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REVIEW ARTICLE

Efficacy of transcranial direct current stimulation in people with multiple sclerosis: a review

Shawn Hiew | **Carine Nguemeni** | **Daniel Zeller**

Department of Neurology, University Hospital of Würzburg, Würzburg, Germany

Correspondence
Carine Nguemeni, Department of Neurology, University Hospital of Würzburg, Josef-Schneider-Str. 11, 97080 Würzburg, Germany.
Email: Nguemeni_C@ukw.de

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Abstract

Background and purpose: Multiple sclerosis (MS) is a chronic inflammatory disease causing a wide range of symptoms including motor and cognitive impairment, fatigue and pain. Over the last two decades, non-invasive brain stimulation, especially transcranial direct current stimulation (tDCS), has increasingly been used to modulate brain function in various physiological and pathological conditions. However, its experimental applications for people with MS were noted only as recently as 2010 and have been growing since then. The efficacy for use in people with MS remains questionable with the results of existing studies being largely conflicting. Hence, the aim of this review is to paint a picture of the current state of tDCS in MS research grounded on studies applying tDCS that have been done to date.

Methods: A keyword search was performed to retrieve articles from the earliest article identified until 14 February 2021 using a combination of the groups (1) 'multiple sclerosis', 'MS' and 'encephalomyelitis' and (2) 'tDCS' and 'transcranial direct current stimulation'.

Results: The analysis of the 30 articles included in this review underlined inconsistent effects of tDCS on the motor symptoms of MS based on small sample sizes. However, tDCS showed promising benefits in ameliorating fatigue, pain and cognitive symptoms.

Conclusion: Transcranial direct current stimulation is attractive as a non-drug approach in ameliorating MS symptoms, where other treatment options remain limited. The development of protocols tailored to the individual's own neuroanatomy using high definition tDCS and the introduction of network mapping in the experimental designs might help to overcome the variability between studies.

KEYWORDS
cognitive, effects, motor, multiple sclerosis, transcranial direct current stimulation

INTRODUCTION

Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by demyelination and neurodegeneration, leading to focal lesions in both the white and the grey matter [1]. The underlying causes and mechanisms behind this chronic disease remain opaque. People with MS (PwMS) are faced with a wide range of symptoms, including disturbances of gait, coordination and vision, as well as pain, fatigue, depression and tremor [2]. Initially, the majority of PwMS present with a relapsing–remitting disease course, but

Shawn Hiew and Carine Nguemeni made equal contributions.

commonly irreversible disability accumulates over time, thus making MS a leading cause of neurological disability in young adults [3]. It is estimated that 40%–60% of PwMS show gait impairment which interferes with daily activities [4]. Additionally, up to 82% of PwMS show cognitive impairment even in the earliest stages of the disease [5]. These factors force many PwMS to withdraw from working life at an early stage.

The development of effective disease modifying therapies within the last three decades has changed the long-term outcome for different subgroups of PwMS [6–8]. Despite those significant developments, there is a continuous need to manage a range of debilitating symptoms including motor and cognitive symptoms. To date, this is mainly achieved by non-pharmacological methods like tailored rehabilitation approaches [9]. The outcome of these impairment-based treatments, which are purely based on clinical grounds, is largely unpredictable in the individual case [10]. Therefore, an improved understanding of the neural processes underlying functional recovery constitutes a clinical necessity. Neural plasticity may play a major role in these processes. For instance, previous works have shown that long-term potentiation-like motor plasticity remains intact in mild to moderately affected PwMS [11]. Moreover, neuronal plasticity decreases with patient's age and with the length of disease duration [12]. The body of literature about neuroplasticity in MS supports the importance of targeting individual structural brain reorganization to achieve successful personalized rehabilitation.

Thus, neuromodulatory approaches, such as non-invasive brain stimulation, have drawn the attention of researchers as they bear potential to enhance the outcomes of pharmacological and physical therapies. A particularly promising approach is transcranial direct current stimulation (tDCS) which delivers weak currents via electrodes on the scalp, altering the cortical excitability of target brain areas [12]. These electrical currents have been shown to modulate the resting membrane potential, thus increasing or decreasing neuronal firing rates [13]. As a result, the combination of tDCS with repetitive low-frequency synaptic activation, as it occurs during training of a specific task, enhances the secretion of brain derived neurotrophic factor. This may induce long lasting neuroplastic responses by means of long-term potentiation-like processes [14]. Anodal and cathodal stimulation have been found to exert opposing effects [15]. Anodal tDCS (atDCS) typically increases the peak amplitude of excitatory post-synaptic potentials which depolarizes the membrane, thus modulating cortical excitability. Conversely, cathodal tDCS hyperpolarizes the membrane by inducing inhibition [16]. Hence, tDCS is able to shift depolarization thresholds and facilitate or hamper the firing of neurons resulting in the modulation of task performance, behaviours and mental states. Indeed, tDCS has been observed to modulate motor learning, sensory perception, attention and memory [17]. The utilization of tDCS is largely facilitated by the fact that it can be easily applied during the performance of a specific task, even in an at-home setting, and that the common devices are rather inexpensive.

