Transcranial Direct Current Stimulation in Neurodegenerative Disorders

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Abstract: Cortical excitability modulation and neuroplasticity are considered essential mechanisms for improving clinical and cognitive abilities in neurodegenerative disorders (NDDs). In such context, transcranial direct current stimulation (tDCS) shows great promise for facilitating remodeling of neurosynaptic organization. The aim of this review was to provide an overview of how tDCS is currently used as a neurorehabilitation strategy in some NDDs. We describe results from studies in which tDCS was applied in mild cognitive impairment, Alzheimer's disease, and primary progressive aphasia. Currently, findings related to the ability of tDCS to restore cognitive dysfunctions and behavioral impairments in these NDDs do not seem to support the notion that tDCS shows clear therapeutic efficacy in patients with mild cognitive impairment, Alzheimer disease, and primary progressive aphasia. This is probably because tDCS research in this area is still in its early stages. Methodological concerns, such as differences in tDCS parameters (eg, intensity or duration), target sites, and study design (eg, the relationship between tDCS and the rehabilitation strategy), or the use of underpowered sample sizes may also contribute to these outcomes. Nevertheless, it is important to note that almost no studies have evaluated how the underlying neurophysiological state of patients should guide the application of tDCS. These results should not prevent the use of tDCS in these NDDs, but they should trigger a deeper evaluation of how tDCS should be used. Transcranial direct current stimulation cannot be considered a neurorehabilitation apparatus by itself but should be instead viewed as a method for weakly modulating existing brain excitability. Future studies should aim to improve our understanding of the neurophysiological mechanisms that underlie the clinical effects of tDCS with the final goal of designing and performing individualized stimulation protocols that can be tailored for each NDD patient and combined with other appropriate neurorehabilitation strategies.

Key Words: Alzheimer, aphasia, dementia, MCI, NDD, neuromodulation, tDCS

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Neurodegenerative disorders (NDDs) represent a complex set of syndromes characterized by several progressive clinical and behavioral dysfunctions. The principal goal of rehabilitation in NDDs is slowing progressive cognitive decline and behavioral impairment and preserving brain functions. The efficacies of pharmacological and other types of treatment (eg, behavioral and cognitive) are often governed by different factors and are not always controllable or manageable. The choice of initial medication is sometimes largely dependent on the incidence of adverse effects.

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Therefore, approaches that are not focused on a specific cortical target or functional system and based on a clear rationale often have limited applicability and efficacy.

In the neurorehabilitation field, cortical excitability modulation and neuroplasticity modification have recently become important mechanisms upon which clinicians rely to improve clinical and cognitive functions. Noninvasive brain stimulation (NIBS) techniques have shown great potential in this field. The principle goal of applying NIBS in neurorehabilitation is to modulate cortical activity/excitability in a given area that subserves a given function in order to facilitate (or suppress) the activity of that area and the areas with which it is interconnected.

Noninvasive brain stimulation should ease the connectivity of a network and thereby enhance a given behavioral or cognitive function produced by that area/network. In this regard, in recent years, a specific NIBS technique that has attracted a great deal of public interest is transcranial direct current stimulation (tDCS). At a general level, tDCS modulates neuronal excitability in a polarity-specific manner by delivering prolonged (10–20 minutes) but weak (1–2 mA) currents to brain tissues via 2 or more electrodes placed on the scalp.[1,2] More specifically, anodal tDCS depolarizes the neuron's resting membrane potential and thereby enhances the rate of spontaneous neuronal firing and increases cortical excitability, whereas cathodal tDCS conversely decreases cortical excitability by shifting resting membrane potential toward hyperpolarization, reducing the neuronal firing rate.[1]

The polarity-dependent changes in cortical excitability observed during tDCS extend beyond the stimulation period. This prompted us to hypothesize that neuroplasticity mechanisms (eg, NMDA-dependent processes) similar to those underlying short- and long-term potentiation and depression may be involved in the effects of tDCS.[3,4]

Evidence has shown that the duration of tDCS after-effects is longer than the stimulation period[5] and that the benefits induced by tDCS may be increased by cumulative applications. Several studies in the neurorehabilitative field have investigated behavioral and cognitive outcomes after repeated tDCS sessions.[6,7] From a neurophysiological point of view, as anticipated, a hypothesis regarding the application of this technique for neurorehabilitative purposes could be founded on the ability of tDCS to modify cortical plasticity by modulating a specific neural network to consequently improve cognitive functions in the stimulated network(s) in a sustained manner. However, efforts to counteract the functional impairments that characterize NDDs must necessarily consider the level of gradually progressive degradation in efficiency and activity that the network(s) have experienced. In this way, rehabilitation can be individualized to the patient's cortical activation patterns and related levels of behavioral and cognitive impairment.

Currently, the application of tDCS in some NDDs, including mild cognitive impairment (MCI), Alzheimer disease (AD), and primary progressive aphasia (PPA), has produced variable levels of clinical improvement. These results have probably been limited by the small sizes of the included sample populations and other methodological problems.[8] Moreover, reviews published on the therapeutic use of tDCS have overestimated the statistical effects

observed in experimental studies, which have often not supported the significance of applying tDCS in clinical trials.

Our principal aim in writing this review was to provide an overview of the current evidence regarding the application of tDCS to ameliorate cognitive functions in MCI, AD, and PPA. Our goals are to present both the strengths and the weaknesses of previous studies and suggest future directions for using tDCS to counteract neurodegenerative processes.

