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40 **Type of article: consensus paper**

41 **Abstract**

42 The cerebellum is involved in multiple closed-loops circuitry which connect the cerebellar modules  
43 with the motor cortex, prefrontal, temporal and parietal cortical areas, and contribute to motor  
44 control, cognitive processes, emotional processing and behavior. Among them, the cerebello-  
45 thalamo-cortical pathway represents the anatomical substratum of cerebellum-motor cortex  
46 inhibition (CBI). However, the cerebellum is also connected with basal ganglia by disynaptic  
47 pathways, and cerebellar involvement in disorders commonly associated with basal ganglia  
48 dysfunction (e.g., Parkinson's disease and dystonia) has been suggested. Lately, cerebellar activity  
49 has been targeted by non-invasive brain stimulation (NIBS) techniques including transcranial  
50 magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) to indirectly affect  
51 and tune dysfunctional circuitry in the brain. Although the results are promising, several questions  
52 remain still unsolved.

53 Here, a panel of experts from different specialties (neurophysiology, neurology, neurosurgery,  
54 neuropsychology) review the current results on cerebellar NIBS (CB-NIBS) with the aim to derive  
55 the future steps and directions needed. We discuss the effects of TMS in the field of cerebellar  
56 neurophysiology, the potentials of cerebellar tDCS (ctDCS), the role of animal models in CB-NIBS  
57 applications and the possible application of CB-NIBS in motor learning, stroke recovery, speech  
58 and language functions, neuropsychiatric disorders, and movement disorders.

59  
60 **Key words:** cerebellum, neuromodulation, non-invasive, tDCS, TMS

## 61 **Introduction**

62 The cerebellum represents 10% of total brain volume, but it contains more than 50% of total brain  
63 neurons, reflecting the complex cellular architecture connecting this subcortical structure to other  
64 parts of the brain. Traditionally, researchers have focused on the role of the cerebellum in the  
65 control and coordination of movement [1], since the motor cortex is one of the main targets of  
66 cerebellar projections. Besides sending inputs through the cortico-ponto-cerebellar or cortico-rubro-  
67 olivo-cerebellar pathway [2], the motor cortex receives inhibitory projections resulting in  
68 cerebellum-motor cortex inhibition (CBI) [3]: Purkinje cells inhibit the dentate nucleus [4], which  
69 reduce excitatory input on the motor cortex from the dentato-thalamo-cortical pathway [5,6].  
70 However, the cerebellum contributes to numerous other functions, such as learning, cognition,  
71 emotions, and behavior, as disclosed by several findings [7,8]. Multiple closed-loop circuits  
72 working in parallel connect the cerebellum and cerebral cortex, allowing the cerebellum to  
73 influence, among many other targets, prefrontal, temporal, and parietal cortical areas [7,9].  
74 Recently, for example, studies combining TMS and electroencephalography (EEG), a combination  
75 that allows to precisely record the neuronal responses as result of TMS [10], have suggested that  
76 cerebellar stimulation strongly affects the activity of different cortical areas forming part of the  
77 parieto-frontal network [11,12], for example those involved in motor learning [12].

78 Moreover, several studies have shown a strict relation between the cerebellum and basal ganglia,  
79 disclosing neural projections from the dentate nucleus and cerebellar cortex to the striatum and  
80 subthalamic nucleus, respectively [13]. This may be one way in which the cerebellum can influence  
81 symptoms in disorders commonly associated with basal ganglia dysfunction (for example,  
82 Parkinson's disease and dystonia) [14,15].

83 These data suggest that cerebellar function, physiology and pathophysiology need to be further  
84 explored, and non-invasive brain stimulation (NIBS) techniques applied to cerebellum have fostered  
85 such knowledge [16]. Transcranial magnetic stimulation (TMS) and transcranial direct current  
86 stimulation (tDCS) studies, indeed, allow for non-invasive investigation of neural networks [16].

87 For example, cerebellar TMS applied in 1995 by Ugawa et al. [6] revealed the physiologic  
88 mechanisms of CBI, further extensively explored in later studies. More recently, it has been shown  
89 that CBI could be modulated by tDCS, although with controversial results. While Galea et al. [17]  
90 showed that anodal tDCS increased CBI – suggesting an excitatory effect on Purkinje cells activity,  
91 Doeltgen et al. [18] observed opposite results, suggesting an excitatory effect on superficial  
92 inhibitory interneurons or on cerebello-thalamo-cortical projections targeting inhibitory  
93 interneurons within the primary motor cortex (M1).

94 The unraveling of the therapeutic mechanisms of NIBS requires the understanding of the effects of  
95 NIBS on (1) the cerebellar cortex, (2) cerebellar nuclei and (3) the inferior olivary complex, three  
96 major structures of the cerebellar circuitry engaged in functional units of the cerebellum. Neurons  
97 of the cerebellar nuclei convey the cerebellar output signals to the spinal cord, brainstem nuclei  
98 (including red nuclei and reticular nuclei), basal ganglia, thalamic nuclei and cerebral cortex.  
99 Cerebellar nuclei are under the profound inhibition of Purkinje neurons, whose activity depends on  
100 mossy fibers, climbing fibers and interneurons of the cerebellar cortex, and mossy fibers, which  
101 transmit sensory and cortical information to granule cells via excitatory synaptic connections; small  
102 granule axons project up into the molecular layer of the cerebellar cortex, bifurcating and forming  
103 excitatory synapses onto Purkinje cell dendrites [19]. Meanwhile, parallel fibers also activate  
104 stellate cells and basket cells, which form inhibitory synapses with Purkinje cells, establishing a  
105 stereotypical feed-forward-inhibition circuit [19]. Reducing the inhibitory effect of Purkinje cells  
106 upon dentate/interpositus/fastigial neurons will increase the excitatory discharges exerted by  
107 cerebellar nuclei upon extra-cerebellar targets [20]. In other words, cerebellar cortex sculpts  
108 cerebellar output by tuning the firing rates and patterns of nuclear neurons [21]. NIBS likely tunes  
109 the inhibitory discharges of the cerebellar cortex, especially the posterior and inferior parts of the  
110 cerebellum (i.e., lobules VI-VIII) which seem particularly susceptible and accessible to  
111 neuromodulation in human [22]. Current views hypothesize that cerebellar NIBS (CB-NIBS) is  
112 mediated by both electrical and non-electrical (vascular, metabolic) effects on the cerebellar cortex

113 [22]. Spectroscopy (MRS) suggests that, in humans, anodal tDCS reduces GABA locally, whereas  
114 cathodal stimulation decreases glutamatergic neuronal activity [23].

115 In this review, we report the advances made on the use of CB-NIBS and reach a consensus on the  
116 future steps to moving forward. For each topic covered, we present the current evidences and  
117 underline the implications for future research. The following specific topics will be discussed: the  
118 use of TMS to explore cerebellar neurophysiology; the current knowledge on cerebello-cerebellar  
119 tDCS; the role of animal models in CB-NIBS applications; the clinical application of CB-NIBS  
120 (motor learning, stroke recovery, speech and language functions, neuropsychiatric and movement  
121 disorders and pain syndromes).

122

### 123 **TMS of the cerebellum: some lessons for the application of tDCS**

124 The first demonstration of cerebellar stimulation was performed using transcranial high-voltage  
125 electrical stimulation (TES); this was quickly followed by attempts using TMS. TES and TMS  
126 directly initiate action potentials in central neurons unlike the mild polarization of neural  
127 membranes produced by tDCS. However, the early experiences with TES and TMS illustrate some  
128 of the potential complexities of cerebellar stimulation as well as the difficulties involved in  
129 interpreting the outcome of experimental interventions that are equally relevant to tDCS and related  
130 paradigms. As we will show, using the example of CBI, these include problems such as: (1)  
131 distinguishing between effects that are attributable to stimulation of cerebellum and those due to  
132 stimulation of skin and scalp or to stimulation of other neural structures in the brainstem; (2)  
133 choosing the optimal coil geometry and stimulus intensity to maximize cerebellar effects; (3)  
134 interpreting which structures in the cerebellum are the primary targets of stimulation.

135

#### 136 *First description of CBI*

137 Ugawa et al. [3,5] were the first to attempt to stimulate structures in the posterior fossa using TES.  
138 They found that TES via electrodes placed on left and right mastoid processes could activate the

139 corticospinal tract (CST) at the level of the pyramidal decussation in the brainstem [3]. Given the  
140 distance of the site of activation from the scalp surface, they reasoned that it should be possible to  
141 use a similar electrode configuration to activate more superficial structures such as the cerebellum.  
142 A later paper [5] provided evidence in support of this possibility by describing the physiology of  
143 what would be termed CBI. Using a conditioning-test design, they showed that TES at an intensity  
144 below the threshold for corticospinal activation suppressed the response of the contralateral motor  
145 cortex to a subsequent TMS pulse given 5 - 15 ms later. Since responses of the motor cortex to TES  
146 were not affected by cerebellar stimulation, it was postulated that a cerebello-thalamo-cortical  
147 pathway was involved. The effect was not due to head movement produced by TES-induced  
148 contraction of neck muscles since movement did not start until at least 11 ms after TES.  
149 However, even in this early study it was clear that the effect was not as simple as it first appeared.  
150 Indeed: (1) locating the TES electrodes superiorly/inferiorly to the optimal site abolished the early  
151 effect at 5 – 8 ms, but had little effect on the later inhibition; (2) the early suppression was maximal  
152 when the anode of the TES was contralateral to the target M1 but the later suppression was equally  
153 prominent whether the anode was ipsilateral or contralateral; (3) early suppression was unaffected if  
154 the experiment was performed in relaxed or active muscle, whereas the late suppression was more  
155 effective during voluntary contraction than at rest. The conclusion was that two different effects  
156 were intermixed. The later period of CBI was thought to be a “non-specific” effect that was the  
157 result of strong peripheral sensation caused by TES. In contrast, CBI at 5 - 8 ms was assumed to be  
158 due to stimulation of the cerebellum. It was proposed that the TES pulse activated Purkinje cells of  
159 the cerebellar cortex which then inhibited deep cerebellar nuclei, withdrawing any tonic facilitation  
160 from the nuclei to motor cortex via thalamus. The following year, Amassian et al. [24] used TMS  
161 over the cerebellum and tried to record the evoked-EEG response from central scalp areas that they  
162 thought would accompany inhibition or withdrawal of facilitation of the motor cortex.

163

164 *The mechanism of CBI*

165 At this stage in the development of cerebellar stimulation, it is important to recall that there was no  
166 direct evidence that the cerebellum was involved in CBI. For example, it remained a possibility that  
167 the transmastoid stimulus had activated sensory fibers in the medial lemniscus and that the  
168 inhibition was, in fact, short-latency afferent inhibition which had been described some years  
169 earlier. There was even less certainty about the postulated mechanism, involving stimulation of  
170 Purkinje cells and CBI.

171 The best evidence we have that CBI depends on the cerebellum and its projections comes from a  
172 series of studies on patients. The first studies [25,26] were performed with electrical stimulation,  
173 but many more followed after the demonstration that CBI could be produced using TMS with a  
174 large double cone coil over the cerebellum, with less discomfort than the electrical technique [6].  
175 Diseases mainly or selectively affecting the cerebellar cortex consist of spinocerebellar ataxias  
176 (SCAs; SCA 6 or SCA 31), cerebellar cortical atrophy (CCA), cerebellar-type multiple system  
177 atrophy (MSA-C), cerebellar stroke, cerebellitis, paraneoplastic CCA, and intoxication from  
178 antiepileptic drugs. All these conditions had impaired CBI [25,27]. The involvement of the dentate  
179 nucleus or superior cerebellar peduncle in dentatorubral–pallidolusian atrophy (DRPLA) and  
180 Wilson’s disease also lead to reduced CBI [27]. In contrast, ataxic patients with lesions in cerebellar  
181 afferent pathways (pontine or middle cerebellar peduncular lesions, shown by blue arrows in Figure  
182 1) had normal CBI, even though the patients showed definite clinical cerebellar ataxia [27].  
183 Similarly, CBI was present in patients with non-cerebellar ataxia, such as sensory ataxia, Miller-  
184 Fisher syndrome, and hypothyroidism [25,27]. Taken together, these studies are strong evidence  
185 that CBI involves activation of structures in the cerebellar cortex and conduction to motor cortex  
186 via the superior cerebellar peduncle, and presumably the deep cerebellar nuclei. Following these  
187 initial studies, CBI has been investigated in healthy subjects performing behavioral tasks which are  
188 known to involve the cerebellum. It was shown that during a locomotion adaptation task, for  
189 example, CBI was reduced during the learning of a new locomotor pattern, but not during the actual  
190 performance. Moreover, the subjects who experienced the best adaptation, had the largest reduction



191 of CBI [28]. Corroborating the concept that CBI can be rapidly modulated in contextual specific  
192 manner, another study showed that CBI was clearly reduced prior to movement onset [29]. CBI has  
193 been also used to investigate cerebellar involvement in disorders in which there is no primary  
194 pathology of cerebellum. In progressive supranuclear palsy (PSP), CBI revealed cerebellar  
195 involvement in patients whose cerebellar clinical ataxic signs were masked by rigidity due to basal  
196 ganglia pathology [30]. CBI and prism adaptation task studies showed cerebellar impairment in  
197 patients with essential tremor [31].

198

#### 199 *Open questions about CBI*

200 TMS over the basal scalp using a large double cone coil activates many structures. Anyone who has  
201 taken part in a CBI study will testify that stimulation activates sensory afferents in the skin and  
202 peripheral motor fibers innervating neck muscles; and given the potential of the double cone coil to  
203 activate corticospinal fibers in the pyramidal decussation, cerebellar stimulation could also activate  
204 many other structures in the brainstem. So how certain can we be that CBI is what we think it is?