Amongst other conditions, beneficial effects of tDCS have been found in patients with major depressive disorder [18], Alzheimer's disease [19] and stroke [20–22]. These beneficial tDCS effects warrant evaluation for potential clinical application in MS. Accordingly, tDCS has been applied to PwMS in order to reduce fatigue and pain, and to improve cognitive and motor functions [23–26].

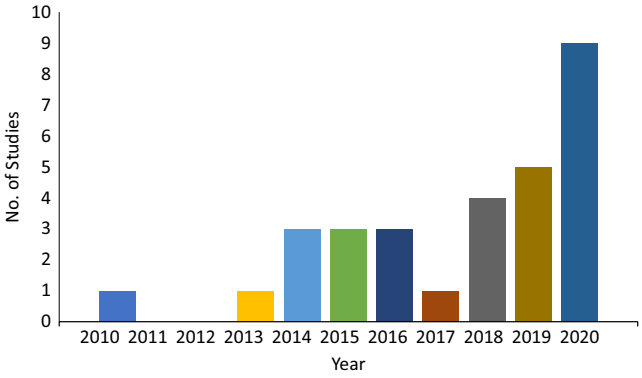

FIGURE 1 Number of publications per year between 2010 and 2020 that were performed in people with multiple sclerosis using transcranial direct current stimulation [Colour figure can be viewed at wileyonlinelibrary.com]

Whilst there has been a rising tide of this technique both in the media and academic literature in the last two decades [27], its use in MS research was first noted in 2010 and has only gained traction in the last 2 years (Figure 1). To date, a number of studies are still in their preliminary stages or have included fairly small sample sizes.

This review aims to present a concise overview of the studies that have applied tDCS in PwMS. Their results are discussed in view of the different stimulation protocols and the potential efficacy of tDCS in MS research.

MATERIALS AND METHODS

Search strategy

The systematic review protocol described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was adopted to guide this review process [28]. A keyword search was performed in Web of Science, PubMed, MEDLINE and Google Scholar to retrieve articles from the earliest article identified until 14 February 2021. The search algorithm included combinations of the groups (1) 'multiple sclerosis', 'MS' and 'encephalomyelitis' and (2) 'tDCS' and 'transcranial direct current stimulation'. Identified articles were screened against the study eligibility criteria (Figure 2). No other review protocol exists, and this current review is not registered online.

Data extraction

A standardized data extraction form was used to collect the following methodological and outcome variables: authors, publication year, location

Inclusion Criteria

Design:

(1) Randomized Controlled Trial
(2) Cohort Study
(3) Pre-post Study
(4) Crossectional Study

Study Subjects: Adults with MS

Main outcome: Motor and non-motor outcomes

Article Type:

(1) Peer-reviewed publication
(2) Clinical Trial
(3) Validation Study
(4) Comparative Study
(5) Corrected or Republished Article

Subject: Human

Language: English

Exclusion Criteria

Study Type:

(1) Case study
(2) Review Study
(3) Letters
(4) Conference Proceedings
(5) Dissertation
(6) Theses

Study Subjects:

(1) With Neurological disorders
(2) Younger than 18 years old

Main Outcome: Non-motor or non-cognitive

Language: Not English

Studies without published outcome variable

Studies with other pharmacological and neuromodulatory interventions

FIGURE 2 Summary of the study's inclusion and exclusion criteria

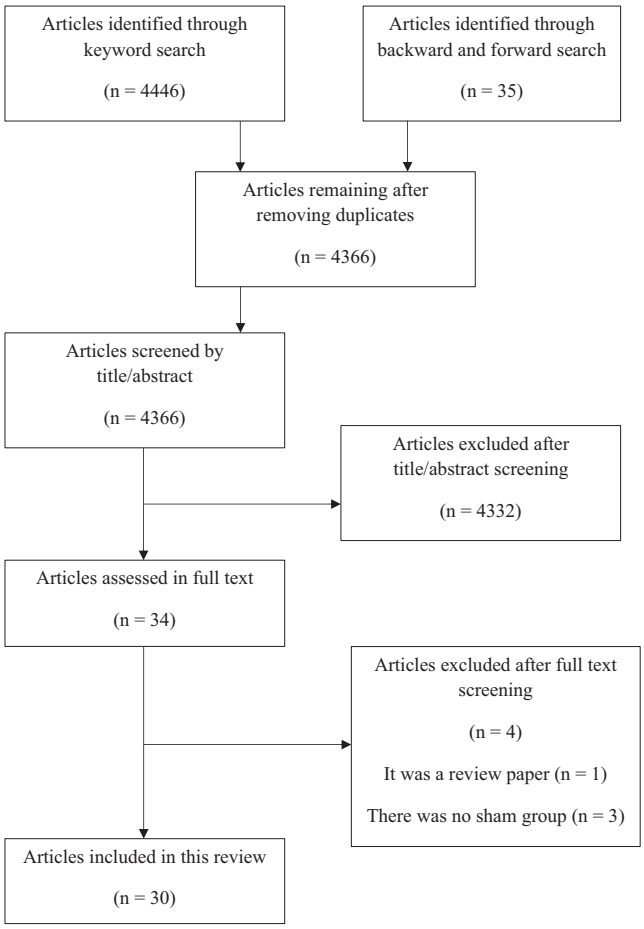

FIGURE 3 Study's extraction flowchart

of study, sample size, age, sex, disability level, disease duration, task, outcome measure, target region, electrode montage, current distribution, duration of stimulation, timing of stimulation, results and conclusion.

RESULTS AND DISCUSSION

Study selection

A total of 30 articles were included in the review (see Figure 3 for study selection flowchart). For a summarized list of studies performed in PwMS with tDCS, see Table 1. The stimulation parameters and schedules used by all the studies included in this article are summarized in Table 2 and Figure 4.

Out of the 30 articles that were selected, a total of 11 studies modulated motor related function including upper limb motor function, gait, spasticity and swallowing, whilst 13 studies applied tDCS to ameliorate fatigue. Two studies reported here investigated its effects in cognition whilst three other studies evaluated the effects of tDCS in relieving pain. A last study investigated tDCS effects on tactile discrimination. The outcome measures of the different studies varied from one study to the next although the most common measure for fatigue used was the Modified Fatigue Impact Scale (MFIS). Thirteen of the studies included in this review had small sample sizes (≤15). The average age of participants with MS in 28 of the studies is 43.9 ± 10.1 years. Two of the studies did not report age of the participants. The included studies used a variety of stimulation parameters such as differently sized electrodes (anode range 20–35 cm^2), current intensities (range 1.0–2.5 mA), electrode positioning on the skull (Figure 4), as well as various stimulation schedules that have been summarized in Table 2 and Figure 4. Novel tDCS approaches were also attempted, namely the implementation of remotely supervised tDCS (Rs-tDCS) where participants applied tDCS to themselves whilst being supervised by video call, was used in two of the studies [29,30], and the stimulation with individualized electrodes, specifically designed based on the individual's own neuroanatomy, was used in four studies [26,31–33].

3.2 tDCS and motor outcomes in PwMS

Upper limb

Four published studies included in this review investigated the effects of tDCS in upper limb tasks in PwMS. Meesen et al. [23] indicated that atDCS applied during a unimanual sequence training task to the contralateral primary motor cortex (M1) did not improve task performance compared to sham stimulation in PwMS. Sham tDCS consists in delivering an active stimulation for a few seconds (up to 30 s) to mimic the sensations observed with active tDCS and keep participants blind to the intervention. This stimulation does not induce neuroplastic changes but is sufficient to produce typical tDCS sensations, such as warmth and itch at the site of stimulation.

In contrast, Masoudian et al. [34] showed greater performance during the execution of the serial response time task (online learning) in the PwMS group that received atDCS to the left M1 compared to sham stimulated patients or healthy controls. Performance improvement in between practice periods, when subjects were at rest (offline learning), was only achieved by patients who received atDCS but not in the sham group, indicating impairment of offline motor learning in PwMS. Another recent study found that whilst atDCS applied to the left M1 after a finger tapping task (FTT, offline stimulation) significantly improved consolidation in healthy controls, this effect was not found in PwMS [35]. In the past decade, an interest in Rs-tDCS has been growing in order to increase access to rehabilitative services. In an ongoing clinical trial, active Rs-tDCS to M1 paired with an at-home hand exercise programme greatly improved grip strength and adaptability as well as fine motor speed [29].