METHODS

A literature search was conducted using the PubMed online database. We then evaluated all published research articles in which tDCS was applied in patients with MCI, AD, and PPA. The following keywords were used: *mild cognitive impairment* AND *tDCS* or *transcranial direct current*; *Alzheimer disease* AND *tDCS* or *transcranial direct current*; and *aphasia* or *primary progressive aphasia* AND *tDCS* or *transcranial direct current*. The abstracts and full texts of the articles were reviewed to eliminate articles that met the following exclusion criteria: (1) review articles and (2) articles that did not include patients with a diagnosis of MCI or AD or PPA. In all, 22 articles met our inclusion criteria, including 3 articles on MCI, 11 articles on AD, and 8 articles on PPA.

### Mild Cognitive Impairment and Alzheimer's Disease

Alzheimer disease is a progressive NDD that is clinically characterized by gradual worsening in memory and other cognitive domains, such as attention, perceptual-spatial abilities, language, and executive functions. From a neuropathological point of view, these cognitive impairments arise from abnormalities in brain regions characterized by the presence of amyloid-b plaques and tau-related neurofibrillary tangles. The appearance of plaques and tangles has been associated with local synaptic disruption,

which leads to regional brain structural abnormalities and changes in the functional connectivity between anatomically distinct brain regions, cortical circuitries, and neuronal pools.[9,10] Within this framework, synaptic dysfunction has been presented as a persuasive hypothesis to explain AD pathogenesis and progression by providing a neurophysiological correlate for the cognitive decline that begins in the early stages of the disease.[11] During this period, although there is a time window during which the brain's anatomy is preserved, synaptic dysfunction has already begun to affect neural networks and will eventually lead to the typical neurodegenerative processes observed in AD.[12] Therefore, AD should be viewed as a biological and clinical continuum that advances from preclinical (ie, MCI) to clinical AD phases.[13]

In the last few decades, intensive effort has been made to develop pharmacological and nonpharmacological interventions that can counteract AD progression during the early stages following its onset. On the one hand, pharmacological treatments have been associated with significant adverse effects and have not been shown to induce changes in the plasticity of specific neural networks; on the other hand, tDCS has achieved some success as a neuromodulatory approach to counteracting the local neurodegenerative processes observed in AD. The principal purpose of applying tDCS in MCI and AD patients is to modulate cortical excitability to thereby induce neuroplasticity and enhance performance in patients with impaired cognitive functions.[14] Studies have explored the effects of applying tDCS in several areas, as shown in Figure 1.

tDCS in Mild Cognitive Impairment

First, we will explore studies that investigated the tDCS-induced changes in MCI because the greatest long-lasting clinical benefits are achieved when treatments are implemented in the early stages of the NDD continuum (ie, the cognitive state intermediate between
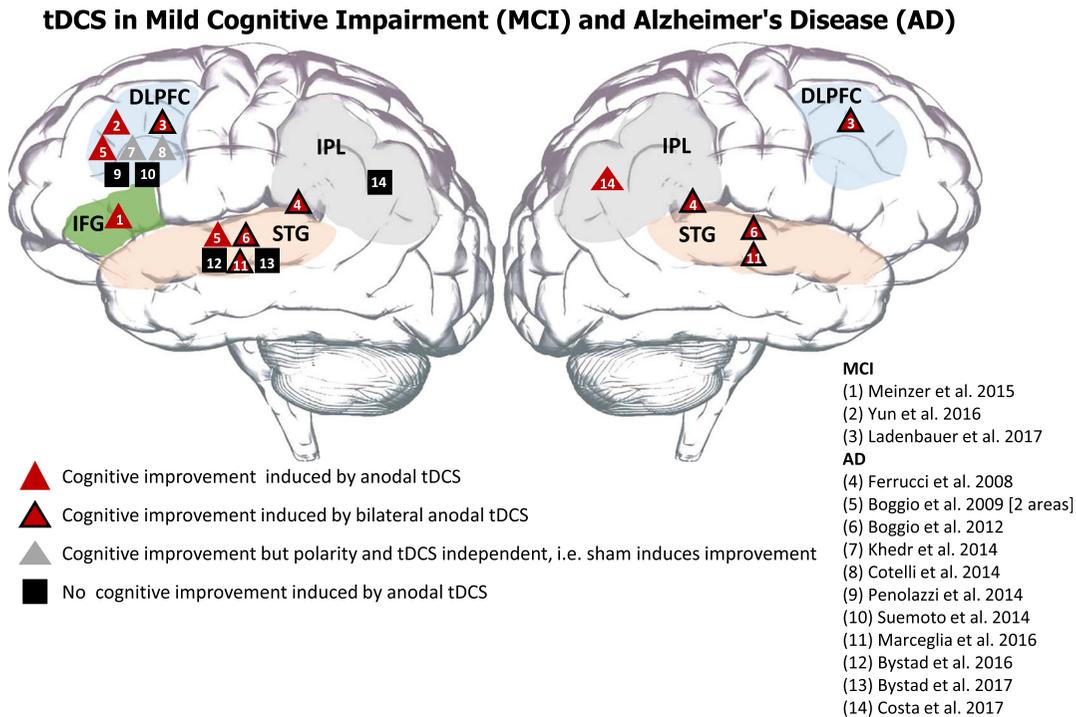
FIGURE 1. Overview of the main results of tDCS studies performed in MCI and AD patients. Lateral views of the left and right hemispheres are shown for each reviewed study, and the stimulated cortical targets are highlighted in different colors. IFG indicates inferior frontal gyrus; IPL, inferior parietal lobule; STG, superior temporal gyrus.

normal ageing and very early AD).[15,16] Details about the relevant stimulation protocols are shown in Table 1.