205

#### 206 *Contamination of CBI by non-cerebellar inhibition*

207 As noted in the original experiments, later timings of CBI appear to be contaminated by effects that  
208 do not originate in the cerebellum. Meyer et al. [32] observed CBI in a patient with a cerebellar  
209 defect, but only with an interstimulus interval of 8-9 ms between cerebellum and M1. The authors  
210 proposed that this was caused by activation of peripheral structures at the neck level. This  
211 conclusion was reinforced by Werhahn et al. [33] who found that inhibition at longer inter-stimulus  
212 intervals (ISIs) (>7 ms) may be produced by peripheral nerve activation. A recent review article  
213 also concluded that CBI involves a cerebellar inhibitory (or disfacilitatory) effect on M1, but does  
214 not always reflect a purely cerebellar effect [34]. As a result of such studies, it is usually  
215 recommended to evaluate CBI at an ISI of 5 ms.

216 Another very important source of contamination is direct stimulation of the CST by the  
217 conditioning stimulus [3,35,36]. Sometimes this can be detected because it causes peripheral muscle  
218 activity (technically a CMEP: a cervico-medullary motor evoked potential), but intensities below  
219 motor threshold may still activate the CST, although the orthodromic volley is insufficient to bring  
220 spinal motoneurons to threshold. There can be two consequences of this subthreshold effect: (1) in  
221 addition to orthodromic activity to the spinal cord, there will also be antidromic action potentials to  
222 the cortex. These can collide with orthodromic activation from M1 stimulation and suppress motor  
223 evoked potentials (MEPs) at short interstimulus intervals of 3 – 4 ms, rather than 5 – 7 ms for CBI;  
224 (2) the orthodromic volley will increase excitability of spinal motoneurons even if it fails to reach  
225 discharge threshold. This could cancel out any CBI, even at 5 – 7 ms, and lead to the erroneous  
226 conclusion that CBI was reduced or absent. Thus, the intensity of cerebellar stimulation should  
227 always be adjusted relative to CST activation. It has been recommended that this should be 5 -10%  
228 below the threshold for evoking a CMEP in preactivated muscle [36].

229

230 *Does CBI involve activation of Purkinje cells?*

231 Figure 1 (red arrows) shows the hypothesized anatomical pathways activated in CBI. Purkinje cell  
232 stimulation inhibits ongoing facilitation from the dentate nucleus, withdrawing facilitation from  
233 motor cortex. However, given that CBI is usually evaluated at rest, can we be sure that there is any  
234 ongoing facilitation that can be withdrawn? And if facilitation is withdrawn would we not expect  
235 that the onset of CBI would be less abrupt than it appears to be? CBI is absent with a 4 ms interval  
236 between cerebellar and cortical stimulation but is present and often maximum if the interval is 5 ms,  
237 which implies a very synchronous and powerful onset. In contrast, withdrawal of facilitation should  
238 be slower and, in the absence of other factors, depend on the duration of the last excitatory  
239 postsynaptic potentials (EPSPs) that occur before facilitation was withdrawn.

240 Although there is no information about resting dentate discharge in humans, studies in primates  
241 show a sustained resting level of discharge [37,38] which could presumably be suppressed by

242 activity of Purkinje cells. In addition, direct electrical stimulation of the superior cerebellar  
243 peduncle leads to activation of neurons in motor and premotor cortex [39], indicating an excitatory  
244 effect. However, facilitation was terminated after only a few ms by a longer lasting and dominant  
245 inhibition, so that the net effect of any ongoing dentate discharge on cortical excitability is unclear.  
246 Given the dominant inhibitory effect of peduncular stimulation, is it possible that CBI is produced  
247 by direct stimulation of cerebellar outflow? This is difficult to dismiss completely. The timing  
248 seems appropriate since peduncular stimulation in primates causes initial facilitation of cortex 4 ms  
249 later. If inhibition began shortly after that, then it would be appropriate to account for the onset  
250 latency of CBI at ISI = 5 ms. However, since there is no sign of facilitation prior to the onset of  
251 CBI, this seems unlikely in human. In addition, the duration of CBI is short compared with the  
252 duration of inhibition seen after direct stimulation. However, since the late component of CBI is  
253 contaminated by activation of peripheral afferents, some uncertainty remains.  
254 Finally, these experiments [39] may provide a way to explain how CBI can produce suppression  
255 with such an abrupt onset. As noted above, initial cortical facilitation is quickly followed by  
256 inhibition which the authors suggested was probably due to feedforward inhibition. Such an  
257 organization would mean that each EPSP produced by activation of a thalamo-cortical axon is  
258 terminated by a disynaptic inhibitory postsynaptic potentials (IPSP): rather than lasting (e.g. 15 ms),  
259 the EPSP may only last 1 -2 ms. Thus, withdrawal of facilitation by Purkinje suppression of dentate,  
260 as postulated for CBI, would result in rapid disfacilitation of the cortex because the duration of the  
261 last EPSPs to arrive at the cortical level is so short.

262

### 263 *Importance of Coil Geometry for evoking CBI*

264 The initial experiments [6] used a large angled figure-of-eight coil to explore CBI; smaller flat coils  
265 that are usually employed to activate M1 could not reliably produce CBI at 5 – 7 ms even though  
266 they always evoked clear suppression at 8 ms or longer [33]. Hardwick et al. [40] reassessed the  
267 problem and again found that CBI could only be evoked reliably with large coils and not with the

268 conventional flat figure-of-eight coils, a fact confirmed by later studies [41]. They also calculated  
269 the distance from the scalp to lobules V and VII, which would be the supposed location of  
270 projections to M1. They found that the distance of the nearest region of cerebellar surface was about  
271 1.5 times as far from the scalp as the surface of M1. However, the distance to lobules V and VII  
272 was even further, being 3 – 3.5 cm. This additional distance is presumably why CBI is difficult to  
273 obtain using coils conventionally employed to activate the M1 hand area. It should be noted  
274 however that such coils may be able to activate regions of the cerebellum closer to the scalp, as  
275 demonstrated, for example by Hashimoto & Ohtsuka [42], who used a flat figure-of-eight coil at  
276 localized scalp sites to stimulate vermal regions of the cerebellum and interact with voluntary  
277 saccadic eye movements.

278 Finally, it should be recalled that the cerebellar surface is highly convoluted such that alignment of  
279 the Purkinje cells (if these are the target of TMS) can be at all angles respective to the direction of  
280 the induced currents in the cerebellum. Those that are parallel to the induced current will have a low  
281 threshold for stimulation whereas those that are perpendicular to the current will have a high  
282 threshold. Thus, TMS may activate very particular populations of Purkinje neurons which may  
283 differ between individuals, and which will vary according to the orientation of the coil on the scalp.

284

### 285 *Implications for future research*

286 The early experiences with TMS of the cerebellum should alert us to three unresolved questions  
287 about ctDCS. Indeed, it is important to know: (1) which effects of tDCS are due to modulation of  
288 the cerebellum itself and what could be caused by the influence of tDCS on other structures both  
289 centrally and in the periphery; (2) what is the optimal tDCS montage to achieve modulation of a  
290 specific target region of the cerebellum, and how will this be affected by the orientation of the  
291 Purkinje neurons of the cerebellar cortex; (3) what specific mechanism mediates the overall effects  
292 of tDCS.

293

294 **Cerebello-cerebellar tDCS: what we know**

295 The interest of the scientific community in tDCS of the cerebellum keeps growing. This is  
296 illustrated by the number of articles published on the topic these last years (Figure 2). Given (1) the  
297 anatomical connectivity between the cerebellum and the spinal cord, brainstem, basal ganglia, and  
298 cerebral cortex, and (2) the multiple roles played by cerebellar circuitry in motor control, cognitive  
299 operations and emotional processing, the potential applications of ctDCS are huge.

300

301 *tDCS and cerebellar plasticity*

302 One of the main objectives of this CB-NIBS technique is to enhance neural plasticity, which is  
303 thought to underlie neuronal excitability and learning in vivo, including semantic prediction, word  
304 generation and verbal working memory [43–46]. In particular, the cerebellum seems to be engaged  
305 in the early acquisition of new motor and non-motor skills, whereas the primary motor cortex is  
306 likely involved in retention and consolidation of memory traces [47–49]. From a mechanistic  
307 standpoint, cerebellar circuitry operates as a forward controller learning to predict the precise timing  
308 of events [50]. Signals entering the cerebellum via the mossy fibers are processed in the granular  
309 layer, transmitted to Purkinje cells via parallel fibers through complex signals mediated by local  
310 interneurons, with a copy relayed in cerebellar nuclei. Purkinje cells inhibit nuclei via GABA. In  
311 other words, the cerebellar cortex orchestrates a side loop blocking or unblocking cerebellar nuclei  
312 [50]. Sites of synaptic plasticity are multiple in the granular layer, the molecular layer and at the  
313 level of cerebellar nuclei. Therefore, the concept of a single form of synaptic plasticity between  
314 parallel fibers and Purkinje neurons under the unique control of climbing fibers originating in the  
315 inferior olive is no longer valid [50]. This makes of the cerebellum a highly complex neuronal  
316 machine characterized by an unparalleled degree of flexibility. Furthermore, Purkinje cells are  
317 chemically heterogeneous, and the mossy fiber system itself is a critical actor in cerebellar plasticity  
318 [51]. Coordination is currently explained by accurate regulation of timing and gain in the different  
319 cerebellar modules composing the cerebellum [51]. Cerebellum is viewed as a timing machine in

320 whom interactions within the cerebellar cortex support sub-second timing, with supra-second timing  
321 requiring cortical and basal ganglia networks [52]. In this scenario, the mechanisms by which  
322 cerebellar polarization may improve learning in humans remain largely unknown, possibly  
323 involving both cortical and subcortical routes. A recent fMRI paper has shown that anodal ctDCS  
324 dampens putamen-cerebellar connectivity, reducing cerebellar inhibition and enhancing sequence  
325 learning in the serial reaction time task [53]. However, this observation does not explain the  
326 increased learning-related BOLD activity in M1, nor the effect of parallel and climbing fibers on  
327 synapses with Purkinje cells in DCN, also considered to play a key role in cerebellar-dependent  
328 learning [54].

329

### 330 *Variability in the outcome of ctDCS*

331 Converging evidence suggests that CBI could be modulated by tDCS, although results are still  
332 unclear. The first neurophysiological evidence was by Galea et al. [17], who showed in healthy  
333 subjects that cathodal ctDCS decreased CBI, anodal ctDCS increased it, and sham stimulation  
334 induced no changes. Other results were reached by a later study [18], in which anodal ctDCS  
335 reduced CBI. Although controversial, such results clearly suggest that ctDCS can modulate  
336 cerebellar control over the motor cortex. Studies combining functional MRI with ctDCS have  
337 shown that ctDCS has a polarity-specific effect on the BOLD activity of the dentate nuclei and on  
338 functional connectivity [55,56]. Unfortunately, these are isolated findings. More systematic studies  
339 combining different imaging techniques are crucially needed to gain more insight into the  
340 underlying mechanisms of ctDCS and the possible impact it can have at neurophysiological level.  
341 Such fundamental studies are necessary, especially since the behavioral results of studies using  
342 ctDCS are divergent [57]. The variability in the outcome of ctDCS might be explained by recent  
343 modeling studies that have shown that different placements of the reference electrode (e.g., on the  
344 buccinator muscle or on the contralateral supraorbital area) can have a significant effect on the  
345 electric field distribution and orientation inside the cerebellum [58]. In addition, significant inter-

346 individual differences in electric field distribution even when using the same sponge electrode  
347 montage have been shown [59]. Since both the distribution and the orientation of the electric field  
348 inside the cerebellum are critical to predict the behavioral effect of cerebellar stimulation future  
349 studies should consider modeling the electric field on an individual level, taking into account the  
350 areas and types of neurons (e.g. synapses between parallel fibers and dendritic trees of Purkinje  
351 cells, or Purkinje cell responsiveness) which are targeted [58]. High definition (HD)-tDCS might  
352 provide more opportunities concerning targeted stimulation, but more research is needed to address  
353 its limitations – such as the lower electric field strengths due to the smaller electrode-skin interface -  
354 and to determine the optimal electrode configuration [58].

355

#### 356 *Cerebello-cerebellar tDCS: an entire field to discover*

357 At this stage of research, the approach of neuromodulation of cerebellar circuitry by application of  
358 tDCS targeting only the cerebellum remains totally open. We are missing data showing whether the  
359 tuning of a given portion of the cerebellar cortex with respect to another portion might impact on  
360 motor, cognitive or emotional processing. In theory, cerebello-cerebellar tDCS paradigms would  
361 enhance the excitability of a given area (area under the anode) and simultaneously reduce the  
362 excitability of the second area (area under the cathode), keeping in mind that the most accessible  
363 portion of the cerebellar cortex below the skull belongs to the posterior lobe (lobules VI-VII-VIII-  
364 IX). Typical applications would be the treatment of defects of the intra-cerebellar distribution of  
365 activity as observed in dyslexia [60] or modulation of aberrant networks as observed in  
366 schizophrenia [61]. The length of parallel fibers in humans extends beyond several millimeters  
367 (mm), an anatomical parameter that needs to be considered for neuromodulation of the cerebellar  
368 cortex.

369

#### 370 *Cerebello-cerebral tDCS*

371 Cerebello-cerebral tDCS has been shown to be effective in very small samples of patients [62]. The  
372 technique can reduce postural tremor, action tremor and motor dysmetria. Both tremor and  
373 dysmetria are landmarks of cerebellar dysfunction. Tremor is particularly responsive in rare genetic  
374 ataxias related to calcium-activated chloride channel involved in neuronal excitation [63]. The  
375 improvement of motor dysmetria is associated with a favorable effect on the onset latency of the  
376 antagonist electromyographic (EMG) activity, a neurophysiological marker of the defect in  
377 programming of timing of motor commands. Again, there is a major need to address the following  
378 points: (1) which patients respond to this technique of stimulation? (2) what is the duration of the  
379 effect? (3) how does the technique impact on the plasticity occurring in the cerebellum? (4) is there  
380 a link with the functional level of the cerebellar reserve, defined as the capacity of the cerebellum to  
381 compensate for tissue damage or loss of function [64]? At a molecular level, the mechanisms of  
382 action include the modulation of ionic gradients in the extracellular space, regulation of channels  
383 and pumps as well as modulation of receptors/neurotransmitters [22]. All these elements are critical  
384 for neuronal plasticity.