The conflicting results in the current literature can at least partially be explained by the varied outcome measures used (FTT [23,35]/serial response time task [34]/grip strength and fine motor speed [29]). It seems possible that the FTT is not sensitive enough to detect small improvements in motor performance, learning and consolidation in PwMS, potentially explaining the lack of effects found by Meesen et al. [23] and Rumpf et al. [35]. Additionally, sequence learning itself may not be impaired in mild to moderate PwMS. Instead, poorer performance on motor tasks like the sequential finger tapping task could be due to other overlapping MS symptoms such as fatigue and reduced cognition. In that case, a sole targeting of the M1 might not be sufficient to produce improvement in motor performance.

Although the nine-hole peg test (9HPT) has been regarded as the gold standard for measuring manual dexterity in MS, it was not used as a measure in any of the included studies [36]. Using a standardized battery of tests including the 9HPT as outcome measures could improve comparability across studies in order to ascertain the efficacy of tDCS in upper limb motor function in PwMS.

In PwMS the motor cortex activation could be impaired, and as a result some aspects of motor learning may rely on spared neural resources in other nodes of a motor network such as the cerebellum. Therefore, M1 may not be the unique target for the modulation of a sequence learning task. Furthermore, motor reorganization such as increased surface area of activation in PwMS compared to healthy controls, activations of ipsilateral regions in hand movement tasks, and an anterior shift of activation during hand movement has been reported [37,38]. Abnormal resting-state functional connectivity measures have also been found to be good indicators of performance on the 9HPT, the gold standard measure for manual dexterity [39]. Findings from these functional magnetic resonance imaging (fMRI) studies, underlining interhemispheric and intrahemispheric motor reorganization occurring in MS, suggest that an electrode configuration that is effective for healthy controls may not be equally beneficial for PwMS. Further, since resting-state functional connectivity measures from specific regions are linked to performance outcomes, these regions could be worth exploring for modulation with tDCS. However, caution is warranted when identifying potential tDCS targets based on abnormal/compensatory brain activities triggered by brain lesions in MS, because the functional connectivity might differ between patients depending on the predominant localization of the lesion in the white or the grey matter [40]. The influence of this variability on sensorimotor networks and brain function underlines the need for a personalized approach to the design of electrode configuration. Recently, individual fMRIs have been used to guide the selection of transcranial magnetic stimulation sites in what is called fMRI navigated transcranial magnetic stimulation [41]. Similar methods could be used to individualize the localization of tDCS target sites. In this line, several studies [42] have attempted to provide a methodology for integration of fMRI with tDCS. Besides functional connectivity, knowledge regarding the effective connectivity, which is the direction of flow of information between two activated regions, may help inform the choice of novel stimulation sites for tDCS beyond the common targets.

A current intensity of at least 2 mA might be required during motor cortex stimulation for the improvement in upper limb function in PwMS to be observed, as positive outcomes at such current intensity were demonstrated [29,34], whilst a lack of effect was found at lower current intensities [23,35]. Conflicting results regarding motor consolidation in upper limb motor learning tasks in PwMS might be due to the different stimulation timings (during [23,29,34] vs. after [35] training) used in the studies. Positive effects of atDCS on motor consolidation in PwMS were found only when applied during the training [29,34]. However, this result is insufficient to confirm the effectiveness of tDCS in improving upper limb motor function and motor consolidation in PwMS.

Transcranial direct current stimulation still holds potential as an option to boost the rehabilitation of upper limb function, as long as care is taken in selecting ideal tDCS protocols and sufficiently sensitive and clinically relevant outcome measures such as the 9HPT. Further investigations regarding motor reorganization as well as effective connectivity in PwMS are warranted in order to aid the selection of target sites.

TABLE 1 A list of studies performed in PwMS with transcranial direct current stimulation (tDCS) interventions