To assess the impact of tDCS on cognition and brain activity in MCI, Meinzer et al[17] designed a functional magnetic resonance imaging (fMRI) study in which anodal tDCS and sham tDCS were delivered over the left inferior frontal cortex while the patient performed a semantic word-retrieval task or while he/she was in a resting state. Both amnestic and multiple domain MCI patients with memory complaints were recruited and compared with age-matched control subjects. During anodal tDCS, performance improved, reaching the level observed in the control subjects. These results were accompanied by a decrease in task-related prefrontal hyperactivity and the normalization of abnormal network configurations on resting-state fMRI. In contrast, in the sham tDCS group, bilateral prefrontal hyperactivity was associated with impaired performance in the semantic word-retrieval task in MCI patients but not in the control subjects. A parallel assessment of cognitive performance and neural mechanisms provided added value to this study and supported a strong rationale for exploring whether repeated stimulation sessions induce long-lasting beneficial effects on cognition in MCI.

Yun et al[18] investigated whether the regular and relatively long-term use of tDCS affects regional cerebral metabolism and enhances cognitive performance in MCI. Two groups (anodal and sham) received tDCS sessions. Cognitive tests were then performed, and positron emission tomography images were collected both before and after tDCS treatment. Transcranial direct current stimulation was applied over the left dorsolateral prefrontal cortex (DLPFC). The results showed that the anodal tDCS group had significantly improved memory. Moreover, although no significant results emerged from the analysis of interactions between time (pre- and post-tDCS) and groups (anodal and sham), the data indicated that regular and frequent stimulation (anodal vs sham tDCS) increased metabolic activity in specific brain areas, especially the medial prefrontal cortex, precuneus, midtemporal regions, and anterior cingulate cortices.

Recently, a specific tDCS approach was introduced to enhance memory consolidation in MCI. The authors started from the hypothesis that the cortical slow oscillations observed in sleep (and their functional coupling) play an active role in the long-term consolidation of memories, Ladenbauer et al[19] applied slow oscillatory tDCS (so-tDCS) bilaterally over the prefrontal cortices in MCI patients. Slow oscillatory tDCS was delivered during an afternoon nap starting a few minutes after the patients had entered stable non–rapid eye movement sleep. Changes in performance were then evaluated after so-tDCS using visuospatial and verbal memory tasks and a procedural task. In addition, the impact of so-tDCS on relevant electroencephalography (EEG)–derived sleep characteristics was also measured. The main finding of the study was that so-tDCS significantly increased slow oscillations overall in addition to spindle power and led to stronger synchronization between slow oscillations and fast spindle power fluctuations. In addition, visual declarative memory was better in the so-tDCS group than in the sham stimulation group.

tDCS in Alzheimer's Disease

The first study in which tDCS was used as a therapeutic intervention in AD[20] sought to evaluate the cognitive effects of a single tDCS session. In that study, the authors applied anodal, cathodal, or sham tDCS bilaterally over the temporoparietal areas in mild AD patients. They then assessed recognition memory and visual attention. Transcranial direct current stimulation induced task-specific and polarity-dependent improvements, with anodal tDCS increasing and cathodal tDCS decreasing the accuracy of

TABLE 1. Transcranial Direct Current Stimulation Study Designs, Stimulation Parameters, and Evaluated Outcomes for MCI

MCI	Patients	Study Design	Stimulation Protocol	Stimulation and Reference Sites	Intensity and Duration	Timing of Evaluation	Primary and Secondary Outcomes
Meinzer et al[17] (2015)	11 amnestic MCI, 7 multiple domain MCI, 18 age-matched controls	Within subjects, sham controlled	1 Session of anodal/sham tDCS, during semantic word-retrieval task and resting-state fMRI	(1) Left ventral inferior frontal gyrus (5 × 7 cm); (2) right supraorbital region (10 × 10 cm)	1 mA, 20 min, single session	Online during task-related and resting-state fMRI	(1) semantic word-retrieval function; (2) task-related brain activity modulations and performance-independent resting-state fMRI
Yun et al[18] (2016)	16 MCI	Between subject	9 Sessions of anodal/sham tDCS (3 times per week for 3 wk)	(1) Left DLPFC (5 × 5 cm); (2) right DLPFC (5 × 5 cm)	2 mA, 30 min daily	Before and after treatment	(1) Cognitive and behavioral functions; (2) metabolic activity with PET scan
Ladenbauer et al[19] (2017)	16 MCI	Within subject, crossover	1 Session of anodal/sham so-tDCS (0.75 Hz), during sleep of afternoon nap	(1) Bilateral DLPFCs (8 mm diameter); (2) bilateral mastoid (not reported)	0.522 mA, 3–5 blocks of 5 min with interblock intervals of 1 min 40 s	Before and after so-tDCS	(1) Visuospatial, verbal memory and procedural functions; (2) EEG-derived sleep characteristics

word recognition memory tasks. There were no effects on a visual attention task, suggesting that the effects induced by tDCS were specific to recognition memory.

Later, Boggio et al[21] sought to evaluate the impact of tDCS on recognition memory, working memory, and selective attention in AD patients. They applied anodal tDCS to 2 areas, the left DLPFC and the left temporal cortex, and compared the resulting data with those obtained in a sham group. Applying tDCS to either location enhanced performance on a visual recognition memory task over that achieved in the sham group. In addition, the authors found that the effects of tDCS were limited to a single task and that tDCS produced no significant effect on working memory or selective attention.

To investigate the hypothesis that daily application of tDCS might improve memory performance in the longer term, Boggio et al[22] next evaluated the effects of multiple tDCS sessions. In their study, they applied anodal tDCS bilaterally over the temporal region for 5 consecutive sessions in a group of AD patients. The results indicated an improvement of performance on a visual recognition memory task and that this effect persisted for up to 4 weeks after the end of the last session. However, this improvement was only weakly significant as compared with baseline.

