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EDITORIAL

Non-invasive Cerebellar Stimulation: Moving Towards Clinical Applications for Cerebellar and Extra-Cerebellar Disorders

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Abstract

The field of non-invasive stimulation of the cerebellum is quickly expanding. The anatomical structure of the cerebellum with a high density of neurons in the superficial layer, its electrical properties, and its participation in numerous closed-loop circuits involved in motor, cognitive, and affective operations both in children and in adults make of the cerebellum a target with very high potential for neuromodulation of both cerebellar and extra-cerebellar disorders, in neurology, psychiatry, and neurosurgery. A common research effort is required to extract the optimal parameters of stimulation and to identify how non-invasive stimulation of the cerebellum modifies cerebellar plasticity and functional connectivity in remote cortical and subcortical areas. A patient stratification should be considered.

Introduction

The experiments of Galvani and Volta investigating the role of electricity in animal organisms during the eighteenth century are cornerstones of current electrophysiology. These pioneers have investigated scientifically the effects of external currents applied on the central and peripheral nervous system [1–3]. About four decades ago, Cooper already showed that cerebellar stimulation modulates motor function [4, 5]. Since the works of Nitsche and Paulus [6] who provided evidence that non-invasive electrical stimulation could successfully modulate motor cortex excitability in a polarity-dependent manner, the number of published studies employing non-invasive brain stimulation (both electrical and magnetic) has increased tremendously (Fig. 1a). Not only the motor region is targeted but also other cortical regions, such as the dorsolateral prefrontal cortex (DLPFC) in the treatment of depression [7], or the inferior frontal gyrus to speed up and enhance speech and language recovery [8]. Recently, the cerebellum has gained a lot of interest as a potential site for neuromodulation (Fig. 1b).

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Due to its numerous connections with the motor and associative cortical regions, its high density of neurons (in particular in the cerebellar cortex), its electrical properties, and its position immediately below the skull, the cerebellum is now considered as a real target to modulate distant cortical regions [9, 10].

The exact cellular/network consequences of cerebellar stimulation are not yet unraveled. Several studies have focused on the neurophysiological effects upon neural networks (especially motor and cognitive) and on cerebellar plasticity. The most recent studies show that cerebellar stimulation using continuous theta-burst stimulation (cTBS) is NMDA receptor-dependent and most likely involves long-term potentiation (LTP) and long-term depression (LTD) [11]. This translates to an altered functional connectivity with remote cortical areas [12], which is also observed after transcranial alternating current stimulation (tACS) [13] and after transcranial direct current stimulation (tDCS) [14]. Although tACS and tDCS modulate cerebellar plasticity and functional connectivity, these electric techniques most likely operate in a different way than the transcranial magnetic stimulation (TMS) techniques such as cTBS [10]. Obviously, more will be learned from animal models [15].

In the last year alone, 42 articles employing non-invasive cerebellar neurostimulation have been published (search on PubMed: "transcranial" AND "cerebell*" AND "stimulation"; 42 of 73 remained after abstract screening). Most of these articles relate to the investigations of the physiological mechanisms of cerebellar stimulation in a healthy population. These studies focus primarily on different motor functions

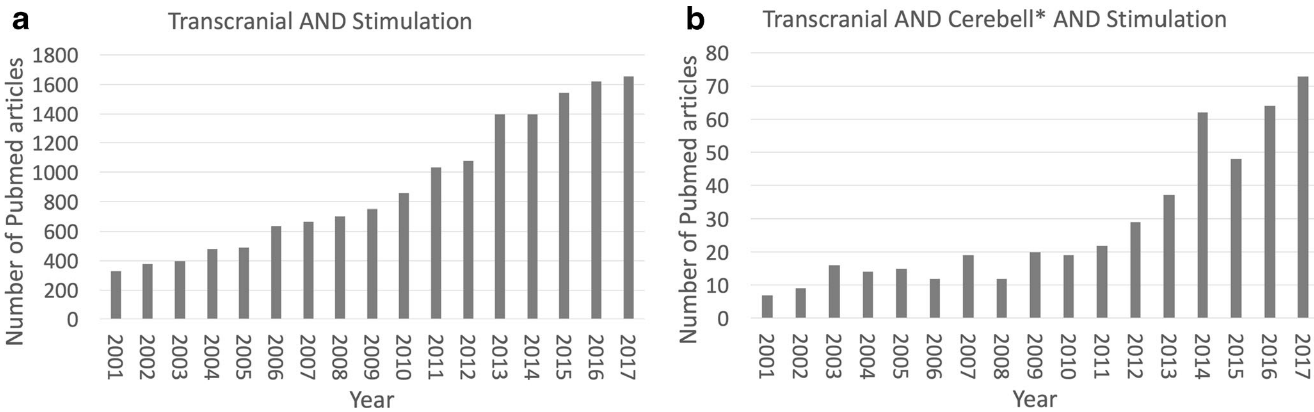

Fig. 1 Evolution of the number of articles found by a Pubmed search using the keywords **a** "transcranial" AND "stimulation" and **b** "transcranial" AND "cerebell*" AND "stimulation" between the years 2001 and 2017