385

### 386 *Transcranial alternating current (tACS) and the cerebellum*

387 Besides tDCS, the use of other transcranial electrical stimulation methods to stimulate the  
388 cerebellum is also increasing. tACS has been suggested as a promising stimulation method due to  
389 the intrinsic cerebellar oscillations. Naro et al. [44] already showed that tACS over the cerebellum  
390 is safe, and that certain frequencies can influence CBI and, consequently, motor adaptation. Other  
391 studies have investigated tACS but used a dual site approach to study the phase specificity of the  
392 stimulation [65,66]. By targeting the cerebellum and M1 at the same time, either in phase or anti-  
393 phase, it has been demonstrated that intercortical functional synchronization is an important feature  
394 of motor performance improvement, irrespective of current intensity [65,66].

395

### 396 *Implications for future research*



397 Physiological and clinical effects of cerebello-cerebellar tDCS, in terms of changes in motor,  
398 cognitive and emotional behaviors, are still missing. However, this represents a scientific field to be  
399 further explored, in lights of its potentialities. Besides direct current (DC) and alternating current  
400 (AC) applications, several other stimulation methods have been sporadically used to manipulate the  
401 oscillatory activity and connectivity of the cerebellum, such as transcranial pulsed current  
402 stimulation (tPCS) [67] and oscillatory transcranial direct current stimulation (otDCS) [68], with  
403 promising effects on cognition and awareness. However, more research is needed to confirm the  
404 effectiveness of these methods and understand how they impact on the various forms of cerebellar  
405 plasticity.

406

#### 407 **Animal models of CB-NIBS**

408 NIBS is expected to become an accepted tool to promote neural plasticity in a wide range of  
409 disabling disorders affecting the human brain, allowing symptomatic alleviation [69]. This is  
410 particularly relevant for cerebellar disorders, from pure cerebellar disorders to disorders affecting  
411 both cerebellar and extra-cerebellar circuits [70]. NIBS also contributes to the discovery of  
412 cerebellar functions [69]. The demonstration of the detailed network/cellular/molecular mechanisms  
413 of action of CB-NIBS will benefit from the analysis of both animal and human studies, provided the  
414 animal models are used in a translational perspective. Historically, disorders of basal ganglia such  
415 as Parkinson's disease have attracted the attention of scientists interested in noninvasive and  
416 invasive neuromodulation techniques, but other nodes of the motor circuitry are gaining in interest  
417 [69,71]. The recent discovery of anatomical connectivity between the cerebellum and basal ganglia  
418 (subthalamic nucleus and striatum) has contributed to a reconsideration of the cerebellum as a  
419 potential target to manage movement disorders [72]. Modulation of basal ganglia might influence  
420 cerebellar circuitry and vice-versa [69].

421

422 *Animal studies assessing NIBS of the motor cortex*

423 We will not review here the details of the invasive approaches such as deep brain stimulation with  
424 implanted electrodes in animal models (including recent genetic approaches such as the Cre/LoxP  
425 model to silence selective tracts or the optogenetic stimulation instead of electrical stimulation)  
426 which have been discussed recently in details in another Consensus Paper [69]. The effects of  
427 TMS/tDCS/tACS of the cerebellum or the motor cortex have been explored mainly in rodents, but  
428 also in other species such as turtles or rabbits [73,74]. In TMS research, application of 4 weeks of  
429 low-intensity repetitive TMS (LI-rTMS) to the mouse cerebellum alters Purkinje cell dendritic and  
430 spine morphology [75]. Furthermore, LI-rTMS induces climbing fiber reinnervation to a denervated  
431 hemocerebellum. High-frequency stimulation increases intra-cellular calcium by releasing the ions  
432 from intracellular stores. tDCS of the motor cortex restores the excitability of the motor cortex  
433 which is observed contralaterally to a hemocerebellar ablation [76], and modulates CBI, as observed  
434 in humans [77]. Using extra-cellular recordings, it has been demonstrated in rats that the simple  
435 spike activity of Purkinje cells is particularly entrained by AC fields, with clear evidence that these  
436 neurons represent the primary cell type affected by electrical stimulation thanks to their  
437 connectivity and the morphology of their dendritic trees [78]. It has also been shown in rats, using  
438 optogenetic techniques that delta frequency optogenetic stimulation of thalamic synaptic terminals  
439 of lateral cerebellar projection neurons improve timing performances in a model of schizophrenia-  
440 related frontal dysfunction [79]. In mouse, anodal stimulation of the cerebellum has an acute post-  
441 stimulation effect on baseline gain reduction of the vestibulo-ocular reflex (VOR), a mechanism  
442 related to long-term potentiation (LTP) and intrinsic plasticity pathways of Purkinje neurons [80].  
443 tACS entrains endogenous neural oscillations in the cerebellar cortex: (1) during the negative phase  
444 of a sinusoidal electric current applied over the cerebellar cortex, the firing rates augments in  
445 cerebellar cortex; (2) during the positive phase of tACS, the neural activity is suppressed [73]. The  
446 orientation of neurons with respect to the direction of the current administered is particularly  
447 relevant, given the highly folded structure of the cerebellar cortex. This is particularly relevant for  
448 neuromodulation due to the major role played by brain oscillations in sensorimotor and cognitive

449 processes. Within the cerebellar cortex, complex spike activity causes low frequency oscillations in  
450 the 1-4 Hz range, whereas simple spikes lead to high frequencies in the 160-260 Hz range, as shown  
451 using tetrode and multisite recording [81]. In vivo electrophysiological measurements in adult rat  
452 brain slices have confirmed marked resonance at 200 Hz in Purkinje neurons, as a result of the  
453 morphology of the Purkinje cell, interacting with a simple spiking mechanism and dendritic  
454 fluctuations [82]. Nevertheless, other studies have found a wide range of frequencies. Overall, it is  
455 assumed that NIBS tunes the patterns and timing of discharges within the cerebellar cortex.

456

#### 457 *Implications for future research*

458 There is a clear need to develop standardized animal experiments to elucidate the mechanisms of  
459 action of NIBS in humans, in order to optimize/maximize the efficiency of cerebello-cerebral  
460 commands for a large list of brain disorders. Invasive approaches such as deep brain stimulation of  
461 the cerebellar cortex or cerebellar nuclei allow the fine characterization of the effects upon  
462 cerebello-cerebral networks and provide complementary data to the results obtained by NIBS  
463 techniques [69]. The community has accepted the safety profile of NIBS but is expecting clear-cut  
464 demonstrations on both its mechanisms of action and its effectiveness in selected disorders. Animal  
465 models are needed, for example, to explore the hypothesis that targeting the cerebellum might  
466 improve motor and cognitive deficits occurring after supra-tentorial stroke, given its massive  
467 connectivity with the cerebral cortex and its high degree of plasticity (see section 6 - Cerebellar  
468 Stimulation: a new Approach for Stroke Recovery). Moreover, NIBS might complement the  
469 pharmacological approach, since pharmacological therapies are effective in specific forms of  
470 cerebellar ataxias, but many progressive cerebellar disorders still lack active drugs (see section 9 -  
471 ctDCS in individuals with hereditary cerebellar ataxia). Therefore, potential complementary effects  
472 of NIBS and drugs should be investigated [83]. Animal models provide the opportunity to do so,  
473 and might contribute to the understanding of long-term neural consequences of NIBS, a question  
474 which still lacks a consensus [16]. Finally, animal models are also required to better understand

475 how NIBS acts upon cerebello-spinal projections, given the discovery that cerebello-spinal NIBS  
476 reduces symptoms in ataxic patients [84].

477

#### 478 **Effects of cerebellar non-invasive brain stimulation on motor learning in healthy and disease**

479 Learning new motor skills is vital for carrying out the daily life activities we perform. Our ability to  
480 learn new motor patterns or to adjust previously learned ones requires the engagement of several  
481 behavioral and plasticity mechanisms that span across a network of cortical and subcortical brain  
482 regions. A key node of the learning network is the cerebellum, which plays a particularly important  
483 role in acquiring new motor patterns when responding to new environmental demands and in re-  
484 learning motor skills after injury [85]. Given the cerebellum's rich neuroplasticity potential, its  
485 modulation through CB-NIBS, like tDCS and theta-burst stimulation (TBS), has received increasing  
486 attention, with the aim to enhance performance during motor tasks.

487 To understand how targeting the cerebellum with stimulation can influence motor learning, it is  
488 critical to distinguish the different types of learning tasks studied in a laboratory setting. This is  
489 because motor learning encompasses multiple processes, which range from an implicit error-driven  
490 mechanism for maintaining calibration of our movements to complex, high-level cognitive  
491 strategies to respond to novel environments [29,45]. Here, we will cover how cerebellar stimulation  
492 affects distinct task categories: motor adaptation and de-novo skill learning.

493 Motor adaptation is the short-term reshaping of a well-practiced action in the face of dynamic  
494 perturbations (e.g., visuomotor rotation, force-field). In these tasks, participants learn to quickly  
495 reduce movement errors that are imposed by the perturbation by generating an internal model that  
496 predicts the consequences of efferent motor commands during movement. The cerebellum is widely  
497 believed to calibrate this model since patients with cerebellar lesions are impaired at adjusting their  
498 movements to novel environments [86]. This is supported by recent evidence showing that Purkinje  
499 cells appear to encode the outcomes of kinematic predictions rather than motor commands [87].

500 Animal studies have shown that adaptation is mediated through synaptic mechanisms of long-term  
501 depression (LTD) in Purkinje cells [88]. Similarly, studies in healthy individuals have shown a link  
502 between changes in cerebellar excitability and motor adaptation [12,28]. Bearing this in mind, along  
503 with the notion that anodal tDCS likely increases Purkinje cell activity, Galea et al. [48]  
504 investigated how applying this technique to distinct brain regions (cerebellum, M1, primary visual  
505 cortex - V1) influenced learning of a visuomotor rotation [48]. ctDCS was found to specifically  
506 speed-up the error reduction process, whereas M1 stimulation enhanced the retention of the newly  
507 learned rotation. No changes were found when stimulating V1, suggesting that modulating the  
508 cerebellum improves acquisition in reaching. Similar effects of ctDCS have been found for force-  
509 field tasks [89] and locomotor adaptation [90]; however, the effects appear limited to the trained  
510 cerebellar hemisphere [91]. Interestingly, applying distinct cerebellar TBS protocols before a  
511 visuomotor rotation produces bidirectional effects on learning [12]. Intermittent TBS (iTBS), a  
512 protocol thought to increase cerebellar excitability by activating LTP of parallel fiber-Purkinje cell  
513 synapses, was found to accelerate adaptation in healthy subjects [12] and stroke patients [92]. For  
514 example, Bonni et al. [92] reported that cerebellar iTBS increased in the performance of 8 chronic  
515 stroke patients during a visuo-motor adaptation task (i.e., during both the learning and re-adaptation  
516 phase of the task). On the other hand, continuous TBS (cTBS) produced an opposite effect by  
517 decreasing the learning rate [12]. Overall, these investigations indicate that cerebellar stimulation  
518 modulates motor behavior by enhancing cerebellar-dependent, error-based learning mechanisms.

519 Unlike motor adaptation, motor skill learning refers to an improvement in both movement speed  
520 and accuracy of a novel motor pattern that goes beyond baseline levels. Indeed, skill learning  
521 requires one to develop movement patterns from scratch, which become automatized through  
522 repeated practice and fine-tuned by cerebellar-dependent learning mechanisms [47]. For example,  
523 successfully performing a tennis forehand swing requires one to learn how to control the tennis-  
524 racket (i.e., develop an internal model) while performing a fluid sequence of movements. Thus, it is  
525 likely that skill learning can also benefit from excitatory cerebellar stimulation. The sequential-

526 visuomotor isometric pinch force task (SVIPT) is a well-characterized task to mimic this kind of  
527 learning since it requires individuals to simultaneously learn how to control a new device in a novel  
528 environment, along with performing a sequence of isometric movements. Interestingly, when  
529 anodal ctDCS was administered during SVIPT performance, healthy individuals showed enhanced  
530 motor skill acquisition [93]. Specifically, skill improvement was marked by reduced errors rather  
531 than movement times. This finding suggests that tDCS may enhance cerebellar-dependent error-  
532 based learning, which likely plays a role in developing an internal representation of skill task  
533 dynamics.

534 It should be noted that skill learning also requires the involvement of cognitive strategies (e.g.,  
535 tennis players will aim to place the ball at a location away from the opponent). Given the  
536 accumulating evidence that the cerebellum plays an important role in cognition and its vast  
537 connections to prefrontal areas [85], tDCS may also enhance the implementation of strategies.  
538 Supporting this notion, inhibitory repetitive TMS (rTMS) over the cerebellum disrupts cognitive  
539 functions like procedural learning, as measured by the serial reaction time task (SRTT), where  
540 individuals must learn to respond as quickly as possible to stimuli that cue a specific keyboard  
541 button response [94]. On the other hand, anodal ctDCS applied during SRTT performance was  
542 found to reduce error rates [95] and reaction time responses [96], indicating that stimulation can  
543 also improve cognitive components that are embedded in motor skills.

544 The work highlighted above importantly demonstrates that the cerebellum has a role in various  
545 motor and cognitive activities, which suggests that applying neuromodulatory strategies to this  
546 brain region may be particularly effective for improving patient recovery. Indeed, a recent clinical  
547 trial found that combining cerebellar iTBS with physical therapy to patients with stroke leads to  
548 improved gait and balance recovery by enhancing motor relearning and promoting cerebello-  
549 cortical reorganization [97]. While the effects of anodal tDCS on motor function in stroke remain  
550 unclear, recent work has shown that cerebellar stimulation enhanced the effects of behavioral  
551 aphasia [98]. Finally, applying a single-session of anodal ctDCS improved the symptoms of patients

552 with ataxia [99], providing preliminary evidence for the efficacy of tDCS, to be further explored in  
553 future rehabilitative approaches.

