



Cerebellar Cortex as a Therapeutic Target for Neurostimulation

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Abstract

Non-invasive stimulation of the cerebellum is growingly applied both in the clinic and in research settings to modulate the activities of cerebello-cerebral loops. The anatomical location of the cerebellum, the high responsiveness of the cerebellar cortex to magnetic/electrical stimuli, and the implication of the cerebellum in numerous cerebello-cerebral networks make the cerebellum an ideal target for investigations and therapeutic purposes. In this mini-review, we discuss the potentials of cerebellar neuromodulation in major brain disorders in order to encourage large-scale sham-controlled research and explore this therapeutic aid further.

Keywords Cerebellar cortex · Purkinje neuron · Transcranial direct stimulation · Therapy

Abbreviations

ADL	Activities of daily living	GN	Golgi neuron
ALFF	Amplitude of low-frequency fluctuation	ICARS	International cooperative ataxia rating scale
atDCS	Anodal transcranial direct current stimulation	IN	GABAergic interneuron
CA	Cerebellar ataxia	IO	Inferior olive
CBI	Cerebellum brain inhibition	iTBS	Intermittent theta burst stimulation
CCAS	Cerebellar cognitive affective scale	L-DOPA	L-3,4-di-hydroxy-phenylalanine
CF	Climbing fiber	LTD	Long-term depression
cTBS	Continuous theta burst stimulation	MF	Mossy fibers
ctDCS	Cathodal transcranial direct current stimulation	PC	Purkinje cell
DCN	Deep cerebellar nuclei	PD	Parkinson's disease
DN	Dentate nucleus	PN	Pontine nucleus
DSM-V	Diagnostic and statistical manual of mental disorders-5th Ed	RN	Red nucleus
DTI	Diffusion tensor imaging	rTMS	Repetitive transcranial magnetic stimulation
EMG	Electromyogram	SARA	Scale for the assessment and rating of ataxia
ET	Essential tremor	SSRI	Selective serotonin reuptake inhibitors
GABA	Gamma aminobutyric acid	tACS	Transcranial alternating current stimulation
		TBS	Theta burst stimulation
		tDCS	Transcranial direct current stimulation
		TMS	Transcranial magnetic stimulation
		UPDRS	Unified Parkinson's disease rating scale

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Introduction

In the past few decades, it has become clear that the cerebellum is involved in more than just motor control. Clinical case reports, neuroimaging, and neuroanatomical evidence also point towards a major role for the cerebellum in cognitive and affective functioning. Recent studies investigating cerebellar topography have convincingly demonstrated that the

cerebellar cortex can be divided into distinct motor and non-motor regions, subserving motor, language, social, working memory, and emotional functions [1–3]. Lobules IV, V, VI, and VIII are engaged in motor tasks, while lobules VI and VII are involved in non-motor processing, which is also reflected in the anatomical connections to the cerebrum [1].

The anatomical location of the cerebellum, especially the posterior cerebellum, right beneath the skull, makes it accessible to non-invasive neurostimulation techniques such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) [4]. tDCS and TMS are promising techniques to modulate neuronal activity in both healthy and patient populations [5, 6]. Different protocols are available to stimulate the brain in a specific manner. In tDCS, the direction of the current determines whether the stimulation will be excitatory (anodal tDCS or atDCS) or inhibitory (cathodal tDCS or ctDCS). Instead of a direct current, it is also possible to use alternating current (tACS) at a given frequency to target specific oscillatory networks [7, 8]. While tDCS and tACS are not powerful enough to induce action potentials and only modulate neuronal excitability, TMS can do both when the intensity of the pulses is adjusted appropriately. It can be administered as a single pulse (single pulse TMS) or as a series of pulses (repetitive TMS or rTMS). Adjusting the frequency will excite (high-frequency rTMS) or inhibit (low-frequency rTMS) neuronal activity. Theta burst stimulation (TBS) is a variation on the rTMS protocol which uses patterns of 3 50 Hz pulses at 1 to 5 Hz frequency. It can be given in a continuous (cTBS, inhibitory) or in an intermittent manner (iTBS, excitatory) [7, 9].

Given the very high concentration of neurons in the cerebellar cortex, their highly organized distribution, and the properties of plasticity in cerebellar microcircuits, these stimulation techniques impacting on neuronal excitability might prove to be very effective when targeting the cerebellum [4, 7]. Modeling studies have already shown that both tDCS and TMS are capable of inducing electric currents inside the cerebellar cortex (tDCS [10–13]; TMS [14, 15]). Experimental studies confirm the effectiveness of the application of currents over the cerebellar cortex to change the activity of cerebellar output [16–18].

While neurodegenerative motor disorders such as ataxias have long been associated with the cerebellum itself [19], new evidence also points to a role for the cerebellum in psychiatric [20], and in neurodevelopmental disorders [21]. A disturbed cerebellar functioning or disrupted cerebello-cerebral functional connectivity is now believed to be at the root of these disorders, which might be solved or improved by specific protocols of cerebellar stimulation. Observation of patients with cerebellar lesions has also led to the description of the cerebellar cognitive-affective syndrome (CCAS) or Schmahmann's syndrome [22]. Symptoms can be grouped in 4 main clusters: (1) executive functioning such as planning,

set-shifting, verbal fluency, abstract reasoning, and working memory; (2) (visuo)spatial cognition including memory and organization; (3) affective behavior resulting in blunting of affect or in disinhibited, inappropriate behavior; and (4) language disturbances including agrammatism and dysprosodia. The description of this syndrome paved the way for research into the cerebellar involvement in several different types of neuropsychiatric disorders lying at the border between neurological sciences and psychiatry. Schmahmann's syndrome is clearly a potential target for cerebellar neuromodulation.

This mini-review is intended to discuss non-invasive cerebellar stimulation in the context of major disorders of the brain and to provide, when possible, provisional recommendations to the type and site of stimulation for different disorders. These recommendations are based on the theoretical knowledge about the cerebellar involvement in these disorders and take earlier studies into account employing cerebellar stimulation as a therapeutic aid in selected populations of patients.

Therapeutic Benefits of Non-invasive Cerebellar Stimulation in Cerebellar Motor Disorders

Cerebellar ataxia (CA) is caused by neurodegenerative or acute lesions to the cerebellum/cerebellar pathways and encompasses a wide spectrum of neurological disorders with ataxia (a motor coordination/planning disorder) as the main symptom [23]. Manto and Marmolino [23] have made a classification of the cerebellar ataxias (CAs), which can be subdivided into hereditary or non-hereditary. There are a lot of different types of CAs with different pathogenesis. Non-invasive cerebellar stimulation (TMS or tDCS) has been used in the management of CAs in the last two decades, and recent studies have evaluated the therapeutic benefits of these treatments on essential tremor (ET) [24–26], based on the consensus that overactivity of the cerebellum underlies ET [24–26]. Interestingly, non-invasive cerebellar stimulation has also been applied to extrapyramidal diseases, such as dystonia and Parkinson's disease (PD), which are considered to be due to pathological changes in the basal ganglia. In this regard, Lozeron et al. [27] advanced the concept of “network pathophysiological model”. The concept assumes that multiple lesions within or outside the basal ganglia and/or defective interactions among different nodes can explain the extrapyramidal symptoms [27].

Cerebellar Ataxias (CAs)

In the systematic review by Nuzzo et al. [28], the therapeutic effects of non-invasive cerebellar stimulation on CAs have been examined in 151 patients in 8 studies [29–36].

These studies included patients with degenerative CAs [29–33, 35, 36] and patients with stroke [34]. TMS was used in 3 studies [34–36], and tDCS in 5 [29–33]. Therapeutic effects were examined in a sham-controlled design in 5 of 8 studies.

