Basal Ganglia 6 (2016) 101–105

Contents lists available at ScienceDirect

Basal Ganglia

journal homepage: www.elsevier.com/locate/baga

Review article

Therapeutic effects of non-invasive brain stimulation for dystonia

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ARTICLE INFO

Article history:
Received 3 November 2015
Accepted 24 January 2016
Available online 6 February 2016

Keywords:
Dystonia
Basal ganglia
Motor loop
Repetitive transcranial magnetic stimulation (rTMS)
Transcranial direct current stimulation (tDCS)

ABSTRACT

Dystonia is a refractory neurological disorder. Although medications, botulinum toxin injections and surgery (e.g. deep brain stimulation) are the main treatments, these treatments are not always satisfactory for patients with dystonia. Non-invasive brain stimulations (NBS) such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are potential novel therapeutic tools and several studies have used them to treat patients with dystonia. To date, there are several positive placebo-controlled studies on the therapeutic effects of rTMS (focal hand dystonia, cervical dystonia and blepharospasm) and tDCS (focal hand dystonia and children's dystonia). However, there is still little information and additional high quality studies are required. Here, we briefly summarize the data on the therapeutic effects of NBS on dystonia.

Contents

1. Introduction

Dystonia is a refractory neurological disorder that is characterized by prolonged muscle contraction that causes sustained twisting movements and abnormal posture of the affected body parts [1,2]. Most lesions responsible for symptomatic dystonia involve the basal ganglia motor loop [3–5]. Medications, botulinum toxin injections and surgery (e.g. deep brain stimulation [DBS]) are the main treatments, but these treatments are not always satisfactory for the patients with dystonia. Non-invasive brain stimulation (NBS) has been investigated as a novel therapeutic tool. In this review, we briefly summarize the research reports on the therapeutic effects of NBS on dystonia. We also comment on the mechanism of NBS and on the background of its therapeutic effects. Finally, we discuss safety and other issues.

2. What is non-invasive brain stimulation?

There are two types of brain stimulation methods: invasive and non-invasive. The main type of invasive brain stimulation is DBS, and non-invasive brain stimulation includes transcranial magnetic

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http://dx.doi.org/10.1016/j.baga.2016.01.006
2210-5336/

stimulation (TMS) and transcranial direct current stimulation (tDCS). TMS and tDCS can activate the human brain non-invasively and painlessly. The mechanisms of TMS are as follows: powerful and rapidly-changing electrical currents flowing through a coil placed over the head and, in accordance with Faraday's law, produce a changing magnetic field. The changing magnetic field penetrates the coil vertically and produces eddy currents that are parallel to the coil in the head (eddy currents are also called induced currents). The induced currents electrically activate cortical neurons [6–8]. Repetitive TMS (rTMS) is a method where TMS pulses are repeatedly applied to the human brain. tDCS is a method where a small amount of direct current is applied transcutaneously and continuously to the brain for a certain period [9,10]. rTMS and tDCS can bi-directionally modulate the cortical excitability, similar to long-term potentiation (LTP) or long-term depression (LTD). High frequency rTMS, e.g. 5–20 Hz, increases the cortical excitability, whereas low frequency rTMS, e.g. 0.2–1 Hz, decreases the excitability. Similarly, anodal tDCS increases the cortical excitability, while cathodal tDCS decreases it. Currently, theta burst stimulation (TBS), a type of rTMS, is available [11]. Intermittent TBS (iTBS) increases the cortical excitability, while continuous TBS (cTBS) decreases it. Therefore, rTMS (including TBS) and tDCS are potential new therapeutic methods for patients with refractory neurological disorders including dystonia.

3. Background of therapeutic effects (pathophysiology of dystonia)

Here, we describe the minimal knowledge that is available about the pathophysiology of dystonia to understand the therapeutic mechanisms of NBS for dystonia. In general, no pathological or morphological findings are found in primary dystonia. Therefore, historically, dystonia has been considered to be a functional disorder. Based on observations of secondary dystonia caused by brain tumors, stroke and other mechanisms, dystonia is thought to be produced by dysfunction of the basal ganglia motor loop [3–5]. However, many symptoms of dystonia cannot be explained solely by motor loop dysfunction. In addition to motor loop dysfunction, i.e. the basal ganglia, thalamus, primary motor cortex and the other motor cortexes, dysfunction of various areas in the central nervous system including the primary sensory cortex, cerebellum, brainstem and spinal cord are thought to be involved [2].