such as visuomotor adaptation [16], motor learning [17], or balance control [18], but some also focus on cognitive functions such as probabilistic classification learning [19], verb generation [20], or attentional control [21]. Recently, Oldrati and Schutter [22] published a quantitative review of 32 sham-controlled studies employing cerebellar tDCS to modulate both motor- and non-motor-related cerebellar functions. They showed that cerebellar tDCS was indeed effective in changing performance, but they could not find the expected polarity-dependent effects as demonstrated in the works of Nitsche and Paulus [6]. Unfortunately, the variability in the various protocols (sites of stimulation, montages, intensities,

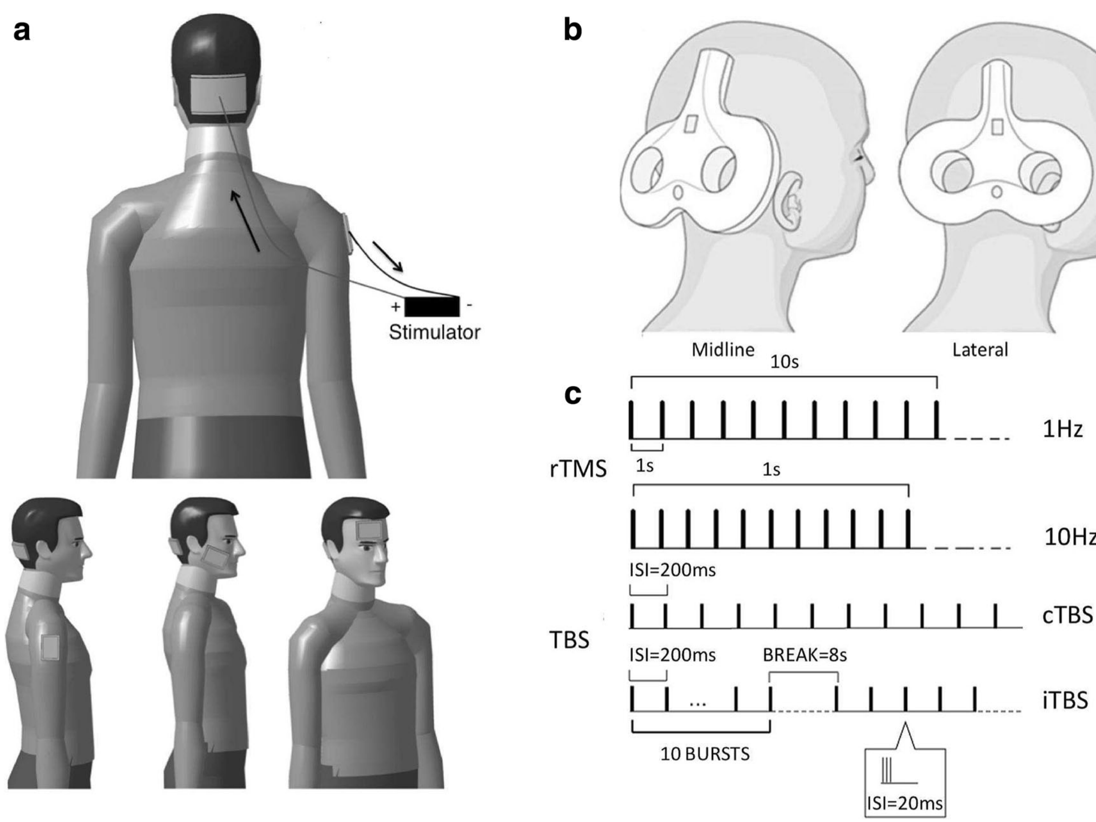

Fig. 2 Common setups for cerebellar stimulation with **a** tDCS and **b** TMS. For tDCS different setups can either stimulate bilaterally (upper figure), or unilaterally (below). The reference electrode can be placed in particular over the deltoid muscle, the buccinator muscle, or the supraorbital area. TMS is applied more focal and can target the midline or the lateral cerebellum. **c** Examples of different TMS protocols. On top, two examples of repetitive TMS (rTMS): slow inhibitory 1 Hz rTMS with 1 s in between the pulses and fast excitatory 10 Hz rTMS with 0.1 s in between the pulses. Underneath, two TBS protocols with 3-pulse bursts at 50 Hz every 200 ms: inhibitory continuous TBS (cTBS) with a continuous train of bursts and excitatory intermittent TBS (iTBS) with separated trains of ten bursts each with 8 s ISI. Adapted from [10, 25, 26]

durations, and patterns of stimulation) and the distinct domains of research make it difficult to predict the exact impact of cerebellar stimulation on specific motor and non-motor functions [10].