554

#### 555 *Implications for future research*

556 Recent evidence demonstrates how modulating cerebellar excitability with NIBS can enhance  
557 motor learning. As the effects of stimulation in healthy individuals primarily enhances the  
558 acquisition of new motor patterns, these interventions have the potential to augment physical  
559 therapy and speed up rehabilitation processes. Given the role the cerebellum plays in numerous  
560 learning paradigms, stimulation over this region might support patient recovery in both motor and  
561 cognitive functions. Further studies are needed with larger sample sizes, homogenous populations,  
562 as well as optimized study designs and stimulation protocols.

563

564

565

#### 566 **Cerebellar Stimulation: a new Approach for Stroke Recovery**

567 Stroke is a major cause for mortality, disability, and resulting economic costs for health care  
568 systems worldwide [100]. Further optimization of post-stroke care, including the development of  
569 novel treatment strategies, is of great importance. One promising novel strategy is the combination  
570 of CB-NIBS with behavioral training.

571

#### 572 *Stroke and cerebellar neurophysiology*

573 Stroke often results in brain network disturbances, frequently impacting the cortico-cerebellar  
574 system. For instance, one pathophysiological consequence frequently described is cerebellar  
575 diaschisis – a reduction of cerebral blood flow and metabolism in the contralateral cerebellar  
576 hemisphere following a supratentorial ischemic stroke [101]. Furthermore, vascular lesions of the  
577 cerebellar cortex, thalamus, or posterior limb of the internal capsule have shown to result in

578 disbalanced cerebellar cortical output, including aberrant CBI [102]. These processes have been  
579 associated with functional impairment, making them a potential mechanistic target to develop and  
580 test novel CB-NIBS protocols. Additionally, CB-NIBS could be used to support intrinsic learning  
581 processes with the aim of augmenting the reacquisition of lost abilities [103]. Of note, this treatment  
582 strategy may be applicable to various syndromes following stroke. For example, frequent target  
583 impairments are hand motor deficits, balance and gait disturbance, or cognitive abnormalities –  
584 affecting ~ 85%, ~ 50%, ~ 60% of stroke survivors respectively [104]. Table 1 summarizes a series  
585 of investigations testing the use of CB-NIBS to treat different impairments in stroke survivors.

586

#### 587 *CB-NIBS studies targeting balance and gait*

588 The largest proportion of research was conducted assessing potential effects on balance and gait  
589 functions. For instance, Zandvliet et al. [105] studied the effect of ipsi- and contralesional anodal  
590 ctDCS in combination with training of a balance tracking task in 15 chronic stroke patients. Their  
591 study followed a randomized, single-blind, sham-controlled, cross-over design. Active  
592 contralesional stimulation led to an improved tandem stance performance at the post-stimulation  
593 evaluation, when compared to sham. This pioneering work is important as it documents the  
594 potential of improving balance function in stroke using ctDCS, in a task, which has considerable  
595 similarity to everyday life activities. Complementary to this work, Koch et al. [97] provided  
596 important evidence that multi-session iTBS of the contralesional cerebellar hemisphere applied in  
597 combination with physiotherapy for a duration of 3 weeks can lead to an improvement in gait and  
598 balance function as quantified with the Berg Balance Scale (BBS) [106]. Picelli et al. [107]  
599 extended the described approach by testing a multi-site stimulation strategy in 20 chronic stroke  
600 patients. In their first pilot trial, the authors compared a group receiving cathodal contralesional  
601 ctDCS plus cathodal spinal tDCS (S-tDCS) with a group receiving anodal tDCS to the ipsilesional  
602 primary motor cortex (M1-tDCS) plus cathodal S-tDCS. The stimulation protocols were applied for  
603 20 minutes over 10 sessions while patients performed robot-assisted gait training (RAGT). The



604 cerebellar-spinal stimulation group reached a larger improvement in the primary outcome (6-minute  
605 walk test – 6MWT) [108], when compared to the M1-spinal group. In a follow-up study, Picelli et  
606 al. [109] compared cathodal cerebellar-spinal stimulation protocol targeting the contralesional  
607 cerebellar hemisphere to an ipsilesional cerebellar hemisphere stimulation group, while the patients  
608 underwent RAGT. No significant group differences in the primary outcome (6MWT), were found.  
609 The work from Picelli et al. [109] is of particular relevance, since it tested an innovative multi-site  
610 stimulation approach and documented the feasibility of combining ctDCS with a neurotechnology-  
611 based intervention (RAGT). CB-NIBS has been also used to target balance and gait functions in  
612 patients with posterior circulation stroke including cerebellar lesions, for example the studies from  
613 Bonni or Kim et al. [110,111]. These studies applied different TMS protocols (iTBS and 1 Hz  
614 conventional rTMS) in different patient cohorts (chronic versus acute stroke) and demonstrated an  
615 improvement in balance and gait function.

616

617

#### 618 *CB-NIBS studies targeting cognitive deficits*

619 Other studies have assessed the effects of CB-NIBS in stroke patients with cognitive abnormalities,  
620 in particular in the language domain. In their pioneering work, Sebastian et al. [98] applied anodal  
621 tDCS to the right cerebellum in a double-blind, sham-controlled, within-subject cross-over case  
622 design studying a mute chronic, stroke patient with bilateral lesions in the middle cerebral artery  
623 territory. The stimulation protocol was applied over 15 sessions concurrently to a behavioral  
624 spelling treatment. Active stimulation improved spelling to dictation performance, when compared  
625 to sham. This case study is important as it provides preliminary evidence for the feasibility of  
626 repetitive application of ctDCS to target language abnormalities following stroke. Of note, the  
627 combined behavioral and ctDCS treatment induced improvements beyond the trained task,  
628 indicating transfer effects to related activities (written picture naming). Similarly, Marangolo et al.  
629 [112] extended this approach by studying the effects of cathodal tDCS applied to the right

630 cerebellum concurrently to a language training. Their study cohort consisted of 12 chronic stroke  
631 patients with left-hemispheric lesions and resulting mild non-fluent aphasia. Active stimulation  
632 resulted in greater improvement in a verb generation task, when compared to sham. This proof-of-  
633 principle work was crucial as it indicates the effectiveness of ctDCS to augment language training  
634 in a small cohort of mildly affected stroke patients. Indeed, in a recent follow-up investigation,  
635 Sebastian et al. [113] performed a randomized, double-blind, sham-controlled, within-subject cross-  
636 over study design, where participants received anodal ctDCS (N = 12) or cathodal ctDCS (N = 12)  
637 plus computerized aphasia therapy as well as sham plus computerized aphasia therapy. The authors  
638 found that tDCS was more effective than sham in the immediate post-treatment phase for  
639 participants who received ‘tDCS first’; a significant effect of tDCS for untrained naming was also  
640 observed immediately and 2 months post-treatment. These interesting findings corroborate the  
641 concept that cerebellar stimulation might be an optimal target site for aphasia rehabilitation solving  
642 the concerns over stimulation of a lesioned brain area.

643

#### 644 *Other applications*

645 ctDCS may also be useful to improve hand motor function following stroke. This novel approach is  
646 supported indirectly by a growing body of evidence documenting beneficial effects of ctDCS on  
647 different motor learning hand skill tasks in young healthy volunteers [93,114]. Yet, to the best of  
648 our knowledge, evidence favoring this treatment approach in the stroke cohort is lacking.

649

#### 650 *Implications for future research*

651 CB-NIBS is a promising alternative approach to reduce a variety of impairments in stroke  
652 survivors. However, to help establish CB-NIBS in clinical practice additional research is needed:  
653 (1) to determine the role of the cerebellum in recovery processes; (2) to investigate the effects of  
654 different stimulation protocols, e.g., effect of stimulation polarity, focality, and duration; (3) to  
655 assess interactions between task-specific training and CB-NIBS; (4) to identify predictors of clinical

656 response; (5) to confirm CB-NIBS efficacy in regular clinical settings by performing larger  
657 randomized controlled trials.

658

### 659 **CB-NIBS in relation to speech and language**

660 Clinical and neuroimaging studies have implicated the cerebellum in the regulation of speech and  
661 language, and CB-NIBS may offer substantial advantages in establishing a causal role in these  
662 functions [115]. This section provides a brief overview of CB-NIBS studies examining such a role  
663 in healthy adults, along with those that have used CB-NIBS as a neurorehabilitation method.

664

#### 665 *Verbal working memory*

666 Cerebellar pathology has been often associated with impairment in verbal working memory, and  
667 functional neuroimaging has disclosed task-related cerebellar activation in verbal working memory  
668 tasks [115]. Consistent with these findings, CB-NIBS effects on Sternberg task performance have  
669 been reported, with single-pulse TMS (right HVI/HVIIa Crus I) increasing response latencies [116],  
670 and with cTBS (right posterolateral cerebellum) impairing accuracy [117]. Further evidence has  
671 been provided by ctDCS studies. In Ferrucci et al. [118], both anodal and cathodal bilateral  
672 posterolateral CB-NIBS compromised the practice-dependent reduction in response latencies; in  
673 Boehringer et al. [119], cathodal ctDCS (right posterolateral cerebellum) decreased forward digit  
674 spans and impaired the practice-induced increase in backward digit spans. In Macher et al. [120],  
675 impaired recognition of items of medium difficulty (memory load) was reported following anodal  
676 ctDCS (right cerebellum), with no effect on items of low or high difficulty. These results suggest  
677 that task difficulty may interact with stimulation effects. Such interactions were also reported in  
678 another study [121], where cathodal ctDCS (right posterolateral cerebellum) increased response  
679 speed on the (difficult) Paced Auditory Serial Subtraction Task [122], but not on the (easier) Paced  
680 Auditory Serial Addition Task [121]. In conditions of high executive demand and memory load,

681 depression of the cerebellar cortex may release cognitive resources by disinhibiting the contralateral  
682 prefrontal cortex and enhancing performance [121].

683

#### 684 *Verbal fluency*

685 Likewise, functional neuroimaging and clinical studies have been corroborated by neurostimulation  
686 research in establishing a cerebellar role in verbal fluency [115]. In Arasanz et al. [123], two groups  
687 completed phonemic and semantic fluency tasks pre- and post-cTBS: one received stimulation over  
688 the right posterolateral cerebellum and the other on the left. Right CB-NIBS induced lower  
689 switching (i.e., exhaustion of a phonemic or semantic cluster and shift to another) scores in the first  
690 15 seconds of phonemic fluency performance, without affecting semantic fluency (but see Rami et  
691 al. [124]). In a tDCS study, facilitatory effects were reported following cathodal ctDCS (right  
692 posterolateral cerebellum) on the rate and consistency of participants' responses in a verb-  
693 generation task [121]. In another study [56], anodal ctDCS (right posterolateral cerebellum)  
694 improved phonemic fluency (trend in the same direction was observed for cathodal stimulation).

695

#### 696 *Predictive language processing*

697 The cerebellum might optimize language processing by supporting predictive mechanisms, as it  
698 does on motor control [125]. Noun-to-noun (forward) phrasal associative priming (but not semantic  
699 categorical priming) was enhanced following right posteromedial cerebellar cTBS [126]. Moreover,  
700 noun-to-verb (forward) semantic associative priming (but not semantic categorical priming) was  
701 enhanced following right posterolateral cerebellar cTBS [127]. In Allen-Walker et al. [128], cTBS  
702 of the left posterolateral cerebellum increased backward associative priming (and no changes for  
703 forward priming). Furthermore, 1-Hz rTMS (right posterolateral cerebellum) slowed participants'  
704 predictions of the final noun in sentences presented verbally [129]. In Miall et al. [130], cathodal  
705 ctDCS (right posterolateral cerebellum) decreased and anodal ctDCS increased the speed advantage  
706 for the predictable sentence items, without changing performance for the nonpredictable ones. In

707 Gatti et al. [131], participants judged whether noun-adjective pairs were semantically related, while  
708 online neuronavigated TMS was administered over a control site or a right posterolateral cerebellar  
709 site implicated in semantic prediction. CB-NIBS caused a selective decrease in accuracy for related  
710 pairs relative to unrelated ones, consistent with theories extending the cerebellar predictive role to  
711 semantic processing. In Dave et al. [132], neuronavigated offline rTMS (beta stimulation) of a right  
712 posterior HVIIa Crus I region (vs. a control site) influenced the N400 ERP component during  
713 semantic prediction in sentence comprehension.

714

#### 715 *Grammar*

716 Cerebellar pathology has also been associated with grammatical deficits [115]. An rTMS study  
717 [133] has disclosed evidence of cerebellar involvement in processing spatial-temporal associations  
718 in verb tenses. Participants indicated whether a verb was past or future tense with right and left  
719 response buttons. Faster and more accurate responses were produced if the left button was  
720 associated with the past and the right with the future tense. Stimulation over both cerebellar  
721 hemispheres decreased such accuracy for identifying future (right) and past (left) tense. Right CB-  
722 NIBS selectively increased response latencies to the future tense of action verbs. These findings  
723 were interpreted as reflecting a cerebellar role in processing grammatical rules for verb conjugation,  
724 and in anticipating future events based on past experiences.

725

#### 726 *Speech motor programming*

727 NIBS may also help to establish whether the cerebellum supports speech production above and  
728 beyond articulatory execution [115]. A low-frequency rTMS study [134] investigated the possibility  
729 of a causal role of the right posterior cerebellum (right or left HVIIa Crus I and II) in speech motor  
730 programming, especially the self-monitoring of speech errors. Performance in a speech production  
731 task was impaired after right CB-NIBS, suggesting that the cerebellum may support internal models  
732 of upcoming speech via verbal working memory processes.

