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Facilitative effects of bi-hemispheric tDCS in cognitive deficits of Parkinson disease patients

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder, primarily characterized by motor symptoms such as tremor, rigidity, bradykinesia, stiffness, slowness and impaired equilibrium.

Although the motor symptoms have been the focus in PD, slight cognitive deficits are commonly found in non-demented and non-depressed PD patients, even in early stages of the disease, which have been linked to the subsequent development of pathological dementia. Thus, strongly reducing the quality of life (QoL).

Both levodopa therapy and deep brain stimulation (DBS) have yield controversial results concerning the cognitive symptoms amelioration in PD patients. That does not seems to be the case with transcranial direct current stimulation (tDCS), although better stimulation parameters are needed. Therefore we hypothesize that simultaneously delivering cathodal tDCS (or ctDCS), over the right prefrontal cortex delivered with anodal tDCS (or atDCS) to left prefrontal cortex could be potentially beneficial for PD patients, either by mechanisms of homeostatic plasticity and by increases in the extracellular dopamine levels over the striatum.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, primarily characterized by motor symptoms such as tremor, rigidity, bradykinesia, stiffness, slowness and impaired equilibrium [1]. Etiologically, PD has been associated to dopaminergic (DA) cells degeneration in the midbrain causing DA depletion in the striatum [2]. This depletion seems to trigger compensatory DA strategies in several areas of the brain that gradually decline with the progression of the disease [3].

Although the motor symptoms have been the focus in PD, slight cognitive deficits, are commonly found in non-demented and non-depressed PD patients, even in early stages of the disease, which have been linked to subsequent pathological dementia [4]. Thus, strongly reducing the quality of life (QoL) [5]. Other studies suggested that these cognitive deficits could even be considered as a mild cognitive impairment (MCI) [6].

These cognitive deficits constitute a heterogeneous profile of impairments that have been already shown to be present at the time of diagnosis [7]. Other studies have suggested potential brain alterations [8] that even precede the onset of the cognitive impairments.

Despite this heterogeneity, most of the cognitive deficits in PD are executive functioning driven [9], involving update or maintenance of information within working memory (WM). In early stages of PD, rule shifting, planning, attentional set shifting, WM, feedback based learning and delayed response inhibition are common cognitive impairments (see [1] for review). Without a global cognitive impairment, these deficits can be similar to a fronto-striatal dysexecutive syndrome [1], and therefore are thought to be related to specific under activations in regions of the basal ganglia or prefrontal cortex (PFC) [10,11]. At later stages of the disease, patients could exhibit dementia with impairments in semantic fluency, auditory verbal learning, visuospatial skills, verbal and visual memory, as well as suffering from hallucinations [1]. Based on animal and computational models, as well as in human cognitive data, Cools [12] proposed an interesting framework where striatal DA would be related to the flexible shift between mental representations, whereas prefrontal DA would be related to the maintenance of such representations. Therefore in early stages of PD, patients would reveal difficulties in the updating of WM, as well as impaired ability to adapt in tasks that required continuous changes in the S–R mappings (i.e. set shifting and task switching tasks). Only in posterior phases of the disease progression, ventral striatum dependent tasks (such as probabilistic reversal learning) would be affected [13]. This could explain why levodopa (or L-DOPA) has yield both positive and negative results in terms of cognitive symptoms

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amelioration – reflecting the spatial–temporal progression of DA depletion, from the dorsal to the ventral striatum [14,15].

Apart from levodopa medication, deep brain stimulation (DBS) over the subthalamic nucleus (STN) has proven to be effective in motor symptoms amelioration in this population. However deficits of speech and gait, as well as cognitive and emotional impairments have been also reported [16–18]. One possible explanation is that the bradykinesia induced by the inhibition or disruption of the excessive flow of information through the STN [19], also disrupts the normal flow of inputs from other prefrontal, associative and even limbic areas [20]. Even though recent studies suggest no cognitive decline after DBS (e.g., [21]), they do not seem promising in terms of cognitive rehabilitation. That seems not to be the case of transcranial direct current stimulation (tDCS).