The long-term efficacy of tDCS treatment was also investigated by Khedr et al.[23] In their study, patients with mild to moderate AD were randomly divided into 3 groups in which the patients received 10 sessions of anodal, cathodal, or sham tDCS applied over the left DLPFC. To assess the resulting changes in cognitive functions, a clinical evaluation was performed at the end of the treatment period and at 1 and 2 months after treatment ended. In addition, neurophysiological measures (ie, motor cortical excitability and the P300 event-related potential) were collected before and after treatment to determine how tDCS modulated cortical activity and to evaluate the spread of its effects to cortical areas distant from the stimulation site. The main finding of this study was that regardless of which tDCS polarity was applied repeated sessions improved cognitive functions and reduced P300 latency, which is pathologically increased in AD.

Cotelli et al[24] observed general tDCS polarity-independent improvement in a face-name association memory task. In their study, the authors tested whether applying anodal or sham tDCS treatment to the left DLPFC for 2 weeks in combination with an individualized computerized memory training task resulted in memory improvements over those observed in a group treated with anodal tDCS combined with a motor training task. To assess the persistence of this effect, neuropsychological and experimental assessments were performed before and at 2 weeks and 3 and 6 months after the start of treatment. Although the results indicated a beneficial effect on individualized memory rehabilitation in AD patients, anodal tDCS did not appear to exert any additional short- or long-lasting effects on memory performance.

In agreement with these findings, Penolazzi et al[25] reported a single case study in which applying anodal tDCS over the left DLPFC, before a computerized task was performed, did not exert a significant effect on mnestic or executive functions. The only observed impact of anodal treatment was a long-lasting stabilizing effect on the patient's global cognitive functions.

In the study of Suemoto et al,[26] patients with moderate AD were randomly assigned to receive 6 sessions of anodal or sham tDCS over the left DLPFC. Repeated anodal tDCS did not induce changes in apathy, the primary outcome, or global cognition and neuropsychiatric symptoms, which were secondary outcomes. Cognitive impairment severity, tDCS dosage, and cortical target were identified as possible reasons for a lack of positive findings.

More recently, based on evidence showing that AD is characterized by impaired cortical patterns as reflected by EEG activity,

Marceglia et al[27] investigated tDCS-induced behavioral and neurophysiological effects. Anodal tDCS and sham tDCS were delivered over the bilateral temporoparietal areas of AD patients during 2 separate sessions. Performance on a word recognition task, EEG recordings, and blood samples were evaluated before and after each tDCS session. Cortical EEG activity was significantly modulated in the AD patients treated with anodal tDCS. Specifically, there was an increase in high-frequency power in the temporoparietal area and an increase in coherence among the temporoparieto-occipital areas associated with improvement on a word recognition task. Moreover, the increase in high-frequency power observed after anodal tDCS was correlated with an increase in plasma levels of nitrites and nitrates. These findings suggested that the modulation of neuronal cortical activity is likely one of the neurophysiological mechanisms underlying the improvement in performance induced by anodal tDCS and indicate that this improvement may be related to an increase in brain perfusion.

Recently, Bystad et al[28,29] conducted 2 separate studies to assess the efficacy of applying tDCS over the left temporal cortex. In the first study, 2 groups of AD patients received anodal or sham tDCS in a total of 6 sessions. Verbal memory functions and general cognitive abilities were not significantly better in the anodal tDCS group than in the sham stimulation group. In their second study, the same protocol was applied, but at home daily and for 8 consecutive months in an early-onset AD patient. Neuropsychological assessments were conducted before and at 5 and 8 months after the first tDCS session. At the end of treatment, performance in immediate and delayed recall was improved over the results of the baseline evaluation. The authors of this study suggested that the patient's cognitive functions had stabilized, prompting us to hypothesize that tDCS may slow the cognitive decline observed in AD.

Finally, a further single case study[30] was performed to evaluate whether applying anodal tDCS over the left angular and supramarginal gyri (Brodmann areas 39 and 40) would promote the recovery of linguistic functions (ie, comprehension and naming). The experiment was composed of 2 phases. First, 3 single sessions of tDCS were applied over the right hemisphere between P6 and CP6 or over the left hemisphere between P5 and CP5. A sham stimulation condition served as the control. The goal was to identify which site stimulation produced the most effective clinical improvement. The authors first observed that verb comprehension was significantly improved after anodal tDCS was applied over the right parietal cortex. Based on this finding, they then delivered a 5-day sham or anodal tDCS treatment over the right Brodmann areas 39 and 40 (between P6 and CP6), while the patient performed a language task. Performance in naming and auditory comprehension of nouns and verbs was measured before and immediately and 14 days after the end of treatment. Short- and long-lasting improvements in performance on the auditory comprehension task were observed in the anodal tDCS treatment group over the results obtained at baseline and in the sham group, whereas performance in the naming and nouns comprehension task remained unchanged. The importance of this study was that it adopted a specific strategy for identifying (ie, with a preliminary single session of stimulation) which cortical target was the ideal target for stimulation in the rehabilitative trial.

Mild Cognitive Impairment and Alzheimer's Disease Summary

The results described in the previous section make it clear that the approaches used thus far are rather heterogeneous and cannot be easily summarized. Regarding the evaluation of tDCS-induced improvements in MCI, only 3 studies that included a total of

50 patients have been performed. Of these, 2 studies applied tDCS in a single session, whereas one describes a trial consisting of repeated tDCS sessions. All 3 studies produced positive results, although the tDCS protocols applied are not comparable in terms of intensity, time, and site of stimulation. Regarding AD, 180 patients have been tested in 11 studies. In 3 of these studies, a single tDCS session was applied; in 7 studies, the tDCS trial included repeated stimulation sessions, and 1 study included a first experiment in which a single session was applied that was followed by a second tDCS trial. Of these 11 studies, 6 produced positive results (2 were single case studies), and 5 reported negative results after repeated tDCS sessions (these studies included most of the tested population, ie, 135 patients). A comprehensive view of these results is shown in Figure 1.