Authors	Sample size	Sample age, mean ± SD (years)	Sample sex (% female)	Handedness	Mean EDSS score (range)	Mean time of disease (years)
Motor—upper limb						
Meesen et al. (2014) [23]	MS (31)	48.61 ± 10.13	70.97	RH (29); LH (2)	3.15 ± 1.22	11.57 ± 7.34
Rumpf et al. (2018) [35]	MS (14); HC (14)	MS 40.4 ± 7.8; HC 37.1 ± 10.3	71.43	RH	2.32 ± 0.64	5.7 ± 3.4
Feinberg et al. (2019) [29]	MS (10)	Not reported	Not reported	Not reported	Not reported	Not reported
Masoudian et al. (2020) [34]	MS (38)	36.08 ± 6.21	64	RH	<4	<2
Motor—gait						
Oveisgharan et al. (2019) [43]	MS (13)	38.9 ± 12.3	77	Not reported	3.8 ± 1.2	11.8 ± 8.9
Workman et al. (2019) [47]	MS (12)	51.4 ± 11.4	50	Not reported	PDDS (3.3 ± 1.4)	17.6 ± 12.2
Nguemeni et al. (2020) [50]	MS (40); HC (30)	42.35 ± 10.2	57.5	Not reported	2.41 ± 0.82	12.65 ± 8
Pilloni et al. (2020) [49]	MS (15)	52.66 ± 11.6	73.33	Not reported	4.98 ± 1.34	Not reported
Pilloni et al. (2020) [48]	MS (17)	53.09 ± 10.8	54.71	Not reported	5.26	Not reported
Motor—swallowing						
Restivo et al. (2019) [55]	MS (18)	38.4 ± 5.6	61.11	Not reported	5.8 ± 0.7	8.9 ± 2.7
Motor—spasticity						
Iodice et al. (2015) [58]	MS (20)	41.8 ± 6	75	Not reported	3.7 ± 0.9	7.4 ± 2.5
Fatigue						
Saiote et al. (2014) [63]	MS (13)	46.8 ± 6.8	76.92	RH	3.38 ± 1.34	9 ± 5.42
Tecchio et al. (2014) [32]	MS (10)	45.8 ± 7.6	70	Not reported	1.5 (0.0–3.5)	7.1 ± 8.2
Tecchio et al. (2015) [33]	MS (21)	42.87 ± 8.44	71.43	Not reported	1.69 (0.0–3.5)	9.85 ± 6.68
Hanken et al. (2016) [68]	MS (46); HC (52)	MS (49.08 ± 9.53) HC (25.69 ± 8.42)	MS (62.5); HC (77)	Not reported	4.18 ± 1.45	12.19 ± 8.33
Malik et al. (2016) [69]	MS (25); HC (27)	Not reported	Not reported	Not reported	Not reported	Not reported
Chalah et al. (2017) [64]	MS (10)	40.50 ± 11.18	40	Not reported	2.3 ± 2.5	14 ± 9.9
Cancelli et al. (2018) [31]	MS (10)	43.2 ± 13.1	80	Not reported	0.9 (0.0–3.5)	6.6 ± 3.7
Charvet et al. (2018) [30]	MS (62)	48.6 ± 13.09	62.73	RH (88.37%)	4.87 (0.0–8.5)	15.24 ± 9.71

Type of MS	Outcome measure	Groups	Key findings
PPMS (2), SPMS (9), RRMS (20)	Correct sequences and presses; inter tap interval on SFTT	Real and sham	No significant effect of atDCS on SFTT
RRMS	Speed and accuracy on SFTT	MS and HC (real and sham)	MS performed worse than HC but increments (learning) were comparable to HC. MS did not benefit from tDCS in terms of motor consolidation but HC did
PPMS and SPMS	Grip strength and adaptability; fine motor speed	Real and sham	Real tDCS showed strong benefit on outcome measures
RRMS	RT and error rate on SRTT	Real, sham and control	Significantly more online learning with atDCS. Offline learning only observed with atDCS
RRMS (3), other (10)	25FWT, MSWS-12, FSS, EDSS and MAS	Real and sham	Real but not sham tDCS improved walking speed but did not improve MSWS-12
RRMS	Distance walked in 6 min and gait characteristics (velocity, stride length and cadence)	Before and during; real and sham	Decreased distance walked for tDCS applied during the task. Increased gait velocity for tDCS applied before the task
RRMS (38), SPMS (2)	Gaitline length symmetry on SBT	HC and MS (real and sham)	No effect of CB-tDCS on locomotor adaptation in both HC and MS
RRMS (5), SPMS (10)	Gait speed and distance walked for 2MWT	Real and sham	Real tDCS improved gait speed and distance walked even at 4-week follow-up
RRMS (5), SPMS (12)	Gait speed and TUG for 10mWT	Real and sham	Single session of atDCS to M1 is insufficient to affect walking and functional gait in MS
RRMS (13), SPMS (5)	PAS	Real and sham	PAS lowered in real tDCS relative to sham. PAS improved post-stimulation only in real tDCS group
RRMS	MAS, MSSS and MSWS	Real and sham	No significant effect on spasticity in real tDCS and sham and no significant difference between real tDCS and sham
RRMS	FSS, MFIS, MSFSS, BDI and HADS	Real and sham	Transcranial DCS had no effect on fatigue
All types	MFIS	Real and sham	Real atDCS to bilateral S1 able to reduce fatigue in all patients but sham did not
RRMS	MEPs, SEPs and MFIS	$S1_{WB}$ (sham/real) and $S1_{Hand}$ (sham/real)	Real $S1_{WB}$ stimulation reduced subjective fatigue whilst $S1_{Hand}$ stimulation did not reduce fatigue relative to sham. M1 excitability increased more for $S1_{Hand}$ stimulation compared to $S1_{WB}$
RRMS (37.5%)	RT on Visual Vigilance Task	HC: right parietal (sham/real) and right frontal. MS: sham and real	Right parietal stimulation and not frontal counteracted the increase in RT associated with vigilance decrement
Not reported	Contraction on vernier grip meter	HC and MS (real and sham)	Dynamic grip improved following real tDCS but not sham
RRMS (9), SPMS (1)	FSS, MFIS, ANT (RT and accuracy) and HADS	Left DLPFC, right PPC and sham	Only left DLPFC stimulation ameliorated subjective fatigue. Mood improvement followed right PPC stimulation. Neither intervention affected attention
Not reported	MFIS	Real and sham	Real tDCS significantly reduced subjective fatigue compared to sham
All types	FSS, PROMIS—Fatigue Short Form, visual analogue fatigue ratings and BDI—Fast Screen	Study 1: real and control. Study 2: real and sham	Modest subjective fatigue reduction in real tDCS vs. control. Significant reduction in subjective fatigue for real tDCS vs. sham (continued)