In the largest cohort study, Shiga et al. [35] studied the effects of TMS on ataxic gaits applying 10 consecutive magnetic pulses for 21 days in 74 degenerative patients. TMS improved time, steps in 10 m walking, and capacities in tandem standing and gaits [35]. Bodranghien et al. [31] also confirmed therapeutic effects of transcranial cerebello-cerebral DCS on a postural tremor in a patient in a sham-controlled study.

The therapeutic effects were also evaluated in limb ataxia [33]. In 2 patients with spinocerebellar ataxia type 2 (SCA2), the combination of atDCS applied over the cerebellum and the motor cortex (single session with 1 mA, 20 + 20 min) was associated with reduction in postural/action tremor as well as hypermetria, compared with sham stimulation [33]. The same treatment also affected the timing of antagonist muscle commands. In a double-blind, randomized, and sham-controlled study, Benussi et al. [30] evaluated the effects of a single session of atDCS (2 mA, 20 min) in 19 patients with degenerative ataxia. The study included comprehensive assessment of the clinical scores (Scale for the Assessment and Rating of Ataxia (SARA), International Cooperative Ataxia Rating Scale (ICARS)), the 9-Hole Peg Test, and the 8-Meter Walking Time. The results showed that atDCS improved performance, compared with sham [30]. The authors also confirmed excellent outcome of the same treatment in another long-term sham-controlled follow-up [29]. In the latter study, 20 patients underwent atDCS (2 mA, 20 min) applied daily over 10 consecutive days. Follow-up evaluation was conducted at 1 and 3 months after the application. atDCS improved SARA by 3% and ICARS by 12%.

Despite these positive effects on ataxia, there are still no rigorous large-scale sham-controlled clinical trials of tDCS and TMS. This is especially important due to the heterogeneity of CAs.

Recent double-blind, randomized studies have shown that aminopyridines, acting as K⁺ channel blockers, reduce attacks of CAs in episodic ataxia 2 [37] and improve downbeat nystagmus of ataxic symptoms [38]. On the other hand, motor rehabilitation improves not only lesion-induced CAs but also degenerative CAs [39]. However, these benefits in daily activities are limited. Combinations of these neuromodulation therapies, which include medications, motor rehabilitation, and non-invasive cerebellar stimulation, will likely be necessary.

Essential Tremor (ET)

ET is characterized by postural and kinetic tremors, mainly in the upper limbs [24]. In the systematic review by Nuzzo et al.

[28], the therapeutic benefits of non-invasive cerebellar stimulation have been examined on 37 patients in 4 articles [25, 40–42].

The first study of Gironell et al. [25] examined the effects of rTMS in 10 patients (30 trains separated by 30 s pauses) in a double-blind, placebo-controlled design. rTMS produced notable improvements in ET Rating Assessment Scale and accelerometer measurements [25]. In a subsequent study by the same group [40], the authors evaluated the therapeutic benefits of 5 daily tDCS sessions (2 mA, 20 min) in 10 patients. The authors concluded that this protocol produced no significant improvement. However, Helvacı Yılmaz et al. [41] examined the effects of atDCS (2 mA, 20 min) over 10 consecutive sessions in 6 patients in an open-label design study. They reported that tDCS improved ET Rating Assessment Scale and Activities of Daily Living (ADL) scale [41].

In another study [42] in which rTMS (900 pulses at 1 Hz) was applied in 11 patients over 10 consecutive sessions in an open-label design study. The effects were assessed at days 5, 12, and 29 after rTMS. The treatment improved tremor (based on the clinical score of Fahn-Tolosa-Marin scale (tremor, drawing, and functional disability)) and reduced tremor amplitude on the electromyogram (EMG) and accelerometer. Importantly, the observed improvement in tremor was associated with re-establishment of defective information processing in the cerebello-thalamo-cortical pathways.

These studies showed an acute or subacute antitremor effect. Further large-scale sham-controlled studies of long-term follow-up assessment are expected.

Dystonia

Dystonia is defined as co-contraction of antagonistic muscles and contraction of unnecessary adjacent muscles [27]. There is an agreement that cerebellar circuitry is involved in the pathogenesis of dystonia [43]. However, there is no consensus on the therapeutic benefits of non-invasive cerebellar stimulation on dystonia. Sadnicka et al. [44] reported that a single session of atDCS (2 mA, 15 min) failed to improve writing abilities in 10 patients with writing cramps. In contrast, Bradnam et al. [45] reported that a single session of atDCS (2 mA, 20 min) improved focal hand dystonia in 8 patients in a sham-controlled study. Ferrucci et al. [46] concluded that the effects of consecutive tDCS sessions and those of the combination of the latter with motor training need to be examined in more detail.

Parkinson's Disease (PD)

Non-invasive cerebellar stimulation has been applied for the treatment of L-DOPA-induced dyskinesia in PD. Although

denervation of dopaminergic neurons reduces their buffer capacities on released dopamine, L-DOPA is pharmacologically delivered in a pulse fashion, leading to large intermittent surges in extracellular dopamine with a resultant supersensitive response of dopamine receptors, responsible for L-DOPA-induced dyskinesia [47]. Ferrucci et al. [46] examined the effects of atDCS applied over the cerebellum or M1 (2 mA, 20 min) in patients with PD and L-DOPA-induced dyskinesia in a randomized, double-blind, cross-over study. They showed that anodal cerebellar and M1 tDCS for 5 days improved Unified Parkinson's Disease Rating Scale (UPDRS) IV (dyskinesia section). Although the sample size was small, their results suggest a promising beneficial effect for anodal cerebellar M1 tDCS in L-DOPA-induced dyskinesia.

Therapeutic Mechanisms for Each Motor Symptom

Possible General Principle

Although the exact mechanisms of the therapeutic effects are uncertain, a long-lasting modulation of the cerebello-thalamo-cortical pathway might underlie the improvements observed in various neurological symptoms.

Cerebellum Brain Inhibition (CBI) Stimulation over the cerebellum reduces excitability of the motor cortex when the cerebellar stimuli are delivered 5–6 ms before cerebral stimulation, as is the case with TMS [48]. This suppression, termed cerebellum brain inhibition (CBI), is currently explained by Purkinje cell (PC)-mediated inhibition of facilitation of the motor cortex (M1) (disfacilitation; see Fig. 1). That is, since the motor cortex is facilitated by the deep cerebellar nuclei (DCN)-thalamo-cortical pathway, cerebellar stimuli can activate PCs, which inhibit DCN neurons, resulting in reduction of motor cortex facilitation [28, 49].