733

734 *Effects on cerebro-cerebellar networks*

735 Further studies have combined NIBS with functional neuroimaging to investigate the effects of CB-  
736 NIBS on the interaction between the cerebrum and the cerebellum within the context of speech and  
737 language processing. In Cho et al. [135], 1-Hz rTMS (left posterolateral cerebellum) was followed  
738 by increased glucose metabolism (fludeoxyglucose PET - FDG PET) in cognition- and language-  
739 related areas, including Wernicke's and Broca's areas, interpreted as reflecting compensatory neural  
740 activity. In Macher et al. [136], anodal ctDCS (right cerebellum) was followed by impaired digit  
741 recognition performance (modified Sternberg task). Attenuated signal (fMRI) was reported in right  
742 HVIIb, along with decreased functional connectivity between HVIIb and the posterior parietal  
743 cortex in the late encoding phase. In another study [56], however, anodal ctDCS (right  
744 posterolateral cerebellum) modulated resting-state functional connectivity in language networks,  
745 increased the functional connectivity between the cerebellum and language and speech-motor  
746 regions, and improved verbal fluency. In D'Mello et al. [55], anodal ctDCS (right posterolateral  
747 cerebellum) increased activation in right HVIIa Crus I/II during semantic prediction and enhanced  
748 resting-state functional connectivity between hubs of the reading/language networks; ctDCS effects  
749 were focal to language-associated regions of the cerebellum and cerebral cortex.

750

751 *Neurorehabilitatory potential*

752 Given the functional and anatomical connectivity of the (right) cerebellar hemisphere with core  
753 language regions in the (left) cerebral hemisphere, CB-NIBS has also been employed in studies of  
754 speech and language rehabilitation [115]. Some studies have employed inhibitory CB-NIBS  
755 protocols. Their facilitatory effects are often attributed to a reduction of CBI over the motor and  
756 nonmotor cerebral areas targeted by the cerebellar nuclei. In Marangolo et al. [112], ctDCS was  
757 combined with language treatment in 12 aphasic patients. Each patient underwent ctDCS in four  
758 conditions (right posterolateral cathodal vs. sham stimulation; verb naming vs. generation), run in

759 five consecutive daily sessions over four weeks. Improvement was only noted for verb generation  
760 following cathodal stimulation, suggesting that ctDCS is efficacious in tasks requiring the  
761 additional employment of non-linguistic strategies. These effects dovetail with those noted  
762 following cathodal ctDCS on the rate and consistency of responses in verb generation in healthy  
763 adults [121]. In Sebastian et al. [113], 24 patients with chronic aphasia received anodal or cathodal  
764 ctDCS and computerized aphasia therapy followed by sham stimulation and computerized aphasia  
765 therapy, or the opposite order. While there was no significant effect of treatment (ctDCS vs. sham)  
766 for trained naming, ctDCS was more effective than sham when it followed treatment immediately.  
767 For untrained naming, there was significant improvement immediately post-treatment, which  
768 persisted for 2 months. The enhancement was larger following cathodal ctDCS for both trained and  
769 untrained naming.

770 Inhibitory CB-NIBS protocols have also been employed in cerebellar pathology. In [137], a low-  
771 frequency rTMS protocol (right posterolateral cerebellum; 21 days of stimulation) was applied on a  
772 patient with idiopathic late-onset cerebellar atrophy that presented with scanning speech dysarthria.  
773 Improvements were noted for limb coordination and gait, but also for speech (louder and clearer  
774 voice), and naming in dual-task conditions, consistent with the enhancement noted in healthy adults  
775 following inhibitory CB-NIBS protocols [121]. In Lin et al. [138], 19 SCA patients underwent  
776 neuronavigated cTBS (right cerebellum vs. sham stimulation) and were then instructed to produce  
777 sustained vowels while perceiving their voice pitch-shifted. Relative to sham, cerebellar cTBS led  
778 to smaller magnitudes of vocal compensations for pitch perturbations, showing that CB-NIBS can  
779 modulate the abnormal auditory-vocal integration in SCA.

780 In other studies, the application of excitatory protocols was accompanied by increased CBI and  
781 facilitatory effects. In Brusa et al. [139], daily sessions of bilateral posterolateral iTBS for 2 weeks  
782 in 10 PSP patients were followed by increased CBI, bilaterally increased BOLD signal in the  
783 caudate nuclei, and alleviation of dysarthria. In Sebastian et al. [98], ctDCS (anodal vs. sham) was  
784 combined with spelling therapy in a patient with aphasia and anarthria due to large bilateral chronic

785 strokes. There was greater improvement with ctDCS relative to sham, especially for untrained  
786 words, with generalization to written picture naming only seen during ctDCS. These improvements  
787 were accompanied by increased resting-state cerebro-cerebellar functional connectivity. However,  
788 in a study of 24 patients with chronic post-stroke aphasia, anodal ctDCS (right cerebellum) did not  
789 enhance language processing, either immediately following treatment or after 3 months [140].

790

#### 791 *Implications for future research*

792 The above findings highlight the need for a better understanding of the effects of different CB-  
793 NIBS protocols on performance in different tasks, as well as how and why these vary between  
794 healthy adults and patients, but also among different types of patients. Methodological  
795 ~~enhancements~~ improvements are required, including preregistered, sham-controlled, double-blind  
796 studies using larger sample sizes and neuronavigated localization of the stimulation site.

797

#### 798 **ctDCS evidence in neuropsychiatric disorders**

799 The cerebellum has been found to have a functional role in psychiatric disorders, such as attention  
800 deficit hyperactivity disorder, autism spectrum disorders, schizophrenia, bipolar disorder (BD),  
801 major depressive disorder, and anxiety disorders [141]. This is not surprising, given the intricate  
802 connections between the cerebellum and other cerebral structures, for example those cortical areas  
803 responsible for cognitive and emotional processes through the cortico-ponto-cerebellar and  
804 cerebello-thalamo-cortical pathways [141]. In this context, ctDCS has both a clinical and  
805 neurophysiological aim, since it might provide a beneficial approach for psychiatric conditions and  
806 a tool to explore pathophysiological processes, similarly to other clinical conditions [22,142].  
807 Indeed, although this field is still in its infancy, some studies have indicated the effect of ctDCS in  
808 psychiatric diseases.

809

#### 810 *Available clinical evidence*



811 Since tDCS has been suggested as a valuable tool for the treatment of neuropsychiatric conditions  
812 such as depression, schizophrenia, addiction and chronic pain [143,144], and cognitive  
813 improvement has been observed in some patients undergoing tDCS [145], montages involving  
814 stimulation over the cerebellum have been tested in several studies. For example, Ho et al. [146]  
815 compared mood and neuropsychological functions (memory and frontal lobe functions) in two  
816 groups of depressed participants (N=14) treated with cortical tDCS and ctDCS. Two montages were  
817 considered: Fronto-Occipital (F-O) and Fronto-Cerebellar (F-C), both with intensity set at 2 mA for  
818 20 min/day for 3 consecutive weeks. No significant neuropsychological changes were found, but  
819 mood improved under the F-O condition, with lesser improvement in the F-C condition. Clearly, the  
820 small sample size and the absence of a sham control group affected this open label pilot study. The  
821 same year, Minichino et al. [147] used prefronto-cerebellar tDCS in 25 euthymic outpatients with a  
822 diagnosis of BD Type I or II to improve sleep quality, as assessed by the Pittsburgh Sleep Quality  
823 Index (PSQI) [148]. The authors demonstrated that the stimulation (2 mA for 20 min/day for 3  
824 consecutive weeks) delivered through a cathodal electrode over the right cerebellar cortex and  
825 anode over the left dorsolateral prefrontal cortex (DLPFC) significantly improved PSQI total score  
826 and all PSQI sub domains. The same protocol was repeated [149] to test neuropsychological  
827 changes of 25 euthymic patients with BD. The Rey Complex Figure Test [150] delayed recall and  
828 copy, as well as the Neurological Examination Scale were used as outcomes, suggesting that such  
829 stimulation might increase visuospatial memory and executive functioning in euthymic BD patients.  
830 Analogously to the previous study, the small sample size and the absence of a sham control group  
831 might have influenced these findings.

832 More recently, cerebellar stimulation was tested in patients with obsessive-compulsive disorder  
833 (OCD). Indeed, an open-label pilot study [151] applied right anodal ctDCS (with cathode over left  
834 orbitofrontal cortex) to 8 patients with treatment-resistant OCD (2mA, twice a day for 5 days). The  
835 study was the first to demonstrate the clinical relevance of ctDCS in combination with selective  
836 serotonin reuptake inhibitors (SSRIs) in patients with treatment-resistant OCD. Indeed, although

837 depressive symptoms were not improved as assessed by the Montgomery and Asberg Depression  
838 Rating Scale (MADRS) [152], the Yale–Brown Obsessive and Compulsive Scale score (Y-BOCS)  
839 [153] decreased by more than 25%, with beneficial effect on the severity of obsessive and  
840 compulsive symptoms lasting for 3 months. Clearly, more knowledge needs to be gathered to  
841 confirm these results.

842

#### 843 *Implications for future research*

844 Current findings provide preliminary support for the safety, feasibility and beneficial effect of  
845 ctDCS for psychiatric conditions. However, such restorative potential must be confirmed through  
846 controlled and methodologically uniform clinical research. Indeed, future works should investigate  
847 several unclear points, such as the characteristics of the patients, the pathological stages or the type  
848 and site of stimulation to reach an optimal response.

849

#### 850 **ctDCS in individuals with hereditary cerebellar ataxia**

851 Hereditary Cerebellar Ataxia (HCA) encompasses a heterogeneous group of autosomal recessive,  
852 autosomal dominant, X-linked and mitochondrial ataxias [154]. The autosomal dominant cerebellar  
853 ataxias (ADCA) are classified into more than 40 subtypes of SCA [154], whilst Friedreich ataxia  
854 (FRDA) is the most common of the autosomal recessive cerebellar ataxias (ARCA) [155]. The most  
855 common group of the ADCAs, the SCAs, arise from trinucleotide expansions, in particular CAG  
856 trinucleotide expansions (SCA1, SCA2, SCA3, SCA6, SCA17, and DRPLA) [155]. The incidence  
857 of SCA in the general population is about three affected people per 100,000 [156]. FRDA, arising in  
858 96% of cases due to homozygosity for a GAA expansion, affects one in 29,000 people [157].  
859 Clinically, these conditions are typified to varying degrees by incoordination of gait, limb, ocular  
860 movement, and speech. Some HCAs have associated features such as neuropathy, spasticity, cardiac  
861 dysfunction and behavioral/cognitive impairment [156]. Age of disease onset is variable but most  
862 often in adulthood, the exception being FRDA, in which the average age at disease onset is 10 years

863 [157]. Although clinical presentation and progression are variable, an universal feature is  
864 progressive deterioration of motor and cognitive function. To date no specific therapies have been  
865 identified that can alter the course of these devastating, life-threatening diseases. The challenge for  
866 clinical researchers is to establish effective non-pharmacological interventions that can modify the  
867 unremitting, declining trajectory towards functional dependency which typifies this group of  
868 diseases. Optimum motor and cognitive function for people with HCA is critical to all aspects of  
869 daily function.

870

#### 871 *Available clinical evidence*

872 There is now increasing evidence that CB-NIBS such as tDCS can produce changes in neural  
873 plasticity that last beyond the period of stimulation and are clinically relevant [16]. Notably the  
874 capacity of ctDCS to modulate neuronal excitability suggests that it may have a therapeutic benefit  
875 in HCA [16]. Indeed, the capacity to influence the excitability of the cerebello-thalamo-cortical  
876 pathway by stimulation of the cerebellar cortex alone, or combined with stimulation to the  
877 contralateral motor cortex, has been the focus of many tDCS studies in individuals with HCA  
878 [62,158–160]. Reflecting the burgeoning interest in this area several systematic literature reviews  
879 appraising the efficacy of ctDCS on motor control in the HCAs have been published [161–164].  
880 Three recent reviews report the findings of various open-label, single and double-blind studies  
881 examining the efficacy of tDCS on improving motor control in individuals with HCA [161–163].  
882 Two of these publications reviewed the same eight studies (N=81) determining the application of  
883 tDCS in improving motor outcomes, particularly in those with less clinical severity [163,164]. In  
884 addition, Benussi et al. [162] reviewed 10 published studies (N=116), confirming the favorable  
885 effect of tDCS on a range of motor domains including gait, balance and upper limb function [162].  
886 Extending the scope of a systematic review, Chen et al. [161] conducted a meta-analysis on five  
887 randomized controlled trials (N=72) examining safety and the effect of tDCS on hand and gait  
888 function in individuals with HCA [161]. This meta-analysis verified the safety and specificity of

889 active (versus sham) tDCS, as demonstrated by a 26.1% ( $p = 0.003$ ) improvement in gait ataxia (as  
890 measured by the 8 Minute Walk Test), and a 28.2% improvement in function after three months ( $p$   
891 = 0.04) of treatment. In contrast there were no significant differences in hand function (as measured  
892 by the Nine Hole Peg Test) [165] following tDCS [161]. Likewise, a study by Hulst et al. [166] did  
893 not find the application of tDCS effective in improving adaptation in a force field reaching task in a  
894 group of 20 individuals with principally dominant HCA, compared to control participants [166].  
895 Similarly John et al. [167] did not find the application of tDCS effective on improving grip force in  
896 14 individuals with cerebellar degeneration [167]. The findings in both these studies give credence  
897 to the premise of Chen et al. [161] that the efficacy of tDCS may be depend on specific tasks,  
898 parameters, or outcome measures.

899

#### 900 *Open questions about ctDCS in HCA*

901 Whilst it would appear that the application of tDCS holds promise as a motor intervention for  
902 individuals with HCA, it is crucial to understand the source of these divergent results particularly in  
903 order to inform the design of future studies. Possible reasons for such variation include: 1) a small  
904 and heterogeneous sample, 2) diversity of primary and secondary outcome measures, 3) varying  
905 stimulation parameters, and 4) inconsistent application of randomization, sham and/or blinding  
906 conditions [162]. Further work is required to establish a consensus regarding tDCS as an effective  
907 therapeutic intervention for individuals with HCA [168].

