible explanation of these results is the duration and intensity of our spelling intervention. Our participants received rather intensive (frequent and

| Time since intervention | Trained item | Untrained items |
|-------------------------|--------------|----------------|
|                         | tDCS vs. sham | Standard error | p-Value | tDCS vs. sham | Standard error | p-Value |
| Immediately after       | 19.70<sup>1</sup> | 4.03<sup>2</sup> | 0.005 | 21.83<sup>3</sup> | 3.39<sup>4</sup> | 0.001 |
| 2 Weeks after           | 22.40<sup>1</sup> | 5.50<sup>2</sup> | 0.015 | 25.50<sup>3</sup> | 3.26<sup>4</sup> | <0.001 |
| 2 Months after          | 21.59<sup>1</sup> | 8.50<sup>2</sup> | 0.064 | 25.70<sup>3</sup> | 5.35<sup>4</sup> | 0.005 |

1Effect sizes: 1.5; 1.8; 1.2.
2Degrees of freedom: (6-1);(6-2);(6-2).
3Effect sizes: 2.7; 2.7; 2.9.
4Degrees of freedom: (6-1);(6-1);(6-1).
relatively many) treatments in both tDCS and sham conditions (15 sessions), whereas in most published studies, the number of sessions is 1–5. Therefore, the effects we see in our sham condition are the same as the well-established and repeatedly found effects of language therapy in PPA: beneficial but short-lived improvement in trained items (Beeson et al., 2011; Graham et al., 1999; Henry et al., 2008; Jokel et al., 2010, 2006; Marcotte & Ansaldo, 2010; McNeil et al., 1995; Newhart et al., 2009; Rapp & Glucroft, 2009; Schneider et al., 1996; Tsapkini & Hillis, 2013).

**LIMITATIONS AND CHALLENGES**

The present study, although preliminary, has provided some interesting findings and certainly avenues for further investigations. There are several limitations, with the most important being the small number of participants. Another possible limitation of the present study is the fact that we had only one baseline evaluation before each stimulation condition. Therefore, our results may have been influenced by practice effects and may additionally reflect the effect of initial exposure to an unfamiliar testing situation. We believe, however, that the randomisation in the order of interventions within and between patients may have reduced the single baseline effect. Even if there was only a single baseline condition, this was the case for both the tDCS + spelling intervention and the sham + spelling intervention in a within-subject crossover design that showed significant advantage of tDCS for augmenting intervention effects.

Also, the effect of stimulation may vary with regard to PPA variant (e.g., if atrophy exists in a stimulated area, then tDCS effects may be less pronounced); therefore, the effects of atrophy in each PPA variant and neuropathology in each PPA patient should be taken into consideration. In our study, we obtained similar effects for all variants. We did not streamline our interventions according to variant since different variants and pathologies may have similar spelling profiles (Sepelyak et al., 2011). In a larger sample, however, it would be of interest to evaluate the possible differences of the effects of tDCS in each PPA variant.

All six participants showed significant improvement on untrained items when spelling therapy was augmented with tDCS, and one participant showed it in sham as well. This generalisation to untrained items yields a more functional intervention. However, we have to note that if a ceiling effect is reached during the first period of intervention, there is much less room for improvement in the second period. For this reason, we have randomised the order of treatments in a within-subject crossover design. Currently, our data do not allow us to exclude the possibility that our tDCS effect may be caused by the fact that tDCS was the first treatment in most patients of our present sample. We have tried to account for this possibility by including the order of treatments as a possible factor that would influence our results in our statistical model. When more data are available, it will be possible to statistically address this question. If tDCS “works” by improving synaptic plasticity (as frequently hypothesised), we would expect it to result in improvement on untrained items as well as on untrained tasks that might engage the neural network being recruited, such as: (1) working memory (digit and word spans forward and backward), (2) apraxia of speech and (3) grammatical sentence production (sentence anagram task). With the limited number of participants we have so far, we cannot demonstrate a causal relationship between tDCS and improvement in other cognitive
functions. More data are needed in order to assess the hypothesis that other language and cognitive functions related to the area of stimulation may improve with tDCS.

The most serious challenge in this kind of study is the effect of neural degeneration in the course of the therapeutic intervention. For this reason, in our analysis, we tried to estimate the effect of the period of intervention as well as possible carry-over effects from one type of intervention to the other using a mathematical formulation. Sometimes, as it was shown in this small sample, these effects are not significant. However, it is important to consider and test for these effects in a larger cohort of patients when these data will be available.