Besides the studies investigating healthy subjects, the use of cerebellar stimulation as a therapeutic aid in patients is gaining great attention not only in cerebellar patients, but also beyond. In particular, it has been shown that several neuropsychiatric disorders, such as bipolar disorder [23] or schizophrenia [24], are associated with dysfunction of cerebello-cerebral networks, which can be normalized by cerebellar stimulation through modulation of the cerebellar brain inhibition (CBI) or surround-motor inhibition (SMI) [23, 24]. The clinical implications extend, therefore, towards neuropsychiatric disorders, filling a gap between conventional neurology and conventional psychiatry.

With the increasing popularity of the cerebellum as a target for non-invasive stimulation and the accumulating evidence that cerebellar stimulation is indeed capable of altering cerebellar plasticity and remote functional connectivity in both healthy and patient populations, the cerebellum is now also considered as a potential target in the rehabilitation of stroke patients. Common setups of cerebellar tDCS and TMS stimulation are shown in Fig. 2a, b. Figure 2c shows the different TMS protocols commonly applied [10, 25, 26].

Cerebellar tDCS might be beneficial for patients with cerebellar neurodegenerative diseases such as ataxia (e.g., spinocerebellar ataxias (SCAs)) [27–29] and tremor (e.g., essential tremor (ET)) [30–32], but only a few studies have assessed the role of cerebellar stimulation during rehabilitation after cerebellar stroke [e.g., 31–34]. Despite the substantial differences in the stimulation protocol (four studies; Calzolari et al. [33]: excitatory anodal tDCS over the lesioned hemisphere; Torriero et al. [34]: inhibitory 1 Hz rTMS over the unlesioned hemisphere; Kim et al. [35]: inhibitory 1 Hz rTMS over the lesioned hemisphere; and Bonnì et al. [36]: excitatory iTBS over the lesioned hemisphere), all studies found have marked improvements after cerebellar stimulation. These findings deserve further attention with focus on the different stimulation protocols.

The cerebellum might also be an interesting target in patients with cerebral cortical damage. Indeed, the cerebellum might provide a structurally intact gateway to the affected neural networks of the cerebrum [37]. Wessel and Hummel (in press) [37] argue that cerebellar stimulation could be an answer to handle the heterogeneous features of stroke. By targeting the cerebellum, the same protocol can be used in different patient populations, leading to a better patient stratification. A recent study by Sebastian et al. [38] showed that cerebellar stimulation indeed improves cognitive functions after stroke. The authors applied tDCS over the right cerebellar hemisphere in order to enhance the effects of behavioral aphasia therapy (spelling to dictation) in a patient who suffered anarthria and aphasia after a large bilateral stroke. A greater improvement after therapy combined with cerebellar tDCS (compared to therapy combined with sham) with better generalization was observed. In addition, an increase in cerebello-cerebral connectivity was demonstrated. Marangolo et al. [39] replicated these results in a study group of 12 patients with chronic aphasia after left-hemispheric stroke for verb generation. However, they did not find an effect on verb naming and argued that cerebellar stimulation might only be meaningful if the language task also involved nonlinguistic processes [39]. Obviously, these findings now require a replication in a large population of patients, but this could indicate that there are opportunities for multi-focal stimulation to target specific networks [37]. By strengthening the entire affected network, and not just the damaged area, a better and/or faster recovery of the lost functions is becoming a realistic goal. Moreover, this type of stimulation might also allow for targeting different functions (motor and non-motor) at the same time. Furthermore, the simultaneous stimulation of the sensorimotor cerebellum and the prefrontal cortex is now technically feasible.

These are very promising results, which could potentially revolutionize the field of rehabilitating techniques. Future large studies should focus on the effects of cerebellar stimulation on clinical progress to envision standardized applications in clinical practice. Overall, cerebellar stimulation could be a potential clinical aid in the rehabilitation of fine motor deficits, gait/balance disturbances, and cognitive/affective impairments, and the applications might reach far beyond the

Table 1 The large spectrum of potential clinical applications of non-invasive cerebellar stimulation

Clinical population/deficit presented	
Extensive bilateral cerebral cortical damage (trauma)	
Control of (multi-focal) seizures	
Pain management	
Essential tremor	
Cerebellar ataxia (cognitive, motor, and affective)	
Neuropsychiatric disorders	Schizophrenia
	Bipolar disorders
Cerebral cortical stroke	Impaired fine motor skills
	Gait disturbances
	Impaired cognitive functions
	Language deficits
Neurodegenerative diseases	Alzheimer's Disease
	Parkinson's Disease
	Spinocerebellar ataxias (SCAs)
	Progressive supranuclear palsy (PSP)
Children	Ataxic cerebral palsy
	Neurodevelopmental disorders
	Developmental deficits in preterm children

stroke-related symptoms [36]. By combining cerebellar stimulation with cortical stimulation, the affected networks could be targeted very specifically. Table 1 lists the potential clinical implications of cerebellar stimulation. A consensus effort is now mandatory to test each opportunity [40].

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Compliance with Ethical Standards

Conflict of Interest None.

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