908

#### 909 *Neurophysiological mechanisms of ctDCS*

910 Further elucidations of the neural mechanisms underlying brain reorganization necessary for  
911 mitigating the effects of disease on motor function is warranted either prior to, or in conjunction  
912 with efficacy studies [161]. In particular, interrogation of CBI and measures of intracortical  
913 inhibition/excitation such as long-interval cortical inhibition (LICI) and short-interval cortical  
914 inhibition (SICI) will provide tangible information about the integrity of cerebello-cerebral

915 connectivity necessary for optimum motor control [34,103]. Some studies have recognized the  
916 utility of CBI in highlighting the possible neurophysiological mechanism underlying improvement  
917 in motor control [162,169], incorporating CBI as an outcome measures alongside neurological and  
918 functional measures. However, further studies are required specifically examining inhibition in  
919 targeted HCAs (for example, those with significant dentate nuclei pathology such as FRDA,  
920 DRPLA and SCA3, as opposed to those with significant loss of function in Purkinje cells such as  
921 SCA6, SCA31, SCA2 and early-onset ataxia with ocular motor apraxia) [170].

922

### 923 *Heterogeneity (and rarity) of clinical phenotypes*

924 Accordingly, the issue of heterogeneity of etiology in HCA warrants consideration in studies of  
925 ctDCS in individuals with HCA. Given the rarity of the sub-types of the HCA, it is unsurprising,  
926 but potentially problematic, that most studies include participants with a mix of dominant,  
927 recessive, and sporadic ataxias in order to achieve sufficient statistical power. Mixed response to  
928 ctDCS may reflect the heterogeneity of the HCAs in regard to both neuropathology and clinical  
929 phenotype. Whilst the cerebellum is a unifying site of pathology across the disorders, associated  
930 spinocerebellar tract, dorsal column, inferior olive, pontine nucleus, red nucleus, ventrolateral  
931 thalamus, vestibular nucleus or peripheral nerve pathology may also be present to varying degrees  
932 [170]. Based on neurodegeneration in cerebellar circuitry, Tada et al. [170] postulated a  
933 classification of individuals with HCA according to the four primary loci of neuropathology that is,  
934 the Purkinje cells, the cortico-ponto-cerebellar system, the spinocerebellar system and the cerebellar  
935 deep nuclei [170]. Understanding the variability of response to tDCS in the context of HCA  
936 neuropathology is crucial to designing targeted ctDCS efficacy studies (see the study by Grimaldi et  
937 al. [62]) considering disease severity as a reflection of cerebellar integrity. A number of studies  
938 suggest that ctDCS may be most beneficial for patients with lesser clinical severity (see Chen et al.  
939 [161] for a review). Stratification of the cohort according to clinical severity may assist in sub-  
940 group analysis of tDCS efficacy. Participants with milder symptoms, perhaps reflecting greater

941 cerebellar volume, may be more suited to ctDCS aimed at facilitating neural compensation for  
942 evolving cerebellar deficiencies than those later in the disease trajectory [164].

943

#### 944 *Sensitivity of the outcomes*

945 Whilst the most common outcome measures for ctDCS trials have been neurological rating scales  
946 such as the International Cooperative Ataxia Rating Scale (ICARS) [171] or Scale for the  
947 Assessment and Rating of Ataxia (SARA) [160], there have also been an assortment of other  
948 measures of gait, balance and upper limb function [161–164]. Returning to the issue of  
949 heterogeneity of neuropathology and clinical phenotype, it is possible that some of these outcome  
950 measures may not entirely reflect targeted cerebellar structures and as such may not capture the  
951 benefits of tDCS on specific aspects of motor control [162].

952

#### 953 *Implications for future research*

954 Despite the growing of evidence supporting the use of tDCS to improve clinical symptoms related  
955 to HCA, further work is needed to verify the ability of tDCS to modulate cerebello-thalamo-cortical  
956 connectivity and, in so doing, deliver a much-anticipated therapeutic intervention not only for motor  
957 deficits, but also for cognitive impairment. Indeed, it should be noted that ctDCS to ameliorate  
958 cognitive impairment related to HCA has received little attention.

959 ctDCS provides a relatively simple, effective and non-invasive treatment option, and the repertoire  
960 of applications continues to expand to settings beyond the clinic [172], and as an adjunct to  
961 traditional interventions such as intensive physiotherapy [172,173]. Therefore, this approach  
962 represents a non-pharmacological intervention capable of bridging the gap between  
963 pathophysiology and the development of new treatment approach.

964

### 965 **Cerebellar stimulation in other movement disorders**

#### 966 *CB-NIBS in Dystonia*

967 Dystonia is a movement disorder characterized by abnormal postures and/or repetitive movements  
968 with many subtypes [174]. Historically, dystonia was conceptualized as a basal ganglia disorder,  
969 however recent evidence that a wider neuronal network is involved has established the cerebellum  
970 as a key node within pathophysiological networks [175]. CB-NIBS is an attractive therapeutic  
971 strategy for dystonia. As a hyperkinetic movement disorder, characterized by hyperexcitability of  
972 M1 and reduced markers of inhibition, NIBS may offer the opportunity to retune inhibitory  
973 influences exerted by the cerebellum or more directly modify cerebellar dysfunction.

974

#### 975 *Available clinical evidence*

976 The major studies that have used cerebellar stimulation to investigate dystonia are summarized in  
977 Table 2. The large majority have examined patients with either cervical dystonia and/or task-  
978 specific dystonia of the hand (in which dystonia occurs during an isolated task such as writing or  
979 playing in musical instrument). Two major types of outcome measure can be identified; studies that  
980 have tried to improve clinical markers of dystonia (e.g., severity scores) and/or those that have  
981 attempted to modulate dystonic biomarkers (e.g., neurophysiological markers, learning deficits).

982 In cervical dystonia, several studies have reported clinical improvement when stimulation is  
983 performed for more than a single session (see table 2). Both cerebellar stimulation that is  
984 considered to inhibit and stimulation that is considered to facilitate cerebellar activity have been  
985 found to be beneficial. This may be because cerebellar stimulation itself does not have a clear  
986 bidirectional effect and/or that any non-specific disruption of cerebellar activity is beneficial within  
987 dystonic networks. Either alternative is encouraging, as future therapeutic interventions such as  
988 non-invasive or invasive stimulation targets are considered. Clinically cervical dystonia is  
989 characterized by its mobile nature responsive to additional sensory input (worse when eyes closed,  
990 sensory trick phenomena) suggesting a dynamic functional disturbance that may be particularly  
991 sensitive to such techniques.

992 Overall, studies evaluating clinical improvements in task-specific dystonia have been negative  
993 (except Bradnam et al. [176]). In task-specific dystonia individuals present with a highly  
994 stereotyped motor impairment, which at the time of diagnosis has often been symptomatic for many  
995 months or even years. It is likely that such a motor impairment will have been consolidated within  
996 encoded network thousands of times, rendering a single isolated session of stimulation unlikely to  
997 produce significant effects. Recognizing an increased influence of environmental factors in task-  
998 specific dystonia may also be important as retraining therapies can be highly effective [177].  
999 Pairing retraining therapy with stimulation is therefore an attractive future area of study [178].

1000 Several studies have examined the effect of cerebellar stimulation on M1 plasticity/excitability,  
1001 with the rationale that modulating the excessive excitability that characterizes dystonia  
1002 neurophysiology could translate into a therapeutic effect. In task-specific dystonia, Sadnicka et al.  
1003 [179] found retained ability of facilitatory cerebellar stimulation (anodal ctDCS) to dampen  
1004 plasticity responses of the motor cortex (similar to controls). However, the marked variability of  
1005 plasticity response within the patient group undermined any theoretical benefit. This contrasted  
1006 another study [180] in which both excitatory (iTBS) or inhibitory (cTBS) failed to modulate the  
1007 plastic responsiveness of the hand in M1, in patients with task-specific dystonia. However, the same  
1008 group also tested a similar study design [181] in cervical dystonia, finding that cTBS suppressed  
1009 paired associative stimulation (PAS) responses and excitation enhanced PAS responses (the  
1010 opposite to controls). Interestingly, in healthy controls [181], mimicking some of the conditions of  
1011 cervical dystonia by turning the head or perturbing proprioceptive feedback inverted cerebellar  
1012 modulation of plasticity in line to that cervical dystonia. Most recently, Bologna et al. [182] have  
1013 shown that cTBS modulates excitability of M1 in cervical dystonia (and healthy controls) but not  
1014 patients with task-specific dystonia. Other studies [183,184] have looked at cerebellar learning  
1015 paradigms (eye blink conditioning) and motor tasks which activate the cerebellum (see table 2).  
1016 Collectively, these studies identify differences between the different subtypes of dystonia. They also



1017 appear to identify the ability of cerebellar stimulation to shift markers of cerebellar function and/or  
1018 dystonic dysfunction.

1019

#### 1020 *Open questions about ctDCS in dystonia*

1021 While studying biomarkers for dystonia remains enticing as it attempts a more mechanistic and  
1022 specific mode of study, some commonly made assumptions and challenges of this literature can be  
1023 highlighted. For example, given the unclear and still debated efficacy and mechanism of the  
1024 different types of cerebellar stimulation [57,171,185], it is not clear if we can reproducibly and  
1025 bidirectionally modulate cerebellar activity in healthy controls. Any clinical studies using these  
1026 techniques with their heterogenous patient populations need careful consideration (particularly if  
1027 bidirectional effects are reported within dystonia). It is also problematic that there are no  
1028 reproducible biomarkers for dystonia. For example, neurophysiological plasticity responses of M1  
1029 are often used as a biomarker for dystonia. However such responses are notoriously variable, non-  
1030 specifically abnormal across a range of diseases, and cannot reliably segregate a dystonic patient  
1031 group from controls [186]. Similarly, we have little ability to quantitatively track hypothesized  
1032 cerebellar involvement in dystonia. For example, CBI was initially thought to be reduced in a pilot  
1033 study in eight individuals with task-specific dystonia and promoted as a possible marker of dystonic  
1034 cerebellar dysfunction [187]. However, the deficit in CBI was not observed in a more recent  
1035 publication in the same patient group [176].

1036

#### 1037 *CB-NIBS in Parkinson's Disease (PD)*

1038 In recent years, growing attention has been focused on the treatment of Parkinson's Disease through  
1039 NIBS techniques. Nonetheless, only few papers have investigated the role of cerebellar stimulation  
1040 for the treatment of the three cardinal signs of the disease (i.e., bradykinesia, rigidity and tremor), as  
1041 well as for the control of levodopa-induced dyskinesias (LIDs). Despite the variability in  
1042 techniques, stimulation settings and protocols' design, current evidence seems to suggest that: 1)

1043 cerebellar TBS represents the best protocol to interfere with cerebellar functions in vivo; 2) NIBS  
1044 (cerebellar TBS) are effective for the control of both resting tremor and LIDs, with a very limited  
1045 impact on rigidity and bradykinesia; 3) cerebellar stimulation does not improve speech  
1046 disturbances, neither axial dysfunctions (e.g. the freezing of gait, FOG). Here, we encompass the  
1047 current knowledge about CB-NIBS, also discussing potential mechanisms of action and rationale  
1048 for the use of cerebellar stimulation in PD.

1049

#### 1050 *Potential mechanism of action*

1051 The cerebellar role in PD pathophysiology has recently gained increasing attention. In particular,  
1052 the cerebellum may interfere with the basal ganglia network at three different levels: 1) it down-  
1053 regulates the striatal D1 receptors as a part of a disynaptic pathway to the dorsolateral putamen and  
1054 the external globus pallidus (GPe), passing through the intralaminar nuclei of the thalamus  
1055 [13,188]; 2) it expresses all types of dopamine receptors receiving inputs from the Substantia Nigra  
1056 pars compacta (SNc) that terminate in the granule and Purkinje cell layers, thus sharing similar  
1057 properties with the striatal dopaminergic system [189–191]; 3) the cerebellum plays an overall  
1058 inhibitory effect on motor and non-motor areas (CBI). In particular, CBI is reduced in degenerative  
1059 disorders, also comprising PD patients, where it could either be compensating or contributing to  
1060 motor deficits [8,15]. Although current evidence remains limited, all these studies seem to suggest  
1061 that the cerebellum may be engaged in specific aspects of the pathophysiology of PD, such as  
1062 levodopa-induced dyskinesias and altered sensory discrimination [192]. Moreover, as concerns  
1063 tremor in PD, there is increasing evidence that the basal ganglia network triggers the onset of  
1064 tremor, whereas the cerebellar network is responsible for its amplitude and maintenance [193].

1065

#### 1066 *Clinical evidence*

1067 Eleven papers have been published to date about the use of CB-NIBS for the treatment of PD.  
1068 Among these, there are only three works on tDCS. In particular, Málly et al. [194] provided the

1069 longest experiment with ctDCS, showing that anodal stimulation, delivered for one week every six  
1070 months for two years, improved all Unified Parkinson's Disease Rating Scale UPDRS-III scores  
1071 (UPDRS-III) [195]. Ferrucci et al. [196] showed that tDCS, applied either over the cerebellum or  
1072 the M1, had similar effects on fluctuations and dyskinesias. Workmann et al. [197] provided the  
1073 first evidence that cerebellar polarization may also improve gait and balance, when delivered at  
1074 high intensities bilaterally (4 mA).

1075 Despite the variability in stimulation settings, protocol design, and clinical outcomes of tDCS  
1076 studies, cerebellar TMS has demonstrated a high reproducibility among different papers when  
1077 delivered as cTBS [198–201]. TBS significantly improves LIDs, as confirmed both by the reduction  
1078 of glucose (F-FDG) uptake in the dentate nucleus [202] and the restoration of sensorimotor  
1079 plasticity of M1 [203]. This improvement may be due to a cTBS-induced modulation of CBI [204],  
1080 as confirmed in mice by the induction of LTD between Purkinje cell and the deep cerebellar nuclei  
1081 [205]. Nonetheless, to date there still is a substantial lack of understanding about physiological  
1082 mechanisms underlying TBS. Also, low-frequency rTMS (1 Hz) seems to dampen CBI, thus  
1083 improving LIDs, although current evidence is based on two papers only, and further confirmation is  
1084 needed [206,207].

