Brain & Language 162 (2016) 35–41

Contents lists available at ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

Transcranial direct current stimulation for the treatment of primary progressive aphasia: An open-label pilot study

Felix Gervits [a,b], Sharon Ash [b,c], H. Branch Coslett [a,b], Katya Rascovsky [b,c], Murray Grossman [b,c], Roy Hamilton [a,b,*]

[a] Laboratory for Cognition and Neural Stimulation, Center for Cognitive Neuroscience, University of Pennsylvania, United States
[b] Department of Neurology, Perelman School of Medicine, University of Pennsylvania, United States
[c] Penn Frontotemporal Degeneration Center, University of Pennsylvania, United States

ARTICLE INFO

Article history:
Received 12 August 2015
Revised 18 April 2016
Accepted 15 May 2016

Keywords:
Primary progressive aphasia
Logopenic PPA
Progressive nonfluent aphasia
tDCS
Neurodegenerative disease
Frontotemporal lobar degeneration

ABSTRACT

Primary progressive aphasia (PPA) is a neurodegenerative condition characterized by gradual deterioration of language function. We investigated whether two weeks of daily transcranial direct current stimulation (tDCS) treatment would improve language abilities in six people with a non-fluent form of PPA. tDCS was applied in an unblinded trial at an intensity of 1.5 mA for 20 min/day over 10 days. At the time of stimulation, patients were engaged in narrating one of several children's wordless picture stories. A battery of neuropsychological assessments was administered four times: at baseline, immediately following the 2-week stimulation period, and then 6-weeks and 12-weeks following the end of stimulation. We observed improvement in linguistic performance in the domains of speech production and grammatical comprehension. Our encouraging results indicate that larger, sham-controlled studies of tDCS as a potential intervention for PPA are warranted.

1. Introduction

1.1. Background

Primary progressive aphasia (PPA) is a neurodegenerative condition characterized by a gradual, irreversible decline of language function (Mesulam, 2001). Linguistic deficits vary between patients, impacting functions such as fluency of conversational speech, single word comprehension, repetition and naming ability. The condition is comprised of three clinical variants: nonfluent/agrammatic, semantic and logopenic. Nonfluent/agrammatic variant PPA (naPPA) is characterized primarily by slowed speech production with grammatical simplifications and errors, and is associated with atrophy of regions of the left frontal lobe (Grossman, 2012). Semantic variant PPA (svPPA) is associated with atrophy of the left anterior and ventral temporal lobe, and produces difficulty with naming and word comprehension that relates to broader deficits in semantic processing (Hodges & Patterson, 2007). Finally, logopenic variant PPA (lvPPA) is marked by atrophy of the left temporal and parietal lobes, which manifests as word-retrieval deficits and difficulty with repetition (Gorno-Tempini et al., 2008). Autopsy studies demonstrate that most patients with PPA have pathologic changes consistent with frontotemporal lobar degeneration (FTLD); however, Alzheimer's Disease (particularly in lvPPA) and other pathologies have also been associated with this syndrome (Grossman, 2010). There are no known treatments for PPA. The relentless progression of PPA symptoms eventually leads to a profound impairment in communication ability and, ultimately, to more generalized deficits of cognition.

1.2. Neuromodulation in PPA patients

While there is no cure for PPA, a few reports have suggested that some symptomatic improvement can be achieved through the use of behavioral (Henry et al., 2013; Louis et al., 2001) and neuromodulatory (Finocchiaro et al., 2006; Trebbastoni, Raccah, de Lena, Zangen, & Inghilleri, 2013) interventions. The two most widely used methods of noninvasive neuromodulation are Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS). TMS is a form of noninvasive brain stimulation in which a magnetic coil is discharged over the skull to induce a brief current which depolarizes neuronal membranes, generating action potentials in neurons over the targeted area. Two small studies to date have explored whether TMS can be

* Corresponding author at: Goddard Laboratories, Room 518, University of Pennsylvania, 3710 Hamilton Walk, Philadelphia, PA 19104, United States.
E-mail address: roy.hamilton@uphs.upenn.edu (R. Hamilton).

http://dx.doi.org/10.1016/j.bandl.2016.05.007
0093-934X/

employed to facilitate language production in patients with PPA (Finocchiaro et al., 2006; Trebbastoni et al., 2013). Finocchiaro et al. (2006) found an improvement in verb production following five days of high-frequency (excitatory) rTMS to the left anterior midfrontal gyrus. In a more recent case study, Trebbastoni et al. (2013) demonstrated that five consecutive days of high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) led to significant improvements in both oral and written language tasks.

In contrast to TMS, tDCS is a form of noninvasive brain stimulation in which small direct currents are applied through the skull in order to influence brain function (Nitsche & Paulus, 2000). Unlike TMS, tDCS does not generate action potentials, but rather may alter neuronal resting membrane potentials in order to increase (or decrease) the rate of cell firing in larger neural populations (Stagg & Nitsche, 2011). Compared to TMS, tDCS has a number of practical advantages including its ease of use, low cost, portability, ability to be paired with existing therapies, and outstanding safety profile (Poreisz, Boros, Antal, & Paulus, 2007). A number of studies have used tDCS for cognitive enhancement in domains such as working memory (Fregni et al., 2005; Gill, Shah-Basak, & Hamilton, 2014; Ohn et al., 2008) and language (Meinzer et al., 2014; Price, McAdams, Grossman, & Hamilton, 2015; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). It has also been extensively used for clinical applications in brain-injured patients (Baker, Rorden, & Fridriksson, 2010; Turkeltaub et al., 2012) as well as in patients with neurodegenerative disease (Benninger et al., 2010; Boggio et al., 2011; Cotelli, Manenti, Cappa, Zanetti, & Miniussi, 2008; Ferrucci et al., 2008; Hansen, 2012).