(Continues)

TABLE 1 (Continued)

Authors	Sample size	Sample age, mean ± SD (years)	Sample sex (% female)	Handedness	Mean EDSS score (range)	Mean time of disease (years)
Fiene et al. (2018) [70]	MS (15)	43.2 ± 14.97	53.33	RH (13), LH (2)	3.54 ± 1.94	9.63 ± 8.57
Porcaro et al. (2019) [26]	MS (18)	44.5 ± 10.4	77.78	Not reported	1.1 (0.0–3.5)	6.9 ± 5.5
Pilloni et al. (2020) [65]	MS (12)	51.15 ± 11.05	Not reported	Not reported	(3.5–6.5)	Not reported
Chalah et al. (2020) [66]	MS (11)	43.91 ± 9.69 (26–57)	72.7	RH	3.14 ± 1.31 (2–6)	6.3 ± 3.83 (1.4–11.3)
Mortezanejad et al. (2020) [67]	MS (36)	32.62 ± 1.71 (SEM)	86.11	Not reported	1.53 ± 0.16 (SEM)	Not reported
Cognition						
Mattioli et al. (2016) [24]	MS (20)	42.8 ± 10.2	80	RH	2.5 ± 1.15	8.8 ± 6.3
Grigorescu et al. (2020) [76]	MS (11)	43.91 ± 9.69	72.73	RH	3.14 ± 1.31	6.3 ± 3.83
Tactile						
Mori et al. (2013) [77]	MS (20)	41.15 ± 11.61	60	Not reported	1.98 ± 0.99	
Pain						
Mori et al. (2010) [78]	MS (19)	44.47 ± 13.75	57.89	Not reported	2.39 ± 1.43	10.21 ± 8.55
Ayache et al. (2016) [25]	MS (16)	48.9 ± 10 (38–67)	81.25	RH	4.25 ± 1.4	11.8 ± 9.4
Young et al. (2020) [79]	MS (30)	50.54 ± 11.1	80	Not reported	Not reported	Not reported

Abbreviations: 2MWT, 2-min walking test; 10mWT, 10-m walking test; 25FWT, 25-ft walking test; ANT, attention network test; atDCS, anodal transcranial direct current stimulation; BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; CB-tDCS, cerebellar transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; EDSS, Expanded Disability Severity Scale; FSS, Fatigue Severity Scale; GOT, Grating Orientation Task; HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; M1, primary motor cortex; MAS, Modified Ashworth Scale; MEPs, motor evoked potentials; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; MSFSS, Multiple Sclerosis Specific Fatigue Severity Scale; MSSS, Multiple Sclerosis Spasticity Scale; MSWS, Multiple Sclerosis Walking Scale; MSWS-12, Multiple Sclerosis Walking Scale 12; PAS, Penetration/Aspiration Scale; PASAT, Paced Auditory Serial Addition Task; PDDS, Patient Determined Disease Steps; PPC, posterior parietal cortex; PPMS, primary progressive multiple sclerosis; PROMIS, Patient Reported Outcomes Measurement Information System; PwMS, people with multiple sclerosis; RH, right-handed; RRMS, relapsing–remitting multiple sclerosis; RT, response time; S1, primary somatosensory cortex; $S1_{Hand}$, hand primary somatosensory cortex; $S1_{WB}$, whole-body primary somatosensory cortex; SBT, split-belt treadmill; SDMT, Symbol Digit Modality Task; SEPs, sensory evoked potentials; SF-MPQ, Short Form McGill Questionnaire; SFTT, sequential finger tapping task; SPMS, secondary progressive multiple sclerosis; SRTT, serial reaction time task; tDCS, transcranial direct current stimulation; TUG, timed up and go; VAS; visual analogue scale; WCST, Wisconsin Card Sorting Task.