1085

#### 1086 *CB-NIBS in Essential Tremor (ET)*

1087 Essential tremor (ET) presents as a postural and kinetic tremor, commonly involving both arms, and  
1088 it is strictly related to cerebellar dysfunction. In particular, both the cerebello-thalamo-cortical and  
1089 the inferior olive-cerebellar networks are impaired [193]. MRS showed diminished N-  
1090 acetylaspartate (NAA) [211], while voxel based morphometry (VBM) studies have recently  
1091 revealed a mild degree of cerebellar atrophy [212]. Nonetheless, only three published studies have  
1092 explored the effects of ctDCS in patients with ET to date. In the first one [213], patients underwent  
1093 ten consecutive sessions of cathodal ctDCS (2.0 mA, 20 minutes) without any acute or long-lasting  
1094 benefits on motor scores and daily living activities. Conversely, in a second paper [214], cathodal

1095 ctDCS improved both Essential Tremor Rating Assessment Scale (TETRAS) [215] and Activities  
1096 of Daily Living (ADL); the authors applied tDCS to the DLPFC (the anode) and to the inion (the  
1097 cathode; 2 mA for 20 min in 10 consecutive sessions with a 2-days break between the first and the  
1098 second 5-days sessions). Different from Gironell et al. [213], five more tDCS sessions were  
1099 administered in an every-other-day manner, one month after the initial course of therapy, possibly  
1100 accounting for the beneficial effects observed in the long-term period. More recently, a third work  
1101 [216] showed that ET is suppressed via electrical stimulation of the cerebellum phase-locked to the  
1102 tremor.

1103

1104 *Cerebellar non-invasive brain stimulation in Huntington's Disease (HD) and Multiple Sclerosis*  
1105 *(MS)*

1106 Although a key cerebellar involvement has been suggested in the pathogenesis of Huntington's  
1107 Disease (HD), both for motor and psychiatric features [217,218], only one study has explored to  
1108 date the putative role of CB-NIBS to date [219]. The authors showed that five-days anodal ctDCS  
1109 improved motor scores in HD, when compared to sham stimulation, with effects lasting for about  
1110 four weeks after protocol completion. In Multiple Sclerosis, recent evidence suggests iTBS, applied  
1111 over the cerebellum, improves both gait and balance, when combined with vestibular rehabilitation  
1112 [220], likely modulating the activity of vestibule-cerebellar pathways.

1113

1114 *Implications for future research*

1115 Converging evidence points to the fact that cervical dystonia may be an attractive candidate for  
1116 treatment via stimulation of the cerebellum and/or its outflow tracts with a modest literature  
1117 suggesting that targeted CB-NIBS may be beneficial for clinical markers. Studies point to the need  
1118 for repeated stimulation sessions in order for CB-NIBS to meaningfully interact with the dystonic  
1119 network. Also, the application of CB-NIBS to PD, ET, HD and MS has shown limited but  
1120 promising results in terms of motor outcomes. Future works should investigate the safety of high

1121 intensity tDCS (> 4 mA), as well as the possibility to simultaneously combine different targets in  
1122 order to optimize tDCS effectiveness (e.g., M1 and the cerebellum; the spinal cord and the  
1123 cerebellum). Further studies are needed to confirm the preliminary data in larger cohorts and in a  
1124 longer follow-up period. Finally, there is a growing interest for the assessment of a “deep cerebellar  
1125 tDCS”, possibly via temporally interfering electric fields [208,209], as recently provided for the  
1126 subthalamic NIBS [210].

1127

### 1128 **Pain and the cerebellum**

1129 During the past 15-20 years, there has been growing interest to define the cerebellar role in pain  
1130 processing and perception [221–224]. Studies in humans have demonstrated that the cerebellum is  
1131 critically involved both in visceral pain [225] and migraine progression and persistence [226].  
1132 Along this view, changes in structural volume and functional connectivity of the cerebellum seem  
1133 to predict chronicization, as well as long-term disability in migraine [226,227]. Moreover,  
1134 functional neuroimaging has demonstrated that the posterior cerebellum plays a key role in pain-  
1135 related adaptations for motor control [228,229]. To date, however, a critical review about the role of  
1136 CB-NIBS for pain treatment is still lacking.

1137

### 1138 *Putative mechanisms of action of ctDCS for pain treatment*

1139 It has been demonstrated that the cerebellum interferes with nociceptive processing following a  
1140 CBI-like mechanism [230]. Consequently, anodal ctDCS may reduce pain perception by increasing  
1141 the inhibitory tone exerted by the cerebellum on different brain targets, whereas cathodal ctDCS  
1142 could elicit opposite effects by inducing hyperalgesia. This tentative model has been recently  
1143 confirmed by a clinical study of Ruscheweyh et al. [231], showing that patients with cerebellar  
1144 infarctions have reduced pain thresholds.

1145 Apart from non-synaptic and synaptic (neuroplastic) changes, tDCS may modulate pain experience  
1146 and processing through different mechanisms. In recent years, a growing body of evidence has

1147 supported the importance of tDCS after-effects on regional blood flow and immune responses.  
1148 Accordingly, animal studies have proved that tDCS elicits neural stem cells activation in vivo,  
1149 influencing the development and the distribution of microglia in the adult brain [232]. Finally,  
1150 tDCS might also modulate the inflammatory response by regulating pro-inflammatory cytokines  
1151 and increasing glutathione levels [233].

1152

### 1153 *Available clinical evidence*

1154 In recent studies, Bocci et al. [234–236] have demonstrated that ctDCS modulates pain processing  
1155 in healthy humans. In particular, ctDCS seems to exert polarity-specific effects on the amplitude of  
1156 Laser Evoked Potentials (LEPs), thus modifying the perception of experimentally induced pain in  
1157 young volunteers. Because tDCS is effective in modulating both N1 and N2/P2 components of  
1158 LEPs, and since these responses are generated by parallel and partially segregated spinal pathways  
1159 reaching different cortical targets [237], the authors argued that the cerebellum is involved in pain  
1160 processing by modulating the activity of both somatosensory and cingulate cortices. Indeed, from a  
1161 functional point of view, the cerebellum may be engaged in the sensory-discriminative, as well as in  
1162 the emotional and cognitive dimension of pain [238,239]. A recent paper by Pereira et al. [240] has  
1163 confirmed these results, showing that anodal ctDCS reduces lower extremity pain perception in  
1164 healthy humans. Another paper [229] has proved that cathodal polarization applied to the right  
1165 cerebellar hemisphere modulates motor adaptation during gait, suggesting the possibility to interfere  
1166 with motor withdrawal by using ctDCS.

1167 However, in a previous study, Zunhammer et al. [241] failed to demonstrate the analgesic effects of  
1168 rTMS applied over the cerebellum. The discrepancy with previous results may be due to different  
1169 factors: the authors evaluated only changes in subjective pain thresholds and used a different  
1170 neuromodulation technique (rTMS vs. tDCS).

1171 The efficacy of ctDCS for pain treatment has been also recently confirmed also in patients suffering  
1172 from “phantom limb pain” (PLP) [236]. Recent studies have shown that tDCS applied over the

1173 motor cortex represents a promising therapeutic tool in PLP, with effects likely arising from a  
1174 transient restoration of the cortical representation of the phantom limb [242–244]. Based on this  
1175 evidence, Bocci et al. [234] have recently shown that anodal ctDCS improves both paroxysmal pain  
1176 and non-painful phantom limb sensations in subjects with upper limb amputations. They argued  
1177 that, differently from other brain targets, ctDCS may reduce both painful and non-painful phantom  
1178 limb sensations, which are induced by maladaptive changes in the sensorimotor network and  
1179 posterior parietal cortex respectively [243].

1180

### 1181 *Implications for future research*

1182 Similarly to other functions of cerebellum, the effects of ctDCS on pain are promising and clinically  
1183 intriguing, but sadly still at their infancy. Moreover, approaching this topic, one needs to consider  
1184 that pain is the result of different neurophysiological mechanisms, and that has different clinical  
1185 manifestations. Thus, neuromodulation needs to be carefully tailored to the pain syndrome to be  
1186 specifically targeted. Still, further studies are needed to expand the current knowledge.

1187

### 1188 **Concluding remarks**

1189 The density of neurons in the cerebellar cortex, the anatomical location and the geometrical  
1190 organization of the cerebellum, the high degree of plasticity of the cerebellar cortex and the high  
1191 degree of connectivity of the cerebellum with spinal cord, brainstem, basal ganglia and cerebral  
1192 cortex all go in the direction of a great potential for CB-NIBS to explore cerebellar functions and  
1193 modulate brain disorders involving primarily cerebellum or extra-cerebellar structures connected to  
1194 the cerebellum. Based on the current knowledge here reviewed, there is a general consensus that  
1195 cerebellar non-invasive stimulation represents a promising tool for therapeutic purposes, both in  
1196 motor, cognitive and psychiatric pathological conditions. Available results suggest that the strategy  
1197 of targeting the cerebellum to indirectly affect cortical and subcortical activities might be effective  
1198 in alleviating the symptoms of several pathologies, likewise in improve cognitive functions or

1199 motor learning in healthy subjects. However, numerous questions remain unsolved and require  
1200 multi-disciplinary and large-scale efforts. There is a clear need to identify the physiological and  
1201 pathophysiological effects CB-NIBS in the areas of motor behaviour, cognitive processes, and  
1202 affect regulation, in addition to clarify its mechanisms of action. Also, short-term, middle-term and  
1203 long-term effects upon the activity of the cerebellar cortex (Purkinje neurons and local  
1204 interneurons), cerebellar nuclei and the inferior olivary complex should be explored. Finally, the  
1205 interaction between neuromodulation protocols and pharmacological therapies is still an unexplored  
1206 line of research that needs to be addressed to safeguard clinical success and credibility of CB-NIBS.  
1207



1208 **Declaration**

1209 The authors declare no conflict of interest.

1210

1211 **Funding**

1212 This work was conducted without any funding from public or private sources.

1213

1214 **Ethical Committee Request**

1215 Not applicable

1216

1217 **Data availability**

1218 The concept reported in this manuscript is not associated with raw data.

1219

1220 **Code availability**

1221 There is no software application or custom code used in this paper.

1222

1223 **Authors' Contribution**

1224 Writing: All authors have read and agreed to the publication.

1225 **References**

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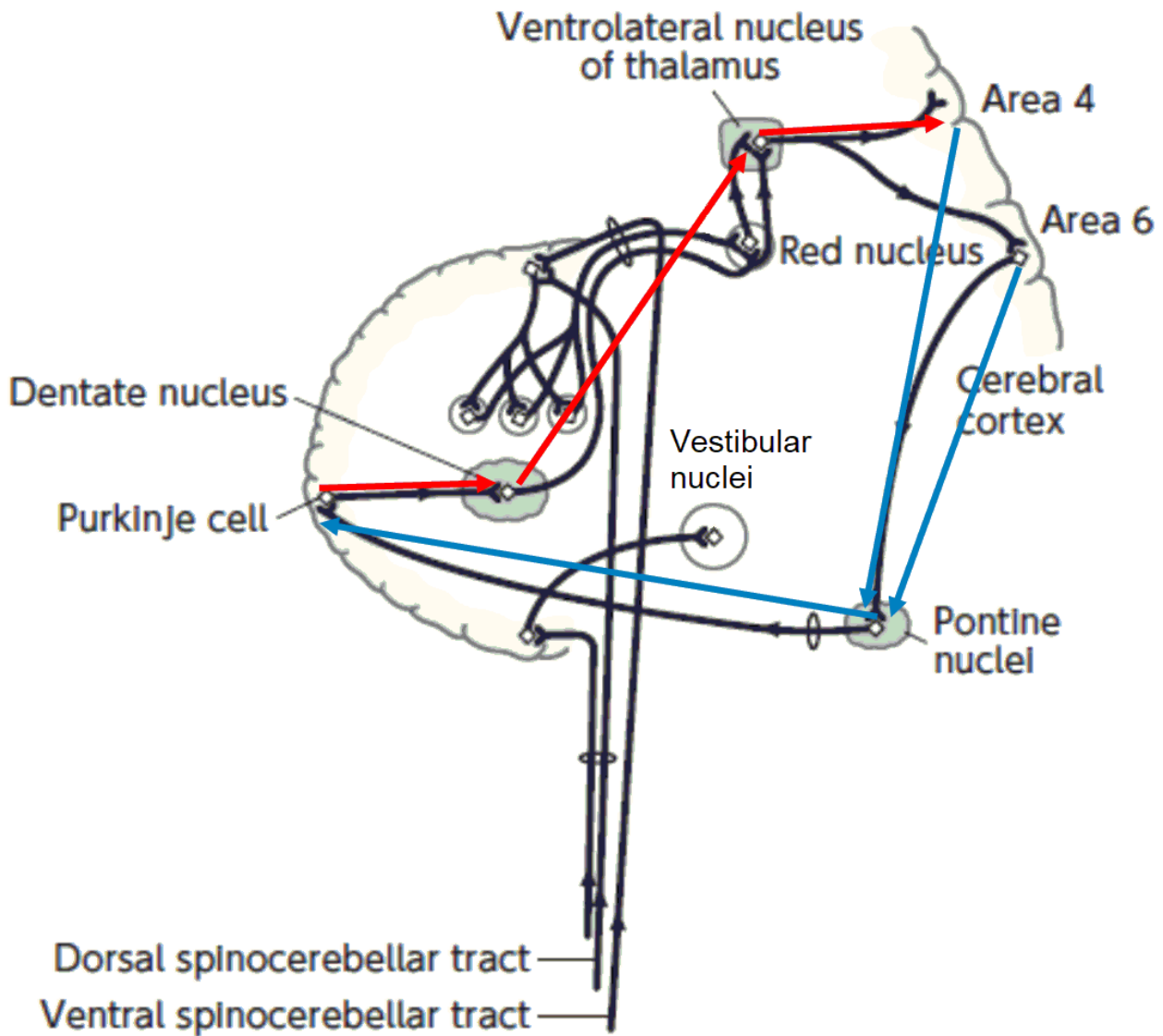
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1891 **Figure 1.** Postulated anatomical pathway (red arrows) responsible for CBI. TMS is hypothesized to  
 1892 activate Purkinje neurons in the cerebellar cortex, which inhibit neurons in the dentate nucleus. This  
 1893 withdraws any ongoing facilitation from dentate via thalamus to area 4, resulting in reduced  
 1894 excitability of motor cortex. The blue arrows indicate the reciprocal connection from area 4 to  
 1895 cerebellum via the pons.