We conclude that although the findings reported in the MCI and AD studies reviewed here may appear promising, there is currently no clear evidence suggesting that tDCS has shown clinical efficacy as a neurorehabilitative tool in the preclinical and clinical phases of AD. In MCI patients, the lack of longitudinal assessments aimed at evaluating the long-lasting clinical improvements induced by tDCS prevents us from clearly supporting the hypothesis that this type of stimulation may actually delay the progression of AD pathology. Moreover, differences in tDCS protocols, in terms of the number of sessions or days of treatment, make any comparison between current treatments and their results truly difficult. However, although the studies available in the literature suffer from an inadequate sample size, short treatment duration, few follow-up assessments, and inaccurate anatomical targeting of electrode positioning, some methodological approaches can be positively highlighted. For example, applying both anodal and cathodal stimulation in addition to a sham procedure allows us to test which tDCS polarity is more efficacious and to consider the well-established hypothesis regarding the characteristic cortex hyperexcitability of AD patients.

Primary Progressive Aphasia

Primary progressive aphasia is defined, from a clinical point of view, as a prominent and selective NDD of language. It has an insidious onset and manifests as a gradually progressive and persistent impairment in language production, object naming, syntax, or word comprehension.[31,32] From a pathophysiological point of view, PPA is considered a cortical degenerative syndrome that affects the activity of specific language networks.

Diagnosing NDD is clinical evidence based and imaging supported and is often complicated by the presence of different variants (ie, logopenic, nonfluent/agrammatic, and semantic variants), each of which manifests as specific linguistic features and patterns of brain atrophy.[32] More specifically, logopenic variant PPA is clinically characterized by impaired single-word retrieval in spontaneous speech and naming, damaged repetition of sentences and phrases, and atrophy localized in the left posterior-superior temporal and inferior parietal regions; nonfluent/agrammatic variant PPA is characterized by poor grammatical comprehension and expression with atrophy in the left posterior frontal and insular regions; and semantic variant PPA presents as impaired semantic knowledge and single-word comprehension with focal left anterior temporal lobe atrophy. Therefore, because the PPA variants are anatomically heterogeneous, it is very important to obtain a specific clinical classification before performing any neurorehabilitative intervention not only to operate on symptoms and disease progression but also because clinical classification defines the neural networks (systems) that should be modulated.[32]

Preliminary findings regarding the application of tDCS in PPA were provided in a case report study by Wang et al.[33] In a patient with nonfluent variant PPA, anodal tDCS was delivered over the left posterior perisylvian region in the morning and the left Broca area in the afternoon for 5 days. The patient showed improvements in picture naming, auditory word comprehension, oral word reading, and word repetition over the results observed in a previous sham intervention. Although this study was lacking in several methodological aspects, its results suggested that tDCS could potentially be used as a tool to improve language performance in patients with PPA. Details on the stimulation protocols used in this study and the studies reported below are shown in Table 2.

To evaluate short- and long-term improvements in language deficits, Cotelli et al[34] applied tDCS over the left DLPFC in patients with agrammatic variant PPA. In this study, the authors administered a combined treatment consisting of anodal or sham tDCS during individualized and computerized anomia training. Cognitive assessments were performed at baseline, after 2 weeks of daily interventions, and at a 12-week follow-up. Transcranial direct current stimulation improved naming, regardless of the tDCS modality (ie, anodal or sham). In addition, anodal tDCS selectively increased naming accuracy and daily living language abilities when evaluated at a follow-up assessment. It was hypothesized that long-term rearrangements in synaptic connections within language networks were the mechanism underlying the clinical improvements observed after anodal tDCS was applied in combination with anomia training.

In a more recent study, the same research group[35] applied a similar protocol in the same agrammatic variant PPA patients. However, in this study, they measured the gray matter density of the left fusiform, left middle temporal, and right inferior temporal gyri before tDCS treatment. The results showed that higher regional gray matter density was strongly associated with a greater treatment response in naming performance, suggesting that applying tDCS as an intervention during the early stages of the disease might produce more successful results.

Following on these studies, Tsapkini et al[36] evaluated the efficacy and persistence of the effects of applying tDCS treatment in combination with a spelling intervention versus applying a spelling intervention alone. Patients with nonfluent/agrammatic variant PPA or logopenic variant PPA were treated with repeated sessions of anodal or sham tDCS applied over the left inferior frontal gyrus in combination with a spelling intervention and then evaluated for performance as well as other language and cognitive tasks at 2-week and 2-month follow-up intervals after each stimulation condition. Improvement was observed in spelling of the treated items in both the anodal and sham intervention groups, although only anodal tDCS combined with the spelling intervention produced consistent and significant improvement on untrained items. Finally, more long-lasting improvement was reported in the anodal tDCS plus spelling intervention group than in the sham plus spelling intervention group.

In contrast to previous studies in which non–language-specific cortical area (ie, frontal cortex) was targeted, Teichmann et al[37] assessed living/nonliving categories and verbal/visual modalities in a semantic matching task to determine the efficacies of 3 tDCS conditions that were applied over the temporal poles (anodal over the left temporal lobe, cathodal over the right temporal lobe, and sham over the left temporal lobe) in semantic PPA patients. Both left-anodal and right-cathodal tDCS improved semantic accuracy in the verbal modality, but only right-cathodal tDCS improved processing speed in living categories and accuracy and processing speed in the combined verbal/living condition. These results support the notion that tDCS is effective in generating intrasemantic effects that produce beneficial effects in semantic PPA variant patients. Moreover, the results of this study emphasize the importance of taking a target-structure-function approach.