On the other hand, tDCS modulates neuronal activity through a constant electrical current during a particular period, generally 20 min [28]. tDCS induces polarity-dependent site-specific modulation of cerebellar activity not only from the electrical standpoint but also by impacting the metabolism [50]. However, controversial effects of tDCS on CBI have been reported. Galea et al. [51] concluded that ctDCS over the cerebellum decreases the ability of TMS to elicit CBI of the motor cortex (inhibitory modulation on PCs), whereas atDCS exerts an opposite effect (excitatory modulation on PCs). However, Doeltgen et al. [52] showed that cerebellar stimulation with atDCS resulted in suppression of CBI, suggesting that atDCS can stimulate the superficial cerebellar inhibitory interneurons, which inhibit PCs, resulting

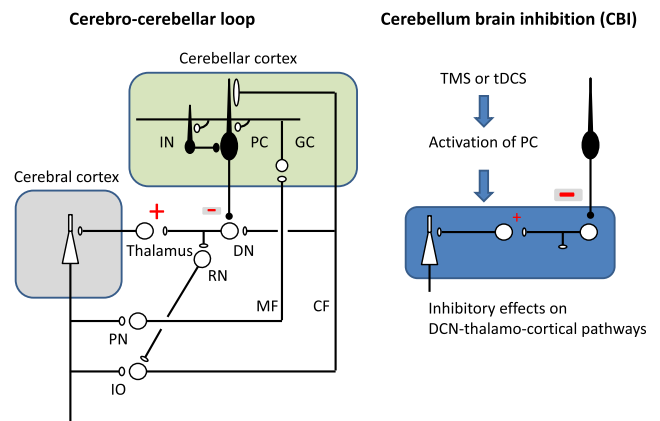


Fig. 1 A schematic diagram of a Cerebro-cerebellar loop (Left panel). PC; Purkinje cells, GC; granule cells, IN; GABAergic interneurons, DN; dentate nucleus, RN; red nucleus, PN; pontine nucleus, IO; inferior olive nucleus, MF; mossy fibers, CF; climbing fibers. Mechanism underlying cerebellum brain inhibition (CBI) (right panel). Transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS; certain modes) activates PC, which inhibits (-) the deep cerebellar nucleus (DCN) neuron, resulting in reduction of motor cortex facilitation

in turn in suppression of PC-mediated inhibition of the DCN-thalamo-cortical pathway [49].

Plasticity of the Cerebellar Cortex The finding that tDCS modulated the degree of CBI [51] suggests that tDCS or rTMS modulates neuronal activity in the DCN-thalamo-cortical pathway with a short-term or long-term time course. Thus, impairment of cerebellar control in the cerebral cortex, which is caused by injury or degeneration in the cerebellar cortex [49], can be compensated for or restored by tDCS or rTMS.

Plasticity of the cerebellar cortex synapses is assumed to be the neural basis for the long-lasting modulation [49]. The cerebellar cortex is endowed with various forms of synaptic plasticity, which allow neural compensation and restoration [53]. In agreement with this concept, animal experiments showed that hyperpolarization current induced long-term increase in the firing rate of Golgi neurons [54].

Taken together, tDCS and rTMS can effectively modulate cerebellar function in the motor domain [33], which could be attributed to cerebellar plasticity and the resultant modulation of activities of the cerebello-thalamo-cortical pathway.

Cerebellar Ataxias (CAs)

A recent physiological study showed that activation of dentate nucleus neurons (DNs) generated by reduced inhibition from PCs, i.e., disinhibition, facilitates the execution of a particular movement, while suppression of the DN by increased PC activity, i.e., inhibition, contributes to the stabilization of unnecessary movement [55, 56]. Accordingly, Panyakaew et al. [57] showed that the cerebellum appears to play important roles in the selection of a particular muscle movement by

reducing CBI. Thus, the cerebellum serves as a predictive modulator through disinhibition/inhibition on the DCN-thalamo-cortical pathway.

Importantly, the tDCS-induced improvement was associated with facilitation on CBI [29], suggesting that tDCS or rTMS resulted in the repair of lost capacities of inhibitory modulation by PCs on the DCN-thalamo-cortical pathways. The restoration of PC activity is necessary for not only the inhibition but also the disinhibition, since suppression of tonic PC activities is a prerequisite for the generation of the disinhibition. Thus, non-invasive cerebellar stimulation that can enhance CBI might appropriately modulate activities of the cerebellar output so as to repair CAs.

Essential Tremor (ET)

The inferior olive nucleus (IO) has been considered the prime generator of tremor in ET through the mechanism of rhythmic oscillatory activity [58]. However, Louis and Lenka [59] argued against any pathogenic role of IO in ET, based on a post-mortem study showing no microscopic changes in the IO. On the other hand, accumulating evidence from post-mortem examinations suggests the role of cerebellar pathologies, such as various functional, metabolic, and structural abnormalities of the cerebellum, intracellular abnormalities of the PCs, and the neuronal network [26]. Louis [26] postulated that ET is a disorder characterized by primary PC dysfunction, resulting in diminished cerebellum-induced cortical inhibition. In accordance with this assumption, the majority of the currently available pharmacotherapeutic agents enhance GABAergic transmission [26]. Thus, non-invasive cerebellar stimulation, which facilitates CBI, could be a promising therapeutic approach.

Although there seems to be a consensus about the pathogenic role of the cerebellum in ET, a secondary role of the IO in ET needs to be reconsidered. This is important since a single DN neuron sends off abundant collaterals to the red nucleus, which in turn projects to the IO [60]. These neuronal interconnections suggest that a single DN neuron provides powerful driving signals to the IO. Thus, when non-invasive stimulation activates PCs, the inhibitory effects do not only modulate the activity of the motor cortex, but also the IO. Activation of the IO, which is conveyed by climbing fibers to the cerebellar cortex, induces depressive plasticity of PC activity through long-term depression (LTD) of parallel fiber excitatory synapses [61] and rebound potentiation of interneuron inhibitory synapses [62]. This IO-mediated long-lasting suppression of PC activities might exaggerate the dysfunction of PCs in ET. Therefore, inhibitory reset of IO activity might be one of the possible mechanisms underlying the therapeutic benefits of non-invasive cerebellar stimulation in ET. Further functional studies are needed to determine whether non-

invasive cerebellar stimulation prevents acceleration of pathology in ET.

Dystonia

Dystonia is considered to be due to dysfunction of the basal ganglia. This is based on the results of various neuroimaging studies (showing abnormalities of the basal ganglia), and improvement of dystonia following pallidotomy or basal ganglia deep brain stimulation [27]. However, recent studies have demonstrated that dysfunction of certain cortical areas is also necessary for the development of dystonia [27]. In patients, surround inhibition or cortical inhibition is assumed to be lost in the cerebral cortex, making the motor cortex (M1) a potential therapeutic target [27]. Siebner et al. [63] showed loss of inhibitory control of the cerebellum. This is the rationale for non-invasive cerebellar stimulation which is designed to facilitate CBI.

Psychiatric Disorders

Schizophrenia

Schizophrenia is a severe psychiatric disorder which manifests itself usually in late childhood, early adulthood. It is mainly characterized by delusions and hallucinations, and may also include disorganized speech, abnormal or catatonic behavior, and negative symptoms such as avolition, flat affect, and anhedonia [64]. Cognitive deficits are also frequently present in patients with schizophrenia, such as impairments in memory, learning, and executive functions [20, 65]. Delusions, hallucinations, anxiety, etc. in schizophrenia are traditionally treated with antipsychotic drugs and psychosocial treatment. However, rehabilitating cognitive deficits is less established [66]. Some studies have explored the impact of pharmacotherapy and functional/cognitive remediation on cognitive impairment, but with varying results [67].

Already in 1979, a role for the cerebellum in schizophrenia was suggested by Heath et al. [68] who noted a pathology of the cerebellar vermis in 40% of their schizophrenic patients. Neuropathological studies have confirmed abnormal cerebellar anatomy [65, 69] which is also reflected in decreased activation during a broad range of tasks as measured by fMRI [65]. Daskalakis et al. [70] observed disturbed CBI in patients with schizophrenia or schizoaffective disorder, indicating abnormal cerebellar functioning or disrupted cerebello-thalamo-cortical connectivity [71]. Andreasen et al. [71] hypothesized that schizophrenia was caused by a disruption of the cerebello-thalamo-cortical circuit which leads to “difficulty in prioritizing, processing, coordinating, and responding to information”.