Gait

Anodal tDCS to the leg area of M1 for 30 min over seven consecutive days improved walking speed in a 25-ft walking test (25FWT) of individuals with moderate MS but did not improve their self-reported mobility in daily activities as measured by the Multiple Sclerosis Walking Scale 12 [43]. These two measures are strongly correlated and the difference in outcomes as measured by the two tests suggests that the change in speed for the 25FWT recorded by Oveisgharan et al. [43] may not have been meaningful. Additionally, it is possible that a dissociation exists between subjective ratings of mobility and speed of walking [44]. PwMS have demonstrated fluctuations of up to 20% on the 25FWT from day to day [45,46]. Hence, changes of greater than 20% are needed to constitute a real change.

Workman et al. [47] demonstrated that stimulation during a 6-min walking test (6MWT), which is a clinical measure of gait

Type of MS	Outcome measure	Groups	Key findings
RRMS (14), SPMS (1)	RT on SRTT and P300 amplitude	Real and sham	Anodal tDCS increased P300 amplitude and eliminated cognitive fatigability increase in RT
RRMS	MFIS	Real and sham	Real tDCS improved subjective fatigue
Not reported	MFIS, sleep efficiency, total sleep time and wake after sleep onset	Real and sham	Improvement in subjective fatigue and sleep only for real tDCS and not sham
RRMS (10), SPMS (1)	FSS and MFIS	Real and sham	Real tDCS improved subjective fatigue and anxiety symptoms but not depression
Not reported	FSS	Left M1, left DLPFC and sham	Significant reduction in FSS scores for real tDCS. Improvement persisted to 4 weeks only in left DLPFC group
RRMS	Select Reminding Test, Spatial Recall Test SDMT, PASAT Word List Generation Task and WCST	Real and sham	Anodal tDCS showed significant improvement in SDMT and WCST after treatment, PASAT at second interval and WCST at 6 months compared to sham. A tDCS group reached highest level faster than sham
RRMS (10), SPMS (1)	N-Back test, SDMT, Faux Pas Test and Eyes Test	Real and sham	Active bifrontal tDCS impaired 1-Back task relative to sham. tDCS had no effect on social cognitive measures or SDMT
RRMS	GOT and VAS	Real and sham	Significant improvement in discriminatory threshold and VAS scores for sensation following atDCS but not sham
RRMS	VAS, SF-MPQ and BDI	Real and sham	Significant reduction in pain after atDCS lasting up to 3 weeks
RRMS (11), SPMS (4), PPMS (1)	BPI, VAS and ANT (RT and accuracy)	Real and sham	Anodal tDCS over left DLPFC yielded significant analgesic effects but had no effect on mood, fatigue or attention
RRMS (16), SPMS (11), PPMS (3)	VAS	Real and sham	Significant reduction in VAS scores after five sessions of atDCS to M1 contralateral to site of pain lasting up to 2 weeks

impairment for PwMS, significantly reduced walking speed, but when the stimulation was applied before the walking test walking speed was increased. However, it must be noted that the duration of the stimulation applied before the task lasted 13 min whereas stimulation applied during the task lasted only 6 min. This result suggests that longer tDCS stimulation duration might be needed to obtain behavioural changes. Pilloni et al. [48] showed that, whilst a single session of atDCS to the M1 during aerobic exercise was unable to improve gait speed in a 10-m walking test, 10 sessions did improve gait speed and distance walked in 2 min even at a 4-week follow-up [49]. Nguemeni et al. [50] examined the changes in gait dynamics, adaptation and consolidation in PwMS who received a single session of cerebellar tDCS immediately after split-belt treadmill walking. They found that anodal cerebellar tDCS did not further enhance locomotor adaptation in people with mild to moderate MS.