Another serious challenge in studying tDCS effects in PPA is the variability of the rate of decline for each patient and at the particular timing of the intervention. It might be the case that tDCS is more beneficial at early stages of PPA when deficits are mild and intervention may be more targeted to few impaired tasks. In our study, we recruited patients from all stages of disease progression. In a larger future longitudinal study, it might be important to look at the effect of the stage of the disease and how tDCS affects the rate of decline for the targeted and non-targeted tasks.

To conclude, our results are preliminary but highlight the therapeutic potential of tDCS to augment language therapy in PPA. Neuromodulation holds considerable promise for designing new rehabilitation strategies in patients with neurodegenerative disease.

REFERENCES

Adlam, A. L., Patterson, K., Rogers, T. T., Nestor, P. J., Salmond, C. H., Acosta-Cabrañero, J., & Hodges, J. R. (2006). Semantic dementia and fluent primary progressive aphasia: Two sides of the same coin? Brain, 129, 3066–3080.

Baker, J. M., Rorden, C., & Fridriksson, J. (2010). Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke, 41, 1229–1236.

Beeson, P., Rapcsak, S., Plante, E., Chargualaf, J., Chung, A., Johnson, S., & Trouard, T. (2003). The neural substrates of writing: A functional magnetic resonance imaging study. Aphasiology, 17, 647–665.

Beeson, P. M., King, R. M., Bonakdarpour, B., Henry, M. L., Cho, H., & Rapcsak, S. Z. (2011). Positive effects of language treatment for the logopenic variant of primary progressive aphasia. Journal of Molecular Neuroscience, 45, 724–736.

Boggio, P. S., Ferrucci, R., Mameli, F., Martins, D., Martins, O., Vergari, M., ... Priori, A. (2012). Prolonged visual memory enhancement after direct current stimulation in alzheimer's disease. Brain Stimulation, 5, 223–230.

Boggio, P. S., Khoury, L. P., Martins, D. C., Martins, O. E., de Macedo, E. C., & Fregni, F. (2008). Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. Journal of Neurology Neurosurgery and Psychiatry, 80, 444–447.

Boggio, P. S., Valasek, C. A., Campanhã, C., Giglio, A. C., Baptista, N. I., Lapenta, O. M., & Fregni, F. (2011). Non-invasive brain stimulation to assess and modulate neuroplasticity in Alzheimer’s disease. Neuropsychological Rehabilitation, 21, 703–716.

Caramazza, A. (1997). How many levels of processing are there in lexical access? Cognitive Neuropsychology, 14, 177–208.

Cotelli, M., Manenti, R., Alberici, A., Brambilla, M., Cossedu, M., Zanetti, O., ... Borroni, B. (2012). Prefrontal cortex rTMS enhances action naming in progressive non-fluent aphasia. European Journal of Neurology, 19, 1404–1412.

Croot, K., Nickels, L., Laurence, F., & Manning, M. (2009). Impairment- and activity/participation-directed interventions in progressive language impairment: Clinical and theoretical issues. Aphasiology, 23, 125–160.

Davies, R. R., Halliday, G. M., Xuereb, J. H., Kril, J. J., & Hodges, J. R. (2009). The neural basis of semantic memory: Evidence from semantic dementia. Neurobiology of Aging, 30, 2043–2052.
Graham, K. S., Patterson, K., Pratt, K. H., & Hodges, J. R. (1999). Relearning and subsequent forgetting. *Neuropsychology, 11*, 493–498.

Finocchiaro, C., Maimone, M., Brighina, F., Piccoli, T., Giglia, G., & Fierro, B. (2006). A case study of primary progressive aphasia: Improvement on verbs after rTMS treatment. *Neurocase, 12*, 317–321.

Fiori, V., Coccia, M., Marinelli, C. V., Vecchi, V., Bonifazi, S., Ceravolo, M. G., ... Marangolo, P., (2011). Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. *Journal of Cognitive Neuroscience, 23*, 2309–2323.

Flöel, A. (2012). Non-invasive brain stimulation and language processing in the healthy brain. *Aphasiology, 26*, 1082–1110.

Flöel, A., Rosser, N., Michka, O., Knecht, S., & Breitenstein, C. (2008). Noninvasive brain stimulation improves language learning. *Journal of Cognitive Neuroscience, 20*, 1415–1422.

Freitas, C., Mondragón-Llorca, H., & Pascual-Leone, A. (2011). Noninvasive brain stimulation in Alzheimer’s disease: Systematic review and perspectives for the future. *Experimental Gerontology, 46*, 611–627.

Fridriksson, J., Richardson, J. D., Baker, J. M., & Rorden, C. (2011). Transcranial direct current stimulation improves naming reaction time in fluent aphasia: A double-blind, sham-controlled study. *Stroke, 42*, 819–821.