Initially, the cerebellar vermis was targeted by neurostimulation, first invasively [72], then non-invasively with iTBS [73], with promising clinical improvements in mood but also in cognitive functioning such as working memory. Both studies only included refractory schizophrenia without a sham-condition. Parker et al. [74] explored a different strategy, targeting disturbed networks instead of a particular area. They confirmed that schizophrenic patients, even on medication, have attenuated delta-frequency interactions between the cerebellum and the medial frontal cortex during an interval timing task. The lower performance on this task due to the attenuated interaction disappeared in rodents after targeting the thalamus at the delta frequency with invasive electric stimulation [74].

Due to the heterogeneity of the symptoms in schizophrenia, it is not easy to pinpoint one specific location to target with neurostimulation. Invasive cerebellar vermis stimulation has been shown to not only alleviate mood, but also seemed to diminish the frequency of delusions and hallucinations [72]. The vermis, especially the lower portion, is easily accessible for non-invasive stimulation, which makes it a potential target in the treatment of schizophrenia. Another strategy could be to target disrupted networks with tACS over the cerebellar hemispheres, trying to replicate the promising results of Parker et al. [74]. Because of the similarities in cognitive impairment as observed in bipolar disorder, though more severe in schizophrenia [66, 67], studies discussed below might also be of interest for the treatment of cognition in schizophrenic patients.

Bipolar Disorder

Bipolar disorder is a psychiatric disorder primarily affecting mood, characterized by episodes of mania and/or depression besides euthymic phases with stable mood [64]. However, even in the euthymic phases, patients with bipolar disorder experience problems in their social life and cognitive functioning, and it has been found that visuospatial memory, concentration/sustained attention, and executive functioning are significantly impaired as compared to healthy controls [75, 76]. Bipolar disorder is usually treated with, sometimes complex, medication regimens, involving lithium, divalproex, or antipsychotics [77]. These medication regimens are primarily intended to control the manic/hypomanic episodes and psychotic symptoms [66]. However, few pharmacotherapies have a proven effect on cognition and potential pharmacological approaches to improve cognitive functioning will require further research [67]. In addition, non-pharmacological treatments such as cognitive/functional remediation have also been explored with some promising results [67].

In the early 1980s, several case reports mentioned cerebellar atrophy in patients with bipolar disorder, which was later quantitatively confirmed with MRI studies [78–80].

Cerebellar atrophy was found in the cerebellar vermis, in particular in V3 and V2, and related to the number of affective episodes. Baldaçara et al. [78] demonstrated diminished cerebellar volume in the hemispheres as compared to healthy controls. In these studies, it was not clear whether the cerebellar atrophy was due to antidepressant exposure or disease progression. However, a recent study by Saxena et al. [81] observed cerebellar abnormalities in the offspring of patients with bipolar disorder and in youths with bipolar spectrum disorder, suggesting that the cerebellum is functionally involved in this disease. Diffusion tensor imaging (DTI) studies also found cerebellar nerve fiber abnormalities linked to a reduced signal in the ponto-cerebellar fibers [82–84].

In order to ameliorate cognitive functioning in patients with bipolar disorder, prefronto-cerebellar tDCS has been used to target the prefronto-thalamic-cerebellar circuitry involved in cognitive processing [75, 85–87]. By applying consecutive sessions of excitatory (anodal) stimulation over the left dorso-lateral prefrontal cortex and inhibitory (cathodal) stimulation over the right cerebellum during 3 weeks, significant improvement in executive functioning and cognitive processing was observed [85, 87], whereas 1 session had no significant effect in an intra-individual sham-controlled study [86]. However, since the 2 studies with positive effects were not sham-controlled, Bersani et al. [75] added a sham control group to control for a placebo effect and confirmed the previous findings of prefronto-cerebellar tDCS on neurocognitive functions in euthymic bipolar disorder patients [75].

This network-targeting approach seems to have a positive impact on the residual cognitive impairments patients with bipolar disorder experience even after recovery from an episode. But since bipolar disorder primarily affects mood and since the vermis seems to be primarily affected, vermal stimulation seems an interesting approach to treat these patients during or immediately after an episode. However, to the best of our knowledge, no studies to date have tried to target the cerebellar vermis with non-invasive stimulation to assess the effect on mood. Although vermal stimulation does not seem to have a significant effect on mood in healthy people [88–90], the promising results of vermal iTBS in patients with schizophrenia [73] might be replicated in patients with bipolar disorder.

Major Depressive Disorder

If a patient only exhibits depressive episodes interfering with social and occupational functioning, the patient is diagnosed with major depressive disorder according to the Diagnostic and statistical manual of mental disorders-5th Ed (DSM-V) [64]. As in bipolar disorder, a tailored approach is sought for each patient using antidepressant medication combined with psychological treatment [91, 92]. The prevalence of depression in patients with a neurodegenerative cerebellar disorder is unusually high up to 68%, of which 35% with a major depression [69].

The pathogenesis of major depressive disorder is believed to be an abnormal limbic-cortical network. Reduced gray matter density has been found in several regions of the limbic-cortical network, including the right dorsolateral prefrontal cortex and the left cerebellum [93]. In addition, regional homogeneity, which may be used to detect abnormal neural activity, is significantly lower in the left cerebellar posterior lobe [94].

Currently, primarily, the dorsolateral prefrontal cortex is being targeted with non-invasive stimulation in patients with major depressive disorder. It is one of the few illnesses where neurostimulation (TMS and tDCS) is used as a recommended clinical practice [95]. Recently, Ho et al. [96] explored alternative setups for tDCS to treat major depression in an open-label pilot study, one of which involved bilateral cathodal cerebellar stimulation combined with left anodal frontal stimulation. Although no conclusions could be drawn from this study regarding the clinical effectiveness of this montage, it did show that an alternative setup (namely anode over the left dorsolateral prefrontal cortex and large cathode over the bilateral occipital region) could reach similar results as previous rTMS and tDCS studies over the dorsolateral prefrontal cortex. However, computer modeling showed that in this setup, less current was induced in the prefrontal cortices, indicating that targeting other regions, such as the subgenual anterior cingulate cortex, might be more effective [96]. On the other hand, targeting the left cerebellum and the right dorsolateral prefrontal cortex has been shown to elevate mood in healthy participants in a single-blind sham-controlled study [97]. Since such a fronto-cerebellar setup targets the disturbed limbic-cortical circuit more specifically, it remains an interesting approach to treat major depressive disorder. Although cognition is less studied in patients with major depressive disorder, it is known that, similar to schizophrenia and bipolar disorder, major depressive disorder can be accompanied by cognitive deficits [66]. Therefore, similar setups as discussed in the section about bipolar disorder might also be beneficial for patients with major depressive disorder who also experience cognitive problems.

Generalized Anxiety Disorder

Generalized anxiety disorder is characterized by excessive anxiety and worry about day to day matters for at least 6 months. It is associated with somatic symptoms such as restlessness, fatigue, concentration difficulties, irritability, muscle tension, and sleep disturbances [64]. In generalized anxiety disorder, psychological treatment (mostly cognitive behavior therapy) is generally preferred over drug treatment and usually has a positive effect on anxiety and comorbid depressive symptoms [98]. Anxiety is also frequently observed in patients with a cerebellar degenerative disorder, with cerebellar abnormalities, and after cerebellar stroke [69].

It has been hypothesized that emotion-regulation difficulties lie at the origin of generalized anxiety disorder. Patients

with generalized anxiety disorder recognize emotions (facial expressions) significantly faster than healthy controls [99]. In addition, Diwadkar et al. [100] recently showed that patients with general anxiety disorder are not able to efficiently activate brain areas involved in control, suppression, and retrieval of memories, especially during memory suppression. This network primarily consists of the frontal lobe, the anterior cingulate cortex, and the cerebellum. Functional connectivity studies, on the other hand, primarily focused on the “fear network” comprising the amygdala, prefrontal cortex, and anterior cingulate cortex [101]. In patients with panic disorder, a significantly higher glucose metabolism in the cerebellum, as part of the amygdala-based fear network, was already demonstrated [102]. Abnormal dynamic functional connectivity of the cerebellum was also observed in patients with generalized anxiety disorder, suggesting an impaired information exchange between the cerebellum and other brain regions as the explanatory mechanism of this disorder [101].