3.1. Motor loop

The basal ganglia are comprised of neural circuits called the basal ganglia-thalamo-cortical loop. Loops between the basal ganglia and the cerebral cortex include the motor loop, cognitive loop, limbic loop and an oculomotor loop. Thus, the basal ganglia-thalamo-cortical loop is related to the cognitive function and emotion in addition to motor control.

There are several pathways in the motor loop, such as the direct and indirect pathways [12,13]. The direct pathway is the pathway projecting from the striatum (mainly putamen) to the internal segment of globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). The indirect pathway, however, is the pathway projecting from the striatum (putamen) to the external segment of globus pallidus (GPe), from the GPe to the subthalamic nucleus (STN), and from the STN to the GPi/SNr. Thus, both pathways project from the striatum (putamen) to the GPi/SNr. The GPi/SNr

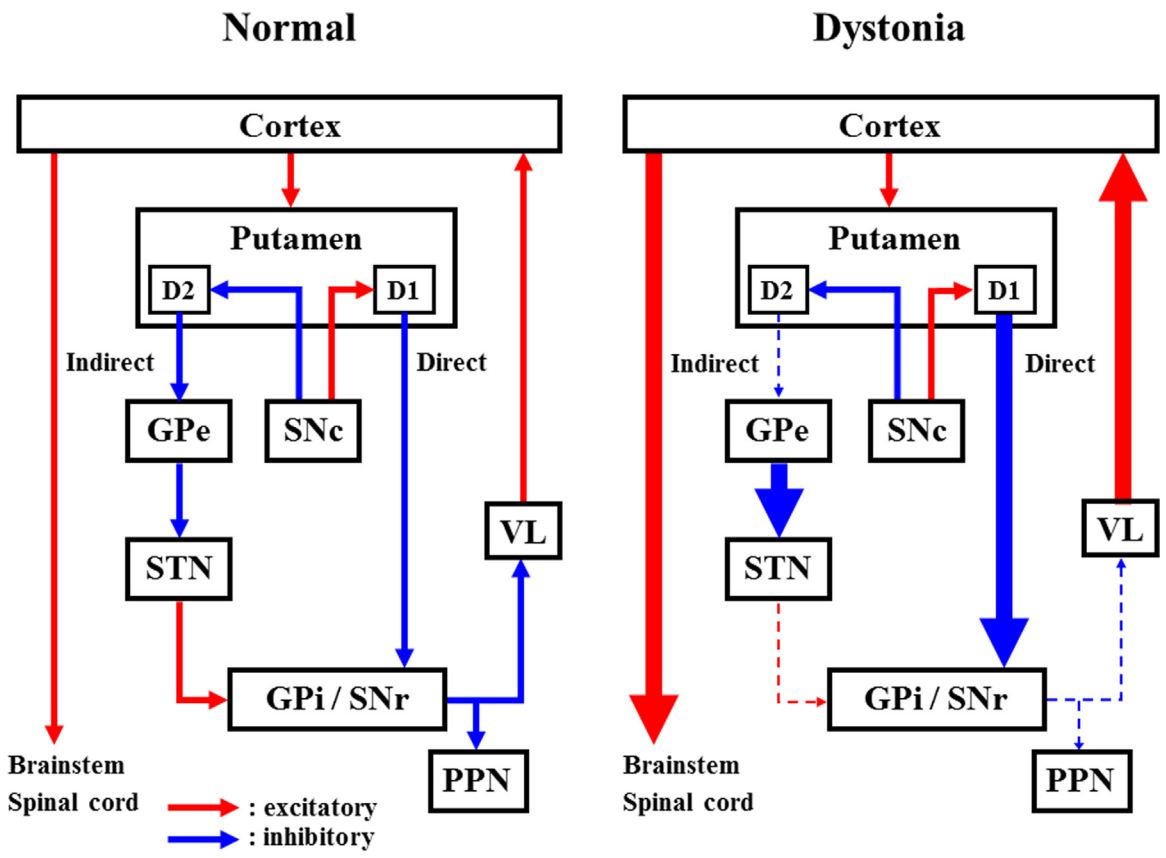

Fig. 1. Basal ganglia motor loop.
GPe, external segment of globus pallidus; GPi, internal segment of globus pallidus; PPN, pedunculopontine tegmental nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VL, the ventro-lateral nucleus of the thalamus.