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: Potential implications for motor learning. *Neuron, 66*, 198–204.

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology, 117*, 845–850.

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., ... Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology, 76*, 1006–1014.

Graham, K. S., Patterson, K., Pratt, K. H., & Hodges, J. R. (1999). Relearning and subsequent forgetting of semantic category exemplars in a case of semantic dementia. *Neuropsychology, 13*, 359–380.

Hamilton, R. H., Chrysikou, E. G., & Coslett, B. (2011). Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. *Brain and Language, 118*, 40–50.

Hansen, N. (2012). Action mechanisms of transcranial direct current stimulation in Alzheimer’s disease and memory loss. *Frontiers in Psychiatry, 3*, 48.

Hastie, T., Tibshirani, R., & Friedman, J. (2008). *The elements of statistical learning* (Chapter 7.10). Springer series in statistics. New York, NY: Springer.

Henry, M. L., Bee Jon, P. M., & Rapcsak, S. Z. (2008). Treatment for anoma in semantic dementia. *Seminars in Speech and Language, 29*, 60–70.

Henry, M. L., Meese, M. V., Truong, S., Babiak, M. C., Miller, B. L., & Gorno-Tempini, M. L. (2013). Treatment for apraxia of speech in nonfluent variant of primary progressive aphasia. *Behavioral Neurology, 26*, 77–88.

Hillis, A. E. (1992). Facilitating written production. *Clinical Communication Disorders, 2*, 19–33.

Hillis, A. E., & Caramazza, A. (1987). Model-driven remediation of dysgraphia. In R. H. Brookshire (Ed.), *Clinical Aphasiology Conference 1987* (pp. 84–105). Minneapolis, MN: BRK Publishers.

Hillis-Trupe, A. (1986). No effect of DC brain polarization on verbal fluency in patients with advanced frontotemporal dementia. *Clinical Neurophysiology, 118*, 1417–1418.

Homan, R. W. (1987). The 10-20 electrode system and cerebral location. *American Journal of EEG Technology, 28*, 269–279.

Huey, E. D., Probascio, J. C., Moll, J., Stocking, J., Ko, M. H., Grafman, J., & Wassermann, E. M. (2007). No effect of DC brain polarization on verbal fluency in patients with advanced frontotemporal dementia. *Clinical Neurophysiology, 118*, 1417–1418.

Jokel, R., & Anderson, N. D. (2012). Quest for the best: Effects of errorless and active encoding on word re-learning in semantic dementia. *Neuropsychological Rehabilitation, 22*, 187–214.

Jokel, R., Rochon, E., & Anderson, N. D. (2010). Errorless learning of computer-generated words in a patient with semantic dementia. *Neuropsychological Rehabilitation, 20*, 16–41.
Jokel, R., Rochon, E., & Leonard, C. (2006). Treating anoma in semantic dementia: Improvement, maintenance, or both? *Neuropsychological Rehabilitation, 16*, 241–256.

Jones, B., & Kenward, M. G. (2003). *Design and analysis of cross-over trials. Monographs on statistics and applied probability.* London: Chapman & Hall/CRC Press.

Kertesz, A. (1982). *The western aphasia battery.* New York, NY: Grune & Stratton.

Lambon Ralph, M. A., Cipolotti, L., Manes, F., & Patterson, K. (2010). Taking both sides: Do unilateral anterior temporal lobe lesions disrupt semantic memory? *Brain, 133*, 3243–3255.

Liang, K. Y., & Zeger, S. L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika, 73*, 13–22.

Marangolo, P., Marinelli, C. V., Bonifazi, S., Fiori, V., Ceravolo, M. G., Provinciali, L., & Tomaiuolo, F. (2011). Electrical stimulation over the left inferior frontal gyrus (IFG) determines long-term effects in the recovery of speech apraxia in three chronic aphasics. *Behavioural Brain Research, 225*, 498–504.

Marcotte, K., & Ansaldo, A. I. (2010). The neural correlates of semantic feature analysis in chronic aphasia: Discordant patterns according to the etiology. *Seminars in Speech and Language, 31*, 52–63.

McNeil, M., Small, S., Masterson, R. J., & Fossett, T. (1995). Behavioural and pharmacological treatment of lexical-semantic deficits in a single patient with primary progressive aphasia. *American Journal of Speech-Language Pathology, 4*, 76–87.

Medina, J., Norise, C., Faseyitan, O., Coslett, H. B., Turkeltaub, P. E., & Hamilton, R. H. (2012). Finding the right words: Transcranial magnetic stimulation improves discourse productivity in non-fluent aphasia after stroke. *Aphasiology, 26*, 1153–1168.

