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Review

Transcranial direct current stimulation in Parkinson's disease: Neurophysiological mechanisms and behavioral effects

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ABSTRACT

Recent research has highlighted the potential of transcranial direct current stimulation (tDCS) to complement rehabilitation effects in the elderly and in patients with neurological diseases, including Parkinson's disease (PD). TDCS can modulate cortical excitability and enhance neurophysiological mechanisms that compensate for impaired learning in PD. The objective of this systematic review is to provide an overview of the effects of tDCS on neurophysiological and behavioral outcome measures in PD patients, both as a stand-alone and as an adjunctive therapy. We systematically reviewed the literature published throughout the last 10 years. Ten studies were included, most of which were sham controlled. Results confirmed that tDCS applied to the motor cortex had significant results on motor function and to a lesser extent on cognitive tests. However, the physiological mechanism underlying the long-term effects of tDCS on cortical excitability in the PD brain are still unclear and need to be clarified in order to apply this technique optimally to a wider population in the different disease stages and with different medication profiles.

Contents

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1. Introduction

Although Parkinson's disease (PD) is currently defined as a widespread neurodegenerative disorder, it is largely characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (Berg et al., 2014; Purves et al., 2008). Loss of dopaminergic neurons results in a lack of coordinated activity between the direct and indirect basal ganglia circuits, as described in widely accepted models of the basal ganglia. This in turn induces abnormal activity within cortico-striatal-thalamic pathways of the central nervous system (Albin et al., 1989; Calabresi et al., 2014; DeLong and Wichmann, 2009; DeLong, 1990; Herz et al., 2014). PD is associated with motor symptoms including bradykinesia, tremor, rigidity and postural instability, as well as with a number of non-motor features (Jankovic, 2008). The burden of the disease leads to a significant loss of productivity, early retirement and decreased self-care and other activities of daily living (Jankovic, 2008; Johnson et al., 2011). Dopaminergic medication continues to be the mainstay of medical treatment of PD, despite the fact that its effects diminish and side effects emerge with time (for review see Aquino and Fox, 2015; Beaulieu-Boire and Lang, 2014; Olanow, 2014; Poewe and Antonini, 2015). Another common treatment in PD involves surgical intervention with implantable electrodes stimulating deep brain structures (i.e. deep brain stimulation). However, together with the risk of serious surgical complications, this invasive intervention is only indicated when very specific criteria are met, excluding the majority of PD patients (Sydow, 2008; Weaver et al., 2009). Therapeutic alternatives and rehabilitation interventions as a complementary treatment are therefore required.

Physiotherapy or other methods of targeted training can improve movement and cognitive impairments in PD patients, albeit for a limited time period (Allen et al., 2012; Goodwin et al., 2008; Petrelli et al., 2014; Petzinger et al., 2010; Speelman et al., 2011; Tomlinson et al., 2013). An important requirement to obtain long-term effects of behavioral interventions is the ability to consolidate new motor skills and store them in the motor memory under the impetus of various mechanisms of neuroplasticity (Penhune and Steele, 2012).

Recent research has highlighted the potential of non-invasive brain stimulation, such as transcranial direct current stimulation (tDCS), to complement and enhance neuroplasticity and learning in patients with neurological disorders and older individuals (for review see Floël, 2014). TDCS is a technique that elicits constant weak electric currents through the scalp via two electrodes (anode and cathode), which has been shown to modulate excitability in cortical and subcortical tissue (Bindman et al., 1964; Nitsche and Paulus, 2000; Nonnekes et al., 2014; Radman et al., 2009). The central research question of this review builds on these findings by examining the question whether tDCS has an effect on motor and cognitive functioning in conjunction with medication and with or without learning-based interventions in PD. Despite the known advantages of providing spatially specific and concentrated stimulation of transcranial magnetic stimulation (TMS), we will focus on tDCS for reasons of clinical applicability and user-friendliness (Nitsche and Paulus, 2000; Nitsche et al., 2008). The present work will therefore perform a systematic review on the evidence available regarding the effects of tDCS on: (i) cognitive and motor outcomes, (ii) motor learning in PD patients and (iii) possible neurophysiological mechanisms. We will first describe the proposed avenues of neuroplasticity in patients with PD with relevance for the possible response to tDCS.

1.1. Neuroplasticity in Parkinson's disease

The human brain is anatomically and physiologically organized into complex networks, which are indispensable for optimal brain function as well as for the acquisition and performance of activities in daily life. During novel skill learning, several neural processes are responsible for the reorganization of specific changes in the patterns of intracortical and subcortical–cortical connectivity (Doyon et al., 2009; Landi et al., 2011; Penhune and Steele, 2012). A recent motor sequence learning model proposed a distinct role of the cerebellum, basal ganglia and primary motor cortex (M1) in motor learning, depending on task demands and the learning stage (Penhune and Steele, 2012).

Motor learning is a relatively permanent change in the capability of a person to execute motor skills as a result of practice or experience (Schmidt and Lee, 1999). It has been studied from different perspectives and a distinction between motor sequence learning (i.e. acquisition of a new sequence of movements) and motor adaptation (i.e. adaptation to environmental changes) can be made (Doyon and Benali, 2005; Doyon and Ungerleider, 2002; Doyon et al., 2003). Motor skill learning proceeds through a fast acquisition phase and a slow consolidation and automatization phase. The basal ganglia are involved in all phases of motor skill learning, though particularly during motor sequence learning in the later stages, i.e. during consolidation and automatization (Agostino et al., 2004; Diedrichsen et al., 2005; Doyon and Ungerleider, 2002; Doyon et al., 2009; Grafton et al., 1995; Laforce and Doyon, 2002; Rauch et al., 1997; Wu and Hallett, 2005). Both behavioral and brain imaging studies have investigated whether (re)learning of motor skills is possible in patients with PD and whether this is correlated with changes in brain activity. Results showed that the efficiency achieved as a result of learning is reduced in PD patients compared with healthy controls (Felix et al., 2012; Smiley-Oyen et al., 2006; Stephan et al., 2011; Swinnen et al., 2000). To compensate for basal ganglia dysfunction, patients recruit additional brain regions and show alterations in effective connectivity to reach similar levels of performance (Mentis et al., 2003; Sehm et al., 2014; Wu and Hallett, 2005; Wu et al., 2010, 2012, 2014). Patients are thus able to improve their performance as a result of practice, though their ability to acquire new motor sequences and consolidate acquired skills is affected (Abbruzzese et al., 2009; Doyon, 2008; Felix et al., 2012; Marinelli et al., 2009; Moisello et al., 2015; Nackaerts et al., 2013; Nieuwboer et al., 2009; Ruitenberg et al., 2015; Terpening et al., 2013; Venkatakrishnan et al., 2011). Moreover, when patients with mild PD achieve automaticity of a motor task via compensatory strategies, re-attention to the task results in a disruption of this modified automatic mode within the striatum (Wu et al., 2014). Thus, the difficulties in learning and performing skills in an