TABLE 2. Transcranial Direct Current Stimulation Study Designs, Stimulation Parameters, and Evaluated Outcomes for AD

AD	Patients	Study Design	Stimulation Protocol	Stimulation and Reference Sites	Intensity and Duration	Timing of Evaluation	Primary and Secondary Outcomes
Ferrucci et al[20] (2008)	10 AD	Within subject	1 Session of anodal/cathodal/sham tDCS	(1) Bilateral temporoparietal areas; (2) right deltoid muscle	1.5 mA, 15 min, single session	Before and 30 min after tDCS	(1) Word recognition function; (2) performance in visual attention task
Boggio et al[21] (2008)	10 AD	Within subject	1 Session of anodal tDCS	(1) Left DLPFC and left temporal cortex (5 × 7 cm); (2) right supraorbital area (5 × 7 cm)	2 mA, 30 min, single session	during tDCS	(1) Visual recognition memory and working memory functions; (2) performance in selective attention task
Boggio et al[22] (2012)	15 AD	Within subject	5 Sessions of anodal/sham tDCS	(1) Bilateral temporal lobes (35 cm²); (2) right deltoid muscle (62 cm²)	2 mA, 30 min daily	Before and after treatment, and at 1- and 4-wk follow-up	(1) Cognitive, visual recognition and visual attention functions
Khedr et al[23] (2014)	34 AD	Between subject	10 Sessions of anodal/cathodal/sham	(1) Left DLPFC (24 cm²); (2) contralateral supraorbital region (100 cm²)	2 mA, 25 min daily	Before and after treatment and at 1- and 2-mo follow-up	(1) Psychometric assessments; (2) motor cortical excitability and the P300 event-related potential
Cotelli et al[34] (2014)	36 AD	Between subject	10 Sessions of anodal/sham during individualized memory training or during motor training	(1) Left DLPFC (5 × 5 cm); (2) right deltoid muscle (6 × 10 cm)	2 mA, 25 min daily	Before and after treatment and at 3 and 6 mo after the beginning of treatment	(1) Performance in face-name association task; (2) cognitive, neuropsychiatric and functional assessments
Penolazzi et al[25] (2014)	1 Probable AD	Within subject	10 Sessions of anodal/sham tDCS followed by computerized tasks	(1) Left DLPFC (5 × 7 cm); (2) right supraorbital area (10 × 10 cm)	2 mA, 20 min daily	Before a pretreatment phase, immediately after treatment phase, and after the posttreatment phase	(1) Word recognition, verbal working memory and phonemic fluency functions, and continuous performance tasks; (2) neuropsychological assessment
Suemoto et al[26] (2014)	40 AD	Sham controlled	6 Sessions of anodal/sham (during 2 wk)	(1) Left DLPFC (35 cm²); (2) right orbit	2 mA, 20 min daily	Before, at weeks 1 and 2, and after 1 wk without intervention	(1) Apathy; (2) global cognition and neuropsychiatric symptoms
Marceglia et al[27] (2016)	7 AD	Within subject	1 Session of anodal/cathodal tDCS	(1) Bilateral temporoparietal areas (25 cm²); (2) right deltoid muscle (64 cm²)	1.5 mA, 15 min, single session	Before and 30 min after tDCS	(1) Recognition memory function; (2) EEG measures and plasma levels of nitrite and nitrate
Bystad et al[28] (2016)	25 AD	Between subjects, sham controlled	6 Session of anodal/sham (during 10 d)	(1) Left temporal cortex (35 cm²); (2) right frontal lobe	2 mA, 30 min daily	Before and after treatment	(1) Verbal memory function; (2) cognitive impairment, visuoconstructive ability, executive function, general cognitive abilities, depressive symptoms, and progressive decline
Bystad et al[29] (2017)	1 Early-onset AD	Case study	8 mo of anodal tDCS	(1) Left temporal cortex; (2) right frontal lobe	2 mA, 30 min daily	Before, after 5 and 8 mo	(1) Cognitive functioning
Costa et al[30] (2017)	1 Possible AD	Within subjects, sham controlled	1 Session of anodal/sham tDCS (exp. 1); 5 sessions of anodal/sham tDCS during language task (exp. 2)	(1) Left, right angular, and supramarginal gyri (exp. 1); right parietal cortex (exp. 2); (2) contralateral frontopolar cortex	2 mA, 30 min, single session (exp. 1); 2 mA, 30 min daily (exp. 2)	Before and during tDCS sessions (exp.1); before, immediately after, and 14-d follow-up (exp. 2)	(2) Linguistic functions of comprehension and naming

With the goal of addressing the methodological gaps of previous studies (eg, a limited range of language abilities, circumscribed targets, or limited sets of linguistic abilities improved), Gervits et al[38] recruited a group of PPA patients with impairments in speech fluency (ie, in PPA patients with logopenic or nonfluent/agrammatic variant PPA) into a pilot study in which follow-up assessments were performed after treatment. The intervention consisted of 10 daily sessions of anodal tDCS during which the patients narrated wordless children's picture books. The decision to combine anodal stimulation with the narration of a story was based on the hypothesis that tDCS should reinforce brain networks that are already engaged in a cognitive task. Moreover, to ensure that tDCS was distributed throughout the language network and could modulate several language abilities, the anode was placed over the left frontotemporal region of the brain, whereas the cathode was placed over the left occipitoparietal region. Although very preliminary, the results of this study showed that there was significant improvement in speech production and grammatical comprehension and that this effect lasted for up to 3 months following anodal tDCS.

A reduced decline in naming ability in PPA was also recently reported in an ongoing longitudinal tDCS treatment study carried out by Hung et al.[39] A 10-day behavioral treatment (semantic feature analysis) paired with online anodal tDCS delivered over the left temporoparietal region was applied in PPA patients (4 diagnosed with a fluent variant of PPA, ie, semantic or logopenic variant PPA, and 1 individual with severe anomia associated with early-onset AD). Treatment produced clear gains that were evident immediately after anodal tDCS and were maintained at a 6-month follow-up, although the patients showed no evidence of generalization from trained to untrained items within semantic categories or improvements in offline standardized naming assessments. It is worth noting that the small cohort of recruited patients and the potential impact of individual differences mean that these findings should be interpreted with caution.