Recently there have been several reports in which tDCS was administered to people with PPA. These appeared to show significant improvement in some language functions in the absence of adverse effects (Cotelli et al., 2014; Tsapkini, Frangakis, Gomez, Davis, & Hillis, 2014; Wang, Wu, Chen, Yuan, & Zhang, 2013). A case study carried out by Wang et al. (2013) on a patient with naPPA demonstrated that five days of anodal tDCS over the left inferior frontal gyrus (IFG) and the left posterior peri-Sylvian region led to improvements in four subtests of the Psycholinguistic Assessment in Chinese Aphasia (PACA) battery. Recent work by Cotelli et al. (2014), also focusing on non-fluent patients, found improvements in naming abilities after two weeks of daily tDCS over the left DLPFC combined with concurrent language therapy in 8 patients. These improvements were sustained for up to 12 weeks after stimulation and, importantly, were not observed in the sham condition. Another recent trial by Tsapkini et al. (2014) demonstrated lasting improvements in word spelling following three weeks of daily tDCS over the left IFG combined with concurrent spelling intervention in 6 patients. Those patients that received active tDCS, as opposed to sham, were better able to spell words on which they were not trained, and these improvements were sustained for two months after stimulation. While these studies are encouraging, they have been limited in terms of the range of language abilities being investigated. Furthermore, the electrode montages employed were chosen for specific linguistic measures, and may not be effective for treating impairments in other language domains. Finally, previous studies have targeted patients with moderate to high disease severity, but it is unclear if tDCS will be effective in patients with relatively recent onset of symptoms. The current pilot study was designed to address these gaps in the literature.

1.3. Current study

In this proof-of-principle pilot study, we sought preliminary evidence to support the efficacy and tolerability of tDCS on PPA patients. We were interested in investigating the potential of tDCS to improve a wide range of language skills, insofar as prior studies have focused on a relatively restricted set of linguistic abilities, such as spelling (Tsapkini et al., 2014) and naming (Cotelli et al., 2014). To that end, in contrast to prior studies in which targets of stimulation were more spatially circumscribed, our tDCS montage was specifically chosen to maximize current distribution over a broad network of left-hemisphere language areas. As a result, we predicted improvement in a variety of linguistic abilities associated with the diagnostic features of the patients in our sample: these included speech production, repetition, grammatical comprehension and semantic processing. Finally, we also predicted that after repeated sessions of tDCS, these improvements would be sustained for several months beyond the initial stimulation period.

2. Methods

2.1. Participants

Patients with a diagnosis of PPA who had slowed speech were recruited from a large cohort of research participants at the Frontotemporal Degeneration Center at the University of Pennsylvania. All participants had also been evaluated previously by a behavioral neurologist at the University of Pennsylvania and had been clinically diagnosed with a variant of PPA. Patients who scored below 15 on the mini-mental state exam (MMSE) were excluded due to concerns that global cognitive impairment might preclude their ability to follow directions and interfere with task performance. Potential participants were also excluded if they were non-native English speakers, or had a history of seizures or unexplained loss of consciousness, pregnancy, surgical breach of the skull, or any other medical or surgical contraindication to receiving noninvasive brain stimulation.

A total of 6 participants were recruited for this pilot study. Four of the patients had a diagnosis of lvPPA; the other two were diagnosed with naPPA, according to published criteria (Gorno-Tempini et al., 2011) and confirmation at a local consensus conference. lvPPA patients have lexical retrieval difficulty and repetition deficits; naPPA patients have slowed, effortful speech with deficits in grammatical expression, and a pattern of speech errors known as apraxia of speech. All participants thus displayed notable impairment in speech fluency. The average age was 66.2 ± 5.7 years and the average disease duration was 4.2 ± 1.8 years (see Table 1 for demographic information of the participants at baseline). The study was approved by the Institutional Review Board at the University of Pennsylvania and each patient provided informed consent to participate.

2.2. Design

This was an unblinded pilot study. All patients received two weeks (10 days) of active stimulation. During each 20-min stimulation session, patients narrated wordless children's picture books (see Section 2.4). Neuropsychological evaluation was administered at baseline (T0) and then immediately following the last tDCS session (T1). Follow-up assessments were performed at 6 weeks (T2)

Table 1
Demographic characteristics of study participants. Age, disease duration, and MMSE score were all determined at the beginning of participation.

Number of males/females	1/5
Age (yrs)	66.2 ± 5.7
Education (yrs)	16.3 ± 2.7
MMSE score	28.2 ± 1.2
Diagnosis (lvPPA/naPPA)	4/2
Disease duration at baseline (yrs)	4.2 ± 1.8