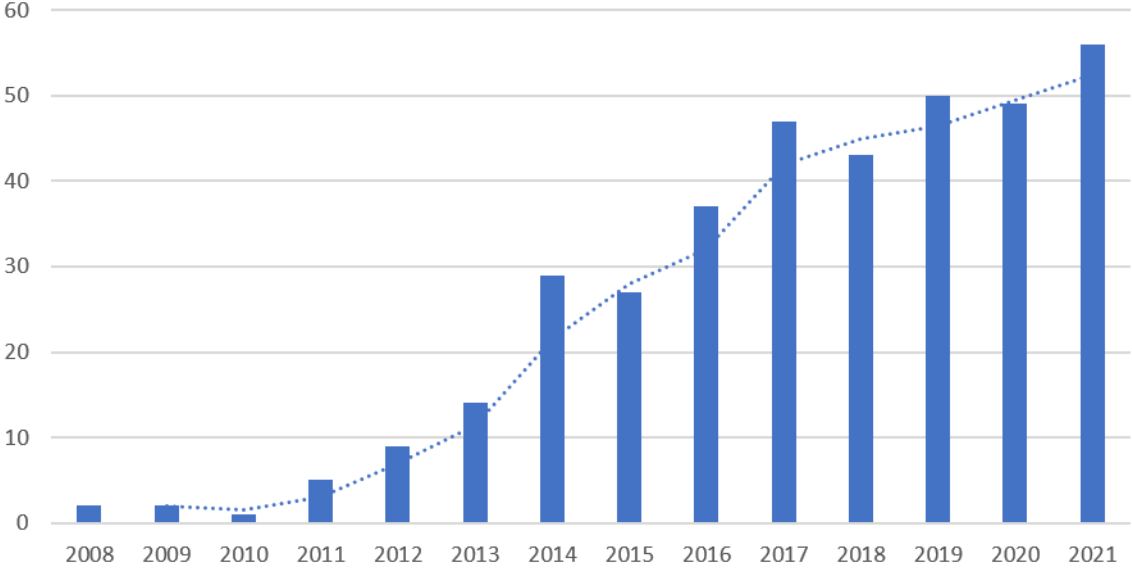
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Number of articles



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1901 **Figure 2.** Number of articles published per year between 2008 and 2020, listed in PubMed (search  
1902 strategy: cerebell\* AND (transcranial direct current stimulation OR tDCS)). A number of 214  
1903 articles are found between 2008 and 2020, of which half (106) were published in the past 4 years

Author	Year	Domain	Cohort (n)	Protocol	Task / therapy	Main finding
<b>tDCS</b>						
Sebastian et al. [98]	2017	Cognition (language)	Chronic bilateral MCA infarct (1, case report)	Randomized, double-blind, sham-controlled, cross-over design; anodal ctDCS (I: 2 mA, T: 20 min (active) or 30 s (sham) consecutive to 2 x 15 training sessions, A: 25 cm <sup>2</sup> , E1: right cerebellum 1 cm below and 4 cm lateral to theinion, E2: over right deltoid muscle)	Behavior spelling treatment	Greater improvement in word spelling to dictation; generalization to written picture naming after active stimulation
Marango et al. [112]	2018	Cognition (language)	Chronic left-hemispheric stroke (12)	Randomized, double-blind, sham-controlled, cross-over design; cathodal ctDCS (I: 2 mA, T: 20 min (active) or 30 s (sham) over 5 consecutive daily sessions, A: 5 x 7 cm, E1: right cerebellum 1 cm below and 4 cm lateral to theinion, E2: over right deltoid muscle)	Verb generation and verb naming task	Active stimulation led to greater improvement in a verb generation task when compared to sham; no effect on verb naming task
Zandvliet et al.	2018	Standing balance	Chronic stroke (15), exclusion	Randomized, single-blinded, sham-controlled, cross-over design; anodal tDCS to contra- or	Postural tracking	Contralesional cerebellar tDCS improved standing balance

[105]			of patients with cerebellar lesions	ipsilesional cerebellum partially overlapping with performance of a tracking task (I: 1.5 mA, T: 20 min (active) or 2 x 30 s (sham), A: 3.14 cm <sup>2</sup> , E1: 3 cm lateral to the inion, E2/3: over ipsilateral buccinator muscle)	task	performance (tandem position)
Picelli et al. [107]	2018	Gait	Chronic stroke patients (20) with unilateral lesions in the anterior circulation	Randomized, single-blind, parallel design; cathodal contralesional ctDCS + cathodal S-tDCS or anodal ipsilesional M1-tDCS + cathodal S-tDCS concurrently to 10 sessions of 20 min RAGT (I: 2 mA, T: 20 min, A: circular 4 cm diameter, E1: 10-20 EEG position O1 or O2, E2: over ipsilateral buccinator muscle)	RAGT, outcome: 6MWT	ctDCS + S-tDCS stimulation group showed greater improvement in 6MWT at 1 <sup>st</sup> post-treatment assessment when compared to the M1-tDCS + S-tDCS group
Picelli et al. [109]	2019	Gait	Chronic first-ever unilateral supratentorial stroke (40)	Randomized, single-blind, parallel design; cathodal contralesional ctDCS + cathodal S-tDCS or cathodal ipsilesional ctDCS + cathodal S-tDCS concurrently to 10 sessions	RAGT, outcome: 6MWT	No significant differences between stimulation groups (contra versus ipsilesional cerebellar hemisphere) at post-

			with lesions in the anterior circulation	of 20 min RAGT (I: 2 mA, T: 20 min, A: circular 4 cm diameter, E1: 10-20 EEG position O1 or O2, E2: over ipsilateral buccinator muscle)		treatment assessments
Sebastian et al. [113]	2020	Cognition (language)	Chronic left-hemispheric stroke patients (24)	Randomized, double-blind, sham-controlled, within-subject cross-over design, 2 phases of 15 treatment sessions starting with anodal or cathodal ctDCS followed by sham or opposite order (I: 2 mA, T: 20 min (active) or 45 s (sham), A: 5 x 5 cm, E1: over the right cerebellum (1 cm under and 4 cm lateral to theinion), E2: over right shoulder	Computerized aphasia therapy	Repetitive ctDCS in combination with computerized aphasia treatment improved picture naming
<b>rTMS / TBS</b>						
Bonni et al. [110]	2014	Gait	Chronic cerebellar stroke (6)	Non-controlled interventional study; iTBS over lesioned cerebellum applied over 10 sessions (C: 1 cm below and 3 cm lateral to theinion, P: 3 pulses at 50 Hz repeated at 5	Standard physical therapy	Improvement in posture and gait subscale of MICARS



				Hz, 20 trains of 10 burst delivered at 8 s intervals, 600 pulses, 80% of AMT)		
Kim et al. [111]	2014	Balance and gait	Acute posterior circulation stroke (32)	Randomized, double-blind, sham-controlled, 2-to-1 ratio design; 1 Hz rTMS ipsilesional cerebellar hemisphere over 5 sessions (C: 2 cm below and 2 cm lateral to the inion, P: 900 pulses at 1 Hz at 100% RMT, sham coil was placed perpendicular to the scalp)	Conventional rehabilitation therapy	Active stimulation resulted in greater improvement in BBS and 10MWT
Koch et al. [97]	2019	Balance and gait	Chronic stroke patients (36) with lesions in the MCA territory	Randomized, double-blind, sham-controlled, parallel design; iTBS to contralesional cerebellar hemisphere over 3 weeks of daily sessions (C: over lateral cerebellum as guided by a neuronavigation system, P: iTBS, 1200 pulses (delivered in 2 runs), 80% of AMT normalized to scalp-to-cortex distance)	Conventional physiotherapy	Active stimulation resulted in an improved BBS score at the immediate post intervention assessment, the effect persisted at a 3-weeks post intervention follow-up

1904 **Table 1. Cerebellar NIBS studies conducted in the stroke cohort.**

1905 Table depicts the summary of identified studies testing CB-NIBS interventions in the stroke cohort assessing effects on cognitive and balance/gait  
1906 functions. Abbreviations: tDCS: transcranial direct current stimulation; ctDCS: cerebellar tDCS; S-tDCS: spinal tDCS; M1: primary motor  
1907 cortex; MCA: middle cerebral artery; I: current strength; T: stimulation duration; A: electrode size; E1: position stimulation electrode; E2:  
1908 position return electrode; RAGT: robot-assisted gait training; 6MWT: 6-minute walk test; rTMS: repetitive transcranial magnetic stimulation;  
1909 iTBS: intermittent theta burst stimulation; C: TMS coil position; P: description of TMS protocol; AMT: active motor threshold; RMT: resting  
1910 motor threshold; MICARS: Modified International Cooperative Ataxia Rating Scale; BBS: Berg Balance Scale; 10MWT: 10-m walk test.

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<b>Data, author</b>	<b>Cerebellar stimulation</b> <i>(inhibitory; <u>facilitatory</u>)</i>	<b>Clinical response</b>	<b>Biomarker response</b>	<b>Main result</b>
<b>Cervical dystonia</b>				
2019, Odorfer et al. [183]	Bilateral <i>cTBS</i> , single session 16 patients		MEP, CSP, fMRI	Increased finger-tapping related cerebellar activation on fMRI in dystonia which was more pronounced after cerebellar stimulation
2018, Popa et al. [181]	sham, <u>iTBS</u> and <i>cTBS</i> . Three sessions. 22 patients 23 controls	TWSTRS	PAS	Cerebellar inhibition suppressed PAS and excitation enhanced PAS (opposite to controls). Turning the head or providing proprioceptive perturbation to neck muscles in healthy controls inverted cerebellar modulation of plasticity.
2016, Bradnam et al. [245]	sham or bilateral <u>iTBS</u> 10 sessions/days 8 patients in each group	TWSTRS, CDQ-24 QoL, hand dexterity	MEP CSP	Clinical markers improved favourably in iTBS group. No change of neurophysiology.
2014, Bradnam et al. [246]	Single patient. 20 varied <u>a-tDCS</u> cerebellar stimulations over 10 weeks	TWSTRS, CDQ-24, CDIP-58	M1 excitability	Stimulation is safe with concurrent botulinum toxin injections.
2014, Koch	sham or bilateral <i>cTBS</i>	TWSTRS,	CBI, SICI,	Small 15% improvement in TWSTRS for one week post

et al. [247]	10 sessions over 2 weeks	BFMDRS	ICF, CSP, PAS	intervention. Stimulation modified CBI and reduced heterotopic PAS potentiation.
2013, Hoffland et al. [184]	<i>cTBS</i> , single session, 11 patients		EBCC	cTBS normalised deficit in eyeblink classical conditioning acquisition. In keeping with a functional and reversible disruption of the cerebellum in dystonia
Task-specific dystonia/focal hand dystonia				
2015, Bradnam et al. [176]	sham, <b>a-tDCS</b> and <i>ctDCS</i> . Each single session. 8 patients	WCRS, ADDS, kinematic	CBI	a-tDCS improved kinematics of handwriting and circle drawing tasks but did not reveal clear neurophysiological mechanism (CBI within normal limits)
2015, Lissen et al. [248]	sham or <i>cTBS</i> . Each single session 10 patients	Writing kinematics		No significant change in writing kinematics
2014, Sadnicka et al. [179]	<b>a-tDCS</b> single session. 10 patients	WCRS	RMT, AMT, CSP, PAS, RC	Anodal stimulation reduced the magnitude of plasticity response (whether they facilitated or inhibited). High variability of PAS response noted. No change in clinical score.
2013, Hubsch et	sham, <b>iTBS</b> and <i>cTBS</i> . Each single session. 21 writer's		PAS, SICI/LICI	Cerebellar cortex excitation and inhibition were ineffective in modulating cortical sensorimotor plasticity (in contrast to

al. [180]	cramp 25 controls.			controls).
Mixed group				
2016, Bologna et al. [182]	Two sessions: sham and <i>cTBS</i> 13 focal hand dystonia, 13 cervical dystonia, 13 controls	Arm and neck kinematics	M1 excitability	cTBS reduced the excitability of contralateral primary motor cortex in healthy subjects and cervical dystonia but not patient with focal hand dystonia. No change in clinical scores.
Secondary dystonia				
2019, Shin et al. [249]	Single case. Five sessions of low frequency TMS	BFMDRS		Leg dystonia secondary to cerebellar infarction. Stimulation applied to side of lesions. Improved dystonia at rest, no change to dystonia during gait

1919 **Table 2. CB-NIBS studies conducted in the dystonia cohort.**

1920 Table depicts the summary of identified studies testing CB-NIBS interventions in the dystonia cohort assessing effects on clinical and  
1921 neurophysiological functions. Abbreviations: ADDS: Arm Dystonia Disability Scale; AMT: active motor threshold; a-tDCS: anodal transcranial  
1922 direct current stimulation; BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale; CBI: cerebellar brain inhibition; CDIP-58: Cervical Dystonia  
1923 Impact Profile; CDQ-24 QoL: Cranio-cervical Dystonia Questionnaire Quality of Life; CSP: cortical silent period; cTBS: continuous theta burst  
1924 stimulation; c-DCS: cathodal transcranial direct current stimulation; EBCC: eyeblink classical conditioning; fMRI: functional magnetic resonance

1925 imaging; ICF: intracortical facilitation; iTBS: intermittent theta burst stimulation; LICI: long-interval intracortical inhibition; MEP: motor evoked  
1926 potential; PAS: paired associative stimulation; RC: recruitment curve; RMT: resting motor threshold; SICI: short-interval intracortical inhibition;  
1927 TWSTRS: Toronto Western Spasmodic Rating Scale; WCRS: writer's cramp rating scale.