Finally, McConathey et al[40] demonstrated that the baseline severity of deficits may be an important factor in predicting which patients will respond positively to language-targeted tDCS therapy. In this study, anodal tDCS and sham tDCS were delivered using the same montage that was used by Gervits et al.[38] The experiment included 10 days of tDCS applied in patients with 2 different variants of PPA (nonfluent/agrammatic and logopenic variant PPA). The main finding was that baseline performance predicted anodal tDCS-mediated improvements in language, with tDCS-related improvements observed in global language performance, grammatical comprehension and semantic processing in patients who performed worse at baseline, and a slight anodal tDCS-related benefit observed in speech repetition metric in patients who performed better at baseline.

Primary Progressive Aphasia Summary

At the general level, the 8 studies reviewed here indicate that anodal tDCS is relatively clinically effective in PPA. These evaluations include 71 patients who were characterized by different variants of neurodegenerative aphasia. A representation of the results and the areas stimulated is shown in Figure 2. The critical point is that the very small total sample size included in these studies does not provide strong support for the reported findings. Although anodal tDCS could be a promising approach for slowing the rate of decline in language skills that characterizes PPA, some concerns should be taken into consideration. The progressive and natural time course of the language declines that characterize PPA syndrome means that any tDCS-induced effect should be viewed as only temporary. Moreover, the pathophysiological heterogeneity of the different PPA variants constrains the recruitment of wide patient cohorts to studies aimed at accurately validating the efficacy of this intervention. Finally, the variable rate of decline observed among patients should prompt us to create a more tailored neuromodulation approach, and baseline performance should be taken into account when predicting which patients will be responders to tDCS interventions. Currently, the lack of studies with large cohorts of patients representative of specific PPA variants makes all previous conclusions too preliminary (Table 3).

Concluding Remarks

The principal aim of this review was to evaluate the effectiveness of tDCS as a neurorehabilitation strategy for improving the clinical conditions of MCI, AD, and PPA patients. Although many
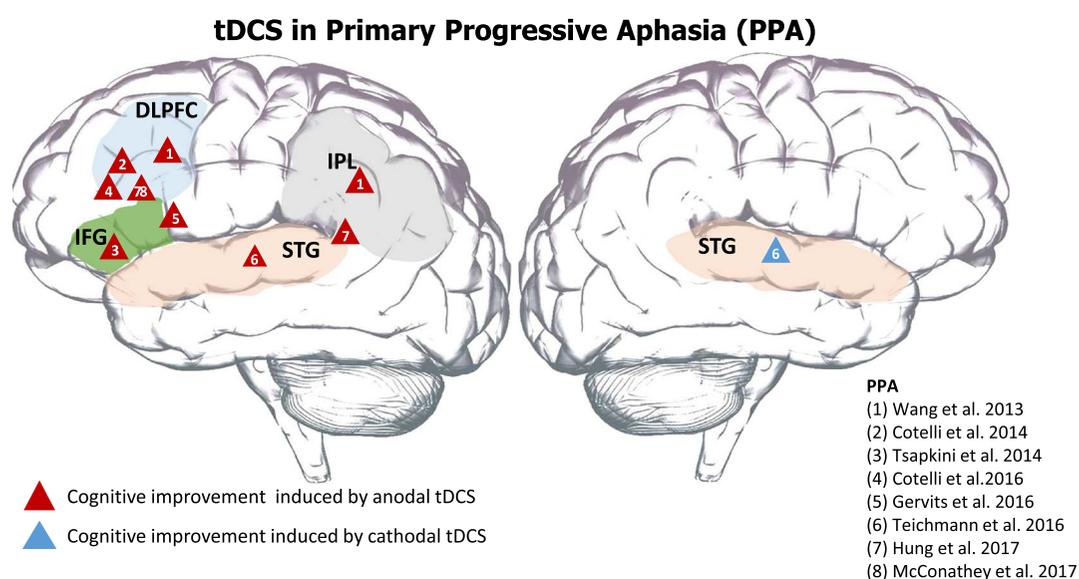
FIGURE 2. Overview of the main results of tDCS studies performed in PPA patients. Lateral views of the left and right hemispheres are shown for each reviewed study, and the stimulated cortical targets are highlighted in different colors. IFG indicates inferior frontal gyrus; IPL, inferior parietal lobule; STG, superior temporal gyrus.

TABLE 3. Transcranial Direct Current Stimulation Study Designs, Stimulation Parameters, and Evaluated Outcomes for PPA