TABLE 2 Transcranial direct current stimulation (tDCS) parameters used by the studies included in this review

Authors	Target site	Moment of stimulation	Electrode size (cm^2)	J (mA/cm^2)	Length of stimulation (min) [days]	Blinding
Motor—upper limb						
Meesen et al. (2014) [23]	M1	Dur SFTT	A, 25; C, 20	A, 0.04; C, 0.02	20	Double
Rumpf et al. (2018) [35]	M1	Aft training	25	0.04	15	Double
Feinberg et al. (2019) [29]	M1	Between measurements	Not reported	Not reported	30	Not reported
Masoudian et al. (2020) [34]	M1	Dur SRTT	25	0.08	20	Double
Motor—gait						
Oveisgharan et al. (2019) [43]	M1	Between examinations	20	0.125	30 [7]	Double
Workman et al. (2019) [47]	M1	Bef (6); Dur (6)	25	0.08	Bef (13); Dur (6)	Double
Nguemeni et al. (2020) [50]	CB	Aft training on day 1	25	0.08	15	Double
Pilloni et al. (2020) [48]	M1	Dur aerobic exercise	25	0.1	20	Double
Pilloni et al. (2020) [49]	M1	Dur aerobic exercise	25	0.1	20 [10]	Double
Motor—swallowing						
Restivo et al. (2019) [55]	Pharyngeal MC	Between measurements	25	0.08	20 [5]	Double
Motor—spasticity						
Iodice et al. (2015) [58]	M1	Between evaluations	35	0.06	20 [5]	Double
Fatigue						
Saiote et al. (2014) [63]	Left PFC	Between ratings	A, 35; C, 120	0.03	20 [5]	Double
Tecchio et al. (2014) [32]	S1	Between ratings	A, 35; C, 70	A, 0.04; C, 0.02	15 [5]	Double
Tecchio et al. (2015) [33]	S1	Between ratings	A, 35; C, 84	A, 0.04; C, 0.02	15 [5]	Double
Hanken et al. (2016) [68]	Right PC and right FC	First 20 min of 40 min task	35	0.04	20	Double
Malik et al. (2016) [69]	Not reported	Between measurements	Not reported	Not reported	20 [10]	Not reported
Chalah et al. (2017) [64]	DLPFC and PPC	Between ratings and testing	25	0.08	20 [5]	Double
Cancelli et al. (2018) [31]	S1	Between ratings	Individualized (A, 35; C, 70)	0.04	15 [5]	Double
Charvet et al. (2018) [30]	DLPFC	Dur 20 min cognitive training games; between ratings	25	0.08	Study 1: 20 [10]. Study 2: 20 [20]	Double
Fiene et al. (2018) [70]	DLPFC	Pre-stimulation (10) and Dur (20)	A, 25; C, 35	A, 0.06; C, 0.04	30	Single
Porcaro et al. (2019) [26]	S1	Between ratings	Individualized	Not reported	15 [5]	Double
Pilloni et al. (2020) [65]	M1	Between measurements	Not reported	Not reported	20 [10]	Not reported
Chalah et al. (2020) [66]	DLPFC	Between ratings	35	0.057	20	Double

TABLE 2 (Continued)

Authors	Target site	Moment of stimulation	Electrode size (cm^2)	J (mA/cm^2)	Length of stimulation (min) [days]	Blinding
Mortezanejad et al. (2020) [67]	DLPFC and M1	Between ratings	35	0.04	20 [6]	Double
Cognition						
Mattioli et al. (2016) [24]	Left DLPFC	Between evaluations	A, 25; C, 60	A, 0.08; C, 0.03	20 [10]	Double
Grigorescu et al. (2020) [76]	PFC	Between examinations	35	0.06	20 [5]	Double
Tactile						
Mori et al. (2013) [77]	S1	Between examinations	35	0.06	20 [5]	Double
Pain						
Mori et al. (2010) [78]	M1	Between evaluations	35	0.06	20 [5]	Double
Ayache et al. (2016) [25]	Left DLPFC	Between ratings and testing	25	0.06	20	Single
Young et al. (2020) [79]	M1	Between ratings	35	0.06	10 × 2 [5]	Single

Abbreviations: A, anode; Aft, after; Bef, before; C, cathode; CB, cerebellum; DLPFC, dorsolateral prefrontal cortex; Dur, during; FC, frontal cortex; M1, primary motor cortex; MC, motor cortex; PC, parietal cortex; PFC, prefrontal cortex; PPC, posterior parietal cortex; S1, primary somatosensory cortex; SFTT, sequential finger tapping task; SRTT, serial reaction time task.