The few studies that have tried to treat generalized anxiety disorder with neurostimulation, have targeted the dorsolateral prefrontal cortex either excitatory with high-frequency rTMS in a double-blind sham-controlled study [103], or inhibitory with ctDCS (single case study) [104], both with promising results. Both studies targeted patients who were drug treatment-resistant. However, since it has been shown that both the “fear circuit” and the “memory network,” both involving the cerebellum, are disturbed in patients with generalized anxiety disorder, the cerebellum might be an interesting target in this disorder as well. Considering the “fear network,” primarily, the cerebellar vermis is anatomically connected to the amygdala [105] and it seems to be functionally involved as well [102]. On the other hand, the left Crus I might be targeted to increase activation during memory suppression. However, more information on the neurobiological substrate of anxiety disorders is needed to identify the proper (cerebellar) target for neurostimulation.

Obsessive Compulsive Disorder

Obsessive compulsive disorder is defined by obsessions, i.e., recurrent and persistent thoughts/impulses that are experienced as unwanted and intrusive, and compulsions, i.e., repetitive behaviors in response to an obsession to reduce anxiety or distress [64]. Various kinds of compulsions and obsessions exist, such as, e.g., symmetry obsession, contamination obsession, or hoarding [106]. Like patients with generalized anxiety disorder, patients with obsessive compulsive disorder have a marked preference for psychological treatments which in most cases have a similar outcome as drug treatments in this type of disorder [107]. Obsessive compulsive traits have also been seen in patients with Schmahmann’s syndrome [69].

Obsessive compulsive disorder has been linked to a disruption in the brain’s serotonin and/or glutamate system. The

excessive doubting and repetitive behaviors suggest involvement of the frontal orbito-striatal area (including the caudate nucleus) and the dorsolateral prefrontal cortex [106]. Neuroimaging studies indeed confirmed abnormal activity in the ventral striatum—orbitofrontal cortex loop which could be linked to symptom severity [108]. In addition, a hyperconnectivity is found between the right putamen and the left cerebellum. This hyperconnectivity is especially apparent in unmedicated patients, indicating that medication, such as SSRI (selective serotonin reuptake inhibitors) modulate this abnormal functional connectivity [108]. Hou et al. [109] showed that this abnormal functional connectivity was paralleled by a decreased amplitude of low-frequency fluctuation (ALFF) in the cerebellum and parietal cortex, and an increased ALFF in the orbitofrontal cortex and the anterior cingulate cortex. Structurally, reduced gray matter volume can be seen in patients with obsessive compulsive disorder in the medial frontal gyrus, the medial orbitofrontal cortex, and the insulo-opercular region. Increased gray matter volume, on the other hand, is found bilaterally in the putamen and in the anterior rostral cerebellum [110].

Many studies have used neurostimulation, invasively (deep brain stimulation) and non-invasively (tDCS and TMS), to treat obsessive compulsive disorder with a variety of protocols. Targets were mainly the dorsolateral prefrontal cortex, the orbitofrontal cortex, and the (pre-)motor area for non-invasive stimulation [111], and different parts of the cortico-striato-thalamo-cortical loops have been targeted with deep brain stimulation [112]. Bation et al. [113] used tDCS in treatment-resistant obsessive compulsive disorder patients to increase activation in the left orbitofrontal cortex, and decrease activation in the right cerebellum (based on the findings of Hou et al. [109]). Their study showed that 10 sessions (twice a day) of tDCS had a positive impact on the severity of obsessive compulsive disorder, which lasted for at least 3 months. However, it should be noted that several other studies targeting the orbitofrontal cortex without stimulating the cerebellum also yielded positive results, indicating that the orbitofrontal cortex might be the area of interest. In addition, none of 12 reported studies by Brunelin et al. [111] were sham-controlled, making further research crucial to confirm these findings.

Unfortunately, while functional connectivity studies, ALFF studies, and structural studies all point to an abnormal cerebellum in obsessive compulsive disorder, the locations found in these studies vary greatly. Structural differences were found in the bilateral anterior rostral cerebellum [110], decreased ALFF was observed in the left and right Crus II [109], while hyperconnectivity was found between the left Crus I and the right putamen [108]. Before a cerebellar stimulation protocol can be designed to help patients with obsessive compulsive disorder, the exact role of the cerebellum in this disorder should be investigated further.

Concluding Remarks

With its unique anatomical configuration and location, the cerebellum appears to be an ideal candidate to modulate cerebello-cerebral networks in major disorders of the brain. Its high density of neurons in the cerebellar cortex and the involvement of the cerebellar circuitry in motor and non-motor functions are major features. Given the strong feasibility, there is a great need to standardize protocols and an urgent need to plan large scale sham-controlled trials to convince health authorities about the benefits of neuromodulation of the cerebellum. We are missing large studies which combine clinical, electrophysiological, behavioral and imaging techniques. There is a clear need to reach a firm consensus about the effectiveness of cerebellar stimulation.

Most studies reported here were conducted with treatment refractory patients for whom neuromodulation was a last resort (in case of neuropsychiatric disorders). For motor disorders, on the other hand, therapeutic benefits of motor rehabilitation and/or drug treatment are limited. Future studies should compare traditional treatment (pharmacotherapy, psychotherapy, etc.) with neuromodulation and should investigate the combined effects. In addition, it might be that different symptoms within a disorder require different treatment approaches. For example, cerebellar neuromodulation could be beneficiary for cognitive improvement in schizophrenia, bipolar disorder, anxiety disorders, and major depressive disorder, while pharmacotherapy will still be necessary to treat the other psychiatric symptoms such as delusions, depression, or anxiety.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Request Ethical request is not applicable in this study.

References

1. Guell X, Gabrieli JD, Schmahmann JD. Triple representation of language, working memory, social and emotion processing in the cerebellum: convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort. *NeuroImage*. 2018;172: 437–49.
2. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. *NeuroImage*. 2009;44:489–501.
3. Stoodley CJ, Valera EM, Schmahmann JD. Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. *NeuroImage*. 2012;59:1560–70.