PPA	Patients	Study Design	Stimulation Protocol	Stimulation and Reference site	Intensity and Duration	Timing of Evaluation	Primary and Secondary Outcomes
Wang et al[33] (2013)	1 nfvPPA	Crossover	5 Sessions of anodal/ sham tDCS	(1) Left posterior perisylvian and left Broca area (4.5 × 5.5 cm); (2) unaffected shoulder (4.5 × 5.5 cm)	1.2 mA, 20 min twice daily (morning and afternoon)	Before and after treatment	(1) Auditory word-picture identifications, picture naming, oral word reading and word repetition; (2) EEG nonlinear index of approximate entropy
Cotelli et al[34] (2014)	16 avPPA	Between subject	10 Sessions of anodal/ sham tDCS during individualized computerized anomia training	(1) Left DLPFC (5 × 5 cm); (2) right arm (6 × 10 cm)	2 mA, 25 min daily	Before and after treatment and at 12-wk follow-up	(1) Neuropsychological assessment: linguistic ability, naming and sentence comprehension; experimental naming assessment: treated and untreated stimuli; (2) functional communication scales
Tsapkini et al[36] (2014)	2 nfvPPA, 4 lvPPA	Within subject, crossover	15 Session of tDCS during spelling intervention	(1) Left inferior frontal gyrus (5.08 × 5.08 cm); (2) not reported	1–2 mA, 20 min daily	Before and after treatment, at 2-wk, and at 2-mo follow-up	(1) No. of correct phoneme-to-grapheme correspondences and no. of correctly spelled word prompts associated with each phoneme; (2) no. of words spelled correctly
Cotelli et al[35] (2016)	18 avPPA	Within subject	10 Sessions of anodal tDCS during individualized computerized anomia training	(1) Left DLPFC (5 × 5 cm); (2) right arm (6 × 10 cm)	2 mA, 25 min daily	Before and after treatment and at 3 mo following stimulation	(1) Standardized neuropsychological and naming assessments; (2) correlation between clinical changes, neuropsychological and behavioral tests, and gray matter density
Gervits et al[38] (2016)	4 lvPPA, 2 naPPA	Unblinded pilot study	10 Sessions of anodal tDCS during the narration of children's wordless picture stories	(1) Left frontotemporal region (5 × 5 cm); (2) left occipitoparietal region (5 × 5 cm)	1.5 mA, 20 min daily	Before, posttreatment and at 6- and 12-wk following stimulation	(1) Speech production, grammatical comprehension, repetition, semantic processing, and global performance
Teichmann et al[37] (2016)	12 svPPA	Sham controlled, Crossover	1 Session of anodal/ cathodal/sham tDCS during a simple visuomotor task	(1) Left or right temporal areas (25 cm²); (2) supraorbital region contralateral to active electrode	1.59 mA, 20 min, single session	Before and after tDCS	(1) Performance at a semantic matching task
Hung et al[39] (2017)	4 svPPA or lvPPA, 1 anomic early AD	Ongoing longitudinal treatment	10 Sessions of anodal tDCS paired with behavioral language therapy	(1) Left temporoparietal cortex (1 cm² rubber electrode placed within 5 cm² sponges); (2) over the center of forehead	1.5 mA, 20 min daily	Before and after treatment, with a 6-mo follow-up	(1) Naming accuracy for trained over untrained items
McConathey et al[40] (2017)	6 nfvPPA, 1 lvPPA	Crossover	10 Sessions of anodal/ sham tDCS during the narration of children's wordless picture stories	(1) Left prefrontal region (5 × 5 cm); (2) left occipital region	1.5 mA, 20 min daily	Before and after treatment and at 6 and 12 wk following stimulation	(1) Global performance, grammatical comprehension, semantic processing, and speech repetition

avPPA indicates agrammatic variant PPA; lvPPA, logopenic variant PPA; naPPA, nonfluent variant PPA; nfvPPA, nonfluent/agrammatic variant PPA; svPPA, semantic variant PPA.

experimental studies and clinical trials have been performed, efficacy of tDCS to restore cognitive dysfunctions and behavioral impairments has yet to be proven in MCI and AD patients, whereas some effectiveness has been achieved in PPA. In general, if there are benefits, they arise when specific combined treatments are applied in the early stage of the disease continuum. The weakness of the current results is probably due to several unsolved issues that should be evaluated with regard to the fact that tDCS only somewhat changes the general excitability of the brain by applying very weak currents.

There are already several critical reviews in this field. In these, methodological concerns, including heterogeneity in tDCS parameters, target sites, study designs and outcome measures, and underpowered sample sizes, have been reported with possible solutions and recommendations.[7,41–42] We should keep in mind that there is a multitude of determinants, such as cortical thinning, brain atrophy, white matter volume and integrity, genetic variants, age at disease onset, and cognitive reserve,[43] which can influence the magnitude and direction of the clinical effects of tDCS in each of the disorders discussed here. Moreover, the brain is subject to specific age-dependent changes in neuroplasticity[44–46] that make it arduous to plan and build an ideal tDCS protocol for all NDDs. In addition, the choice of whether to use an online, off-line, or alternative mixed (ie, tDCS before and during a task) approach should be supported by clearer assumptions about the mechanisms that are being modulated to obtain clinical and behavioral improvements.[8]

To date, a variety of studies have applied tDCS over different brain regions and assessed both cognitive and behavioral outcomes, but only a few studies have combined assessments of cognitive and behavioral improvements with evaluations of the underlying neurophysiological changes that are caused by tDCS.[17–19,27] Using these surrogate measures could allow us to assess clinical efficacy and obtain a better understanding and characterization of the neuronal mechanisms underlying the tDCS-induced changes. Future studies should be guided by an understanding of the neurophysiological mechanisms underpinning clinical tDCS-induced effects and should exploit the advantages of neuroimaging techniques with the final aim of designing and performing tailored stimulation protocols ad hoc for each NDD and each stage of the NDD's pathology. It might also be important to invest in combined neurophysiological recording to produce stimulation that is directly guided by online brain state activity.

The final remark of this review is that the results presented here should not prevent clinicians from using tDCS in MCI, AD, and PPA but should instead trigger a deeper discussion about when and how we should use tDCS because applying a simplistic, sliding-scale rationale (inhibition vs facilitation) does not always produce the desired results. In future studies, we should more accurately evaluate the activity of the stimulated area and bear in mind that tDCS is not a neurorehabilitation strategy; it should instead be viewed as a pedestal for modulating brain excitability. Therefore, tDCS should be used to facilitate the recruitment of brain networks "weakened" because of a decrease in synaptic efficacy and paired with a specific cognitive/behavioral rehabilitation protocol with the aim of maintaining the activity of specific brain networks and the ability of individuals to carry out functions associated with daily living.

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