Transcranial direct current stimulation (or simply tDCS) consists of applying weak electrical constant currents to the scalp. Physiologically, anodal tDCS (or atDCS) causes a membrane depolarization, while cathodal tDCS (or cTDCS) seems to hyperpolarize the neural membrane [22]. Several studies suggest positive effects on the physical and cognitive rehabilitation of PD patients, in both motor and non-motor symptoms. Anodal tDCS (atDCS) over M1 was associated with an increase in motor function in the UPDRS scale [23], as well as increases in WM performance over the PFC [24]. atDCS is also able to increase performance in tasks that require continuous changes in the S–R mappings in healthy controls (HC) [25,26] which are thought to be affected in PD patients. Despite the obvious potential of the use of tDCS in PD patients, better stimulation parameters need to be established, prior to the use of tDCS as a clinical tool [27].

The hypothesis

We hypothesize that ctDCS over the right prefrontal cortex simultaneously delivered with atDCS over the left prefrontal cortex can be able to increase the ability to flexibly shift between mental representations. This seems somewhat counterintuitive, as the research shows that PD patients seem to have a hypometabolic activity in the right prefrontal cortex [28]; and thus the logic course of action would be to use atDCS to increase the cortical activity, as it has been show that atDCS is able to increase the energy consumption in the brain, with the bonus of reducing neurohormonal stress [29]. Also, bilateral atDCS (i.e. one anode in each hemisphere) has been used with success in other patient population (e.g., visual memory enhancement in Alzheimer disease) [30]. But other studies have also been finding promising results when delivering simultaneously atDCS to the left PFC while ctDCS is delivered to the right one, in both basic cognitive functioning (e.g., [31,32]), and in clinical symptoms amelioration (e.g., [33]). Additionally, the use of ctDCS does not imply that the produced effects will be inhibitory, as there are several studies where ctDCS was found to be able to increase task performance [34,35].

Also, the hypometabolic activity in the right PFC could impact the direction of the ctDCS effects, as it has been already shown that a cortical excitability change, due to a ctDCS preconditioning, was able to render facilitatory and inhibitory stimulation [36]. This example of homeostatic plasticity was further exemplified using valproate, where increases in the dosage (i.e. decreases in the cortical excitability) interacted positively with and inhibitory stimulation, producing as an outcome, increases in the cortical excitability [37].

But there is another reason to explore the role of ctDCS in PD patients. Animal studies have shown that ctDCs, and not atDCS was able to increase the extracellular levels of DA in the rat striatum [38].

Another important question that remains to be addressed concerns the tDCS parameterization. From the literature about cognitive functioning and tDCS, it seems that 2 mA of atDCS is able to increase performance, but the same does not seem to be true with 1 mA atDCS [24,39]. Also, 2 mA atDCS over the PFC seems to be effective in changing connectivity in distinct functional brain networks of the brain [40,41], thus producing effects in the proximity of the stimulation site, but also in the connected brain regions. Therefore, for now, 2 mA tDCS seems a promising starting point. Nonetheless in order to increase the effectiveness of tDCS in clinical interventions, non-invasive closed-loop systems need to be perfected.

This hypothesis is not without caveats. First of all, the assumption that ctDCS could produce the same outcome in terms of extracellular dopamine in humans, as it produced in rats, needs to be tested. Also, research shows that effects of atDCS over the human PFC are more consistently reported than ctDCS (see [22] for review); and we certainly do not know if ctDCS in this specific population will produce the same hypothesized homeostatic plasticity outcome. Another potential caveat is that there is some controversy about the role of extracellular dopamine in the striatum (i.e. detrimental levodopa effects) which seems to increase more in the depleted striatum when compared to the normal one [42,43]. A possible way to surpass this was to use *De Novo* patients, closely monitoring their response to the tDCS, and only then comparing the outcomes with those from patients in advanced stages of the disease.

Implications and further studies

If future research validates these hypotheses, important implications may be derived. If proven accurate, tDCS has the potential of inducing cognitive benefits in tasks where there are no benefits from levodopa (i.e. extra-dimensional set shifting, task switching abstract rules, pattern and spatial recognition memory, associative learning, verbal memory) (see [1] for review). The success of a combined neurorehabilitation program with tDCS could delay the introduction of levodopa, thus protecting for undesired side effects, and contributing for a better quality of life.

Conflicts of interest

There are not any financial, relationship and organizational conflict of interests that may bias any of the authors in the establishment of the hypotheses discussed in this article.

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