4. van Dun K, Bodranghien F, Manto M, Mariën P. Targeting the cerebellum by noninvasive neurostimulation: a review. *Cerebellum*. 2017;16:695–741.
5. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul*. 2012;5:175–95.
6. Coffman BA, Clark VP, Parasuraman R. Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *NeuroImage*. 2014;85:895–908.
7. van Dun K, Bodranghien FCAA, Mariën P, Manto M. tDCS of the cerebellum: where do we stand in 2016? Technical issues and critical review of the literature. *Front Hum Neurosci*. 2016;10:199.
8. van Dun K, Overwalle FV, Manto M, Marien P. Cognitive impact of cerebellar damage: is there a future for cognitive rehabilitation? *CNS Neurol Disord Drug Targets*. 2018;17:199–206.
9. van Dun K, Manto M. Non-invasive cerebellar stimulation: moving towards clinical applications for cerebellar and extra-cerebellar disorders. *Cerebellum*. 2018;17:259–63.
10. Parazzini M, Rossi E, Ferrucci R, Liomi I, Priori A, Ravazzani P. Modelling the electric field and the current density generated by cerebellar transcranial DC stimulation in humans. *Clin Neurophysiol*. 2014;125:577–84.
11. Priori A, Ciocca M, Parazzini M, Vergari M, Ferrucci R. Transcranial cerebellar direct current stimulation and transcutaneous spinal cord direct current stimulation as innovative tools for neuroscientists: cerebellar and spinal tDCS. *J Physiol*. 2014;592:3345–69.
12. Rahman A, Toshev PK, Bikson M. Polarizing cerebellar neurons with transcranial direct current stimulation. *Clin Neurophysiol*. 2014;125:435–8.
13. Rampersad SM, Janssen AM, Lucka F, Aydin U, Lanfer B, Lew S, et al. Simulating transcranial direct current stimulation with a detailed anisotropic human head model. *IEEE Trans Neural Syst Rehabil Eng*. 2014;22:441–52.
14. Hardwick RM, Lesage E, Miall RC. Cerebellar transcranial magnetic stimulation: the role of coil geometry and tissue depth. *Brain Stimul*. 2014;7:643–9.
15. Sekino M, Hirata M, Sakihara K, Yorifuji S, Ueno S. Intensity and localization of Eddy currents in transcranial magnetic stimulation to the cerebellum. *IEEE Trans Magn*. 2006;42:3575–7.
16. Das S, Spoor M, Sibindi TM, Holland P, Schonewille M, de Zeeuw CI, et al. Impairment of long-term plasticity of cerebellar Purkinje cells eliminates the effect of anodal direct current stimulation on vestibulo-ocular reflex habituation. *Front Neurosci*. 2017;11:444.
17. Oulad Ben Taib N, Manto M. Trains of epidural DC stimulation of the cerebellum tune corticomotor excitability. *Neural Plast*. 2013;2013:1–12.
18. Oulad Ben Taib N, Manto M. The in vivo reduction of afferent facilitation induced by low frequency electrical stimulation of the motor cortex is antagonized by cathodal direct current stimulation of the cerebellum. *Cerebellum Ataxias*. 2016;3:15.
19. Bodranghien F, Bastian A, Casali C, Hallett M, Louis ED, Manto M, et al. Consensus paper: revisiting the symptoms and signs of cerebellar syndrome. *Cerebellum*. 2016;15:369–91.
20. Phillips JR, Hewedi DH, Eissa AM, Moustafa AA. The cerebellum and psychiatric disorders. *Front Public Health*. 2015;3:66.
21. Stoodley CJ. The cerebellum and neurodevelopmental disorders. *Cerebellum*. 2016;15:34–7.
22. Schmähmann JD, Sherman JC. The cerebellar cognitive-affective syndrome. *Brain*. 1998;121:561–79.
23. Manto M, Marmolino D. Cerebellar ataxias. *Curr Opin Neurol*. 2009;22:419–29.
24. Filip P, Lungu OV, Manto M-U, Bareš M. Linking essential tremor to the cerebellum: physiological evidence. *Cerebellum*. 2016;15:774–80.
25. Gironell A, Kulisevsky J, Lorenzo J, Barbanjo J, Pascual-Sedano B, Otermin P. Transcranial magnetic stimulation of the cerebellum in essential tremor: a controlled study. *Arch Neurol*. 2002;59:413–7.
26. Louis ED. Essential tremor and the cerebellum. *Handb Clin Neurol*. 2018;155:245–58.
27. Lozeron P, Poujois A, Richard A, Masmoudi S, Meppiel E, Woimant F, et al. Contribution of TMS and rTMS in the understanding of the pathophysiology and in the treatment of dystonia. *Front Neural Circuits*. 2016;10:90.
28. Nuzzo C, et al. Non-invasive cerebellar stimulation in cerebellar disorders. *CNS Neurol Disord Drug Targets*. 2018;17:193–8.
29. Benussi A, Dell’Era V, Cotelli MS, Turla M, Casali C, Padovani A, et al. Long term clinical and neurophysiological effects of cerebellar transcranial direct current stimulation in patients with neurodegenerative ataxia. *Brain Stimul*. 2017;10:242–50.
30. Benussi A, Koch G, Cotelli M, Padovani A, Borroni B. Cerebellar transcranial direct current stimulation in patients with ataxia: a double-blind, randomized, sham-controlled study. *Mov Disord*. 2015;30:1701–5.
31. Bodranghien F, Oulad Ben Taib N, Van Maldergem L, Manto M. A postural tremor highly responsive to transcranial cerebellar direct current stimulation in ARCA3. *Front Neurol*. 2017;8:71.
32. Grimaldi G, Manto M. Anodal transcranial direct current stimulation (tDCS) decreases the amplitudes of long-latency stretch reflexes in cerebellar ataxia. *Ann Biomed Eng*. 2013;41:2437–47.
33. Grimaldi G, Oulad Ben Taib N, Manto M, Bodranghien F. Marked reduction of cerebellar deficits in upper limbs following transcranial cerebellar DC stimulation: tremor reduction and reprogramming of the timing of antagonist commands. *Front Syst Neurosci*. 2014;8:9.
34. Kim C, Choi HE, Jung H, Lee BJ, Lee KH, Lim YJ. Comparison of the effects of 1 Hz and 20 Hz rTMS on motor recovery in subacute stroke patients. *Ann Rehabil Med*. 2014;38:585–91.
35. Shiga Y, Tsuda T, Itoyama Y, Shimizu H, Miyazawa KI, Jin K, et al. Transcranial magnetic stimulation alleviates truncal ataxia in spinocerebellar degeneration. *J Neurol Neurosurg Psychiatry*. 2002;72:124–6.
36. Shimizu H, Tsuda T, Shiga Y, Miyazawa K, Onodera Y, Matsuzaki M, et al. Therapeutic efficacy of transcranial magnetic stimulation for hereditary spinocerebellar degeneration. *Tohoku J Exp Med*. 1999;189:203–11.
37. Strupp M, Kalla R, Claassen J, Adrion C, Mansmann U, Klopstock T, et al. A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. *Neurology*. 2011;77:269–75.
38. Kalla R, Glasauer S, Buttner U, Brandt T, Strupp M. 4-Aminopyridine restores vertical and horizontal neural integrator function in downbeat nystagmus. *Brain*. 2007;130:2441–51.
39. Ilg W, Brötz D, Burkard S, Giese MA, Schöls L, Synofzik M. Long-term effects of coordinative training in degenerative cerebellar disease. *Mov Disord*. 2010;25:2239–46.
40. Gironell A, Martínez-Horta S, Aguilar S, Torres V, Pagonabarraga J, Pascual-Sedano B, et al. Transcranial direct current stimulation of the cerebellum in essential tremor: a controlled study. *Brain Stimul*. 2014;7:491–2.
41. Helvacı Yılmaz N, Polat B, Hanoglu L. Transcranial direct current stimulation in the treatment of essential tremor: an open-label study. *Neurologist*. 2016;21:28–9.
42. Popa T, Russo M, Vidailhet M, Roze E, Lehericy S, Bonnet C, et al. Cerebellar rTMS stimulation may induce prolonged clinical benefits in essential tremor, and subjacent changes in functional connectivity: an open label trial. *Brain Stimul*. 2013;6:175–9.