Mesulam, M. M. (2001). Primary progressive aphasia. *Annals of Neurology, 49*, 425–432.

Mesulam, M. M. (2008). Primary progressive aphasia pathology. *Annals of Neurology, 63*, 124–125.

Monti, A., Cogiamanian, F., Marcellia, S., Ferrucci, R., Mameli, F., Mrakic-Sposta, S., … Priori, A. (2008). Improved naming after transcranial direct current stimulation in aphasia. *Journal of Neurology, Neurosurgery and Psychiatry, 79*, 451–453.

Nardone, R., Bergmann, J., Christova, M., Caleri, F., Tezzon, F., Ladurner, G., … Golaszewski, S. (2012). Effect of transcranial brain stimulation for the treatment of alzheimer disease: A review. *International Journal of Alzheimer’s Disease, 2012*, 687909.

Newhart, M., Davis, C., Kannan, V., Heidler-Gary, J., Cloutman, L., & Hillis, A. E. (2009). Therapy for naming deficits in two variants of primary progressive aphasia. *Aphasiology, 23*, 823–834.

Patterson, K., Nestor, P. J., & Rogers, T. T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience, 8*, 976–987.

Philippose, L. E., Gottesman, R. F., Newhart, M., Kleinman, J. T., Herskovits, E. H., Pawlak, M. A., … Hillis, A. E. (2007). Neural regions essential for reading and spelling of words and pseudowords. *Annals of Neurology, 62*, 481–492.

Planton, S., Jucla, M., Roux, F. E., & Demonet, J. F. (2013). The “handwriting brain”: A meta-analysis of neuroimaging studies of motor versus orthographic processes. *Cortex, 49*, 2772–2787.

Purcell, J. J., Turkeltaub, P. E., Eden, G. F., & Rapp, B. (2011). Examining the central and peripheral processes of written word production through meta-analysis. *Frontiers in Psychology, 2*, 239.

Rapcsak, S. Z., Beeson, P. M., Henry, M. L., Leyden, A., Kim, E., Rising, K., … Cho, H. (2009). Phonological dyslexia and dysgraphia: Cognitive mechanisms and neural substrates. *Cortex, 45*, 575–591.

Rapp, B., & Caramazza, A. (1997). From graphemes to abstract letter shapes: Levels of representation in written spelling. *Journal of Experimental Psychology: Human Perception and Performance, 23*, 1130–1152.

Rapp, B., & Gluurof, B. (2009). The benefits and protective effects of behavioural treatment for dysgraphia in a case of primary progressive aphasia. *Aphasiology, 23*, 236–265.

Schneider, S., Thompson, C., & Luring, B. (1996). Effects of verbal plus gestural matrix training on sentence production in a patient with primary progressive aphasia. *Aphasiology, 10*, 297–317.

Schwartz, M. F., Kimberg, D. Y., Walker, G. M., Faseyitan, O., Brecher, A., Dell, G. S., & Coslett, H. B. (2009). Anterior temporal involvement in semantic word retrieval: Voxel-based lesion-symptom mapping evidence from aphasia. *Brain, 132*, 3411–3427.

Sepelyak, K., Crinion, J., Molitoris, J., Epstein-Peterson, Z., Bann, M., Davis, C., … Hillis, A. E. (2011). Patterns of breakdown in spelling in primary progressive aphasia. *Cortex, 47*, 342–352.

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist, 17*, 37–53.
Trebbastoni, A., Raccah, R., de Lena, C., Zangen, A., & Inghilleri, M. (2013). Repetitive deep transcranial magnetic stimulation improves verbal fluency and written language in a patient with primary progressive aphasia-logopenic variant (LPPA). *Brain Stimulation, 6*, 545–553.

Tsapkini, K., Frangakis, C. E., & Hillis, A. E. (2011). The function of the left anterior temporal pole: Evidence from acute stroke and infarct volume. *Brain, 134*, 3094–3105.

Tsapkini, K., & Hillis, A. E. (2013). Spelling intervention in post-stroke aphasia and primary progressive aphasia. *Behavioural Neurology, 26*, 55–66.

Tsapkini, K., & Hillis, A. E. (2014). The cognitive neuroscience of written language: The neural substrates of reading and writing. In K. Ochsner & S. M. Kosslyn (Eds.), *The Oxford handbook of cognitive Neurosciences: Volume 1: Core topics*. New York, NY: Oxford University Press.

Wassermann, E. M., & Grafman, J. (2005). Recharging cognition with DC brain polarization. *Trends in Cognitive Sciences, 9*, 503–505.