43. Shakkottai VG, Batla A, Bhatia K, Dauer WT, Dresel C, Niethammer M, et al. Current opinions and areas of consensus on the role of the cerebellum in dystonia. *Cerebellum*. 2017;16:577–94.
44. Sadnicka A, Hamada M, Bhatia KP, Rothwell JC, Edwards MJ. Cerebellar stimulation fails to modulate motor cortex plasticity in writing dystonia: cerebellar stimulation and writing dystonia. *Mov Disord*. 2014;29:1304–7.
45. Bradnam LV, Graetz LJ, McDonnell MN, Ridding MC. Anodal transcranial direct current stimulation to the cerebellum improves handwriting and cyclic drawing kinematics in focal hand dystonia. *Front Hum Neurosci*. 2015;9:286.
46. Ferrucci R, Bocci T, Cortese F, Ruggiero F, Priori A. Cerebellar transcranial direct current stimulation in neurological disease. *Cerebellum Ataxias*. 2016;3:16.
47. Rylander Ottosson D, Lane E. Striatal plasticity in L-DOPA- and graft-induced dyskinesia; the common link? *Front Cell Neurosci*. 2016;10:16.
48. Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum in humans. *Ann Neurol*. 1995;37:703–13.
49. Ferrucci R, Cortese F, Bianchi M, Pittera D, Turrone R, Bocci T, et al. Cerebellar and motor cortical transcranial stimulation decrease levodopa-induced dyskinesias in Parkinson's disease. *Cerebellum*. 2016;15:43–7.
50. Grimaldi G, Argyropoulos GP, Bastian A, Cortes M, Davis NJ, Edwards DJ, et al. Cerebellar transcranial direct current stimulation (ctDCS) a novel approach to understanding cerebellar function in health and disease. *Neuroscientist*. 2016;22:83–97.
51. Galea JM, Jayaram G, Ajagbe L, Celnik P. Modulation of cerebellar excitability by polarity-specific noninvasive direct current stimulation. *J Neurosci*. 2009;29:9115–22.
52. Doeltgen SH, Young J, Bradnam LV. Anodal direct current stimulation of the cerebellum reduces cerebellar brain inhibition but does not influence afferent input from the hand or face in healthy adults. *Cerebellum*. 2016;15:466–74.
53. Mitoma H, Manto M, Hampe CS. Time is cerebellum. *Cerebellum*. 2018;17:387–91.
54. Hull CA, Chu Y, Thanawala M, Regehr WG. Hyperpolarization induces a long-term increase in the spontaneous firing rate of cerebellar Golgi cells. *J Neurosci*. 2013;33:5895–902.
55. Ishikawa T, Kakei S, Mitoma H. Overlooked Holmes' clinical signs: reevaluation by recent physiological findings. *Cerebellum Ataxias*. 2015;2:13.
56. Ishikawa T, Tomatsu S, Tsunoda Y, Lee J, Hoffman DS, Kakei S. Releasing dentate nucleus cells from Purkinje cell inhibition generates output from the cerebrocerebellum. *PLoS One*. 2014;9:e108774.
57. Panyakaew P, Cho HJ, Srivaniachapoom P, Popa T, Wu T, Hallett M. Cerebellar brain inhibition in the target and surround muscles during voluntary tonic activation. *Eur J Neurosci*. 2016;43:1075–81.
58. Lamarre Y, Mercier L-A. Neurophysiological studies of harmaline-induced tremor in the cat. *Can J Physiol Pharmacol*. 1971;49:1049–58.
59. Louis ED, Lenka A. The olivary hypothesis of essential tremor: time to lay this model to rest? *Tremor Other Hyperkinet Mov (NY)*. 2017;7:473.
60. Shinoda Y, Futami T, Mitoma H, Yokota J. Morphology of single neurones in the cerebello-rubrospinal system. *Behav Brain Res*. 1988;28:59–64.
61. Ito M. Cerebellar circuitry as a neuronal machine. *Prog Neurobiol*. 2006;78:272–303.
62. Kawaguchi S, Hirano T. Signaling cascade regulating long-term potentiation of GABAA receptor responsiveness in cerebellar Purkinje neurons. *J Neurosci*. 2002;22:3969–76.
63. Siebner HR, Tormos JM, Baumann AOC, Auer C, Catala MD, Conrad B, et al. Low-frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. *Neurology*. 1999;52:529.
64. American Psychiatric Association. Diagnostic and statistical manual of medical disorders (DSM-5). Virginia: American Psychiatric Association; 2013.
65. Andreasen N, Pierson R. The role of the cerebellum in schizophrenia. *Biol Psychiatry*. 2008;64:81–8.
66. Martinez-Aran A, Vieta E. Cognition as a target in schizophrenia, bipolar disorder and depression. *Eur Neuropsychopharmacol*. 2015;25:151–7.
67. Solé B, Jiménez E, Torrent C, Reinares M, Bonnin CM, Torres I, et al. Cognitive impairment in bipolar disorder: treatment and prevention strategies. *Int J Neuropsychopharmacol*. 2017;20:670–80.
68. Heath RG, Franklin D, Shraberg D. Gross pathology of the cerebellum in patients diagnosed and treated as functional psychiatric disorders. *J Nerv Ment Dis*. 1979;176:585–92.
69. Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum - insights from the clinic. *Cerebellum*. 2007;6:254–67.
70. Daskalakis ZJ, Christensen BK, Fitzgerald PB, Fountain SI, Chen R. Reduced cerebellar inhibition in schizophrenia: a preliminary study. *Am J Psychiatry*. 2005;162:1203–5.
71. Andreasen N, Paradiso S, O'Leary DS. "Cognitive Dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull*. 1998;24:203–18.
72. Heath RG. Modulation of emotion with a brain pacemaker: treatment for intractable psychiatric illness. *J Nerv Ment Dis*. 1977;165:300–17.
73. Demirtas-Tatlidede A, Freitas C, Cromer JR, Safar L, Ongur D, Stone WS, et al. Safety and proof of principle study of cerebellar vermal theta burst stimulation in refractory schizophrenia. *Schizophr Res*. 2010;124:91–100.
74. Parker K, et al. Delta-frequency stimulation of cerebellar projections can compensate for schizophrenia-related medial frontal dysfunction. *Mol Psychiatry*. 2017;22:647–55.
75. Bersani FS, Minichino A, Bernabei L, Spagnoli F, Corrado A, Vergnani L, et al. Prefronto-cerebellar tDCS enhances neurocognition in euthymic bipolar patients. Findings from a placebo-controlled neuropsychological and psychophysiological investigation. *J Affect Disord*. 2017;209:262–9.
76. Deckersbach T, Nierenberg AA, Kessler R, Lund HG, Ametrano RM, Sachs G, et al. RESEARCH: cognitive rehabilitation for bipolar disorder: an open trial for employed patients with residual depressive symptoms: cognitive rehabilitation for bipolar disorder. *CNS Neurosci Ther*. 2010;16:298–307.
77. Hodgkin D, Stewart MT, Merrick EL, Pogue YZ, Reilly-Harrington NA, Sylvia LG, et al. Prevalence and predictors of physician recommendations for medication adjustment in bipolar disorder treatment. *J Affect Disord*. 2018;238:666–73.
78. Baldaçara L, Nery-Fernandes F, Rocha M, Quarantini LC, Rocha GGL, Guimarães JL, et al. Is cerebellar volume related to bipolar disorder? *J Affect Disord*. 2011;135:305–9.
79. DelBello M. MRI analysis of the cerebellum in bipolar disorder a pilot study. *Neuropsychopharmacology*. 1999;21:63–8.
80. Mills NP, DelBello MP, Adler CM, Strakowski SM. MRI analysis of cerebellar Vermal abnormalities in bipolar disorder. *Am J Psychiatry*. 2005;162:1530–3.
81. Saxena K, Tannous J, Mwangi B, Kahlon R, Arvind RP, Zunta-Soares G, et al. 7.2 structural cerebellar abnormalities in youth with bipolar spectrum disorders and bipolar offspring. *J Am Acad Child Adolesc Psychiatry*. 2017;56:S311.
82. Ambrosi E, Chiapponi C, Sani G, Manfredi G, Piras F, Caltagirone C, et al. White matter microstructural characteristics in bipolar I

- and bipolar II disorder: a diffusion tensor imaging study. *J Affect Disord.* 2016;189:176–83.
83. Ishida T, Donishi T, Iwatani J, Yamada S, Takahashi S, Ukai S, et al. Elucidating the aberrant brain regions in bipolar disorder using T1-weighted/T2-weighted magnetic resonance ratio images. *Psychiatry Res Neuroimaging.* 2017;263:76–84.
 84. Mahon K, Wu J, Malhotra AK, Burdick KE, DeRosse P, Ardekani BA, et al. A voxel-based diffusion tensor imaging study of white matter in bipolar disorder. *Neuropsychopharmacology.* 2009;34:1590–600.
 85. Bersani FS, Minichino A, Fattapposta F, Bernabei L, Spagnoli F, Mannarelli D, et al. Prefrontocerebellar transcranial direct current stimulation increases amplitude and decreases latency of P3b component in patients with euthymic bipolar disorder. *Neuropsychiatr Dis Treat.* 2015;11:2913–7. <https://doi.org/10.2147/NDT.S91625>.
 86. Martin DM, Chan HN, Alonzo A, Green MJ, Mitchell PB, Loo CK. Transcranial direct current stimulation to enhance cognition in euthymic bipolar disorder. *Bipolar Disord.* 2015;17:849–58.
 87. Minichino A, Bersani FS, Bernabei L, Spagnoli F, Vergnani L, Corrado A, et al. Prefronto-cerebellar transcranial direct current stimulation improves visuospatial memory, executive functions, and neurological soft signs in patients with euthymic bipolar disorder. *Neuropsychiatr Dis Treat.* 2015;11:2265–70.
 88. George MS, Wassermann EM, Williams WA, Steppel J, Pascual-Leone A, Basser P, et al. Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. *J Neuropsychiatry Clin Neurosci.* 1996;8:172–80.
 89. Schutter DJ, van Honk J. The cerebellum in emotion regulation: a repetitive transcranial magnetic stimulation study. *Cerebellum.* 2009;8:28–34.
 90. Schutter DJ, van Honk J, d'Alfonso AA, Peper JS, Panksepp J. High frequency repetitive transcranial magnetic over the medial cerebellum induces a shift in the prefrontal electroencephalography gamma spectrum: a pilot study in humans. *Neurosci Lett.* 2003;336:73–6.
 91. Parikh SV, Quilty LC, Ravitz P, Rosenbluth M, Pavlova B, Grigoriadis S, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 2. Psychological treatments. *Can J Psychiatr.* 2016;61:524–39.
 92. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. Pharmacological Treatments. *Can J Psychiatr.* 2016;61:540–60.
 93. Peng J, Liu J, Nie B, Li Y, Shan B, Wang G, et al. Cerebral and cerebellar gray matter reduction in first-episode patients with major depressive disorder: a voxel-based morphometry study. *Eur J Radiol.* 2011;80:395–9.
 94. Guo W, Liu F, Xue ZM, Yu Y, Ma CQ, Tan CL, et al. Abnormal neural activities in first-episode, treatment-naïve, short-illness-duration, and treatment-response patients with major depressive disorder: a resting-state fMRI study. *J Affect Disord.* 2011;135:326–31.
 95. Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation Treatments. *Can J Psychiatr.* 2016;61:561–75.
 96. Ho K-A, Bai S, Martin D, Alonzo A, Dokos S, Puras P, et al. A pilot study of alternative transcranial direct current stimulation electrode montages for the treatment of major depression. *J Affect Disord.* 2014;167:251–8.
 97. Newstead S, Young H, Benton D, Jiga-Boy G, Andrade Sienz ML, Clement RM, et al. Acute and repetitive fronto-cerebellar tDCS stimulation improves mood in non-depressed participants. *Exp Brain Res.* 2018;236:83–97.
 98. Cuijpers P, Sijbrandij M, Koole S, Huibers M, Berking M, Andersson G. Psychological treatment of generalized anxiety disorder: a meta-analysis. *Clin Psychol Rev.* 2014;34:130–40.
 99. Bui E, Anderson E, Goetter EM, Campbell AA, Fischer LE, Barrett LF, et al. Heightened sensitivity to emotional expressions in generalised anxiety disorder, compared to social anxiety disorder, and controls. *Cognit Emot.* 2017;31:119–26.
 100. Diwadkar VA, Re M, Cecchetto F, Garzitto M, Piccin S, Bonivento C, et al. Attempts at memory control induce dysfunctional brain activation profiles in generalized anxiety disorder: an exploratory fMRI study. *Psychiatry Res Neuroimaging.* 2017;266:42–52.
 101. Yao Z, Liao M, Hu T, Zhang Z, Zhao Y, Zheng F, et al. An effective method to identify adolescent generalized anxiety disorder by temporal features of dynamic functional connectivity. *Front Hum Neurosci.* 2017;11:492.
 102. Sakai Y, Kumano H, Nishikawa M, Sakano Y, Kaiya H, Imabayashi E, et al. Cerebral glucose metabolism associated with a fear network in panic disorder. *NeuroReport.* 2005;16:927–31.
 103. Dilkov D, Hawken ER, Kaludiev E, Milev R. Repetitive transcranial magnetic stimulation of the right dorsal lateral prefrontal cortex in the treatment of generalized anxiety disorder: a randomized, double-blind sham controlled clinical trial. *Prog Neuro-Psychopharmacol Biol Psychiatry.* 2017;78:61–5.
 104. Shiozawa P, Leiva APG, Castro CDC, da Silva ME, Cordeiro Q, Fregni F, et al. Transcranial direct current stimulation for generalized anxiety disorder: a case study. *Biol Psychiatry.* 2014;75:e17–8.
 105. Heath RG, Dempsey CW, Fontana CJ, Myers WA. Cerebellar stimulation: effects on septal region, hippocampus, and amygdala of cats and rats. *Biol Psychiatry.* 1987;13:501–29.
 106. Abramowitz JS, Taylor S, McKay D. Obsessive-compulsive disorder. *The Lancet.* 2009;374:9.
 107. Baldwin DS, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol (Oxf).* 2014;28:403–39.
 108. Anticevic A, Hu S, Zhang S, Savic A, Billingslea E, Wasylink S, et al. Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. *Biol Psychiatry.* 2014;75:595–605.
 109. Hou J, Wu W, Lin Y, Wang J, Zhou D, Guo J, et al. Localization of cerebral functional deficits in patients with obsessive-compulsive disorder: a resting-state fMRI study. *J Affect Disord.* 2012;138:313–21.
 110. Pujol J, Soriano-Mas C, Alonso P, Cardoner N, Menchón JM, Deus J, et al. Mapping structural brain alterations in obsessive-compulsive disorder. *Arch Gen Psychiatry.* 2004;61:720–30.
 111. Brunelin J, Mondino M, Bation R, Palm U, Saoud M, Poulet E. Transcranial direct current stimulation for obsessive-compulsive disorder: a systematic review. *Brain Sci.* 2018;8:37.
 112. Kohl S, Baldemann JC. Progress and challenges in deep brain stimulation for obsessive-compulsive disorder. *Pharmacol Ther.* 2018;186:168–75. <https://doi.org/10.1016/j.pharmthera.2018.01.011>.
 113. Bation R, Poulet E, Haesebaert F, Saoud M, Brunelin J. Transcranial direct current stimulation in treatment-resistant obsessive-compulsive disorder: an open-label pilot study. *Prog Neuro-Psychopharmacol Biol Psychiatry.* 2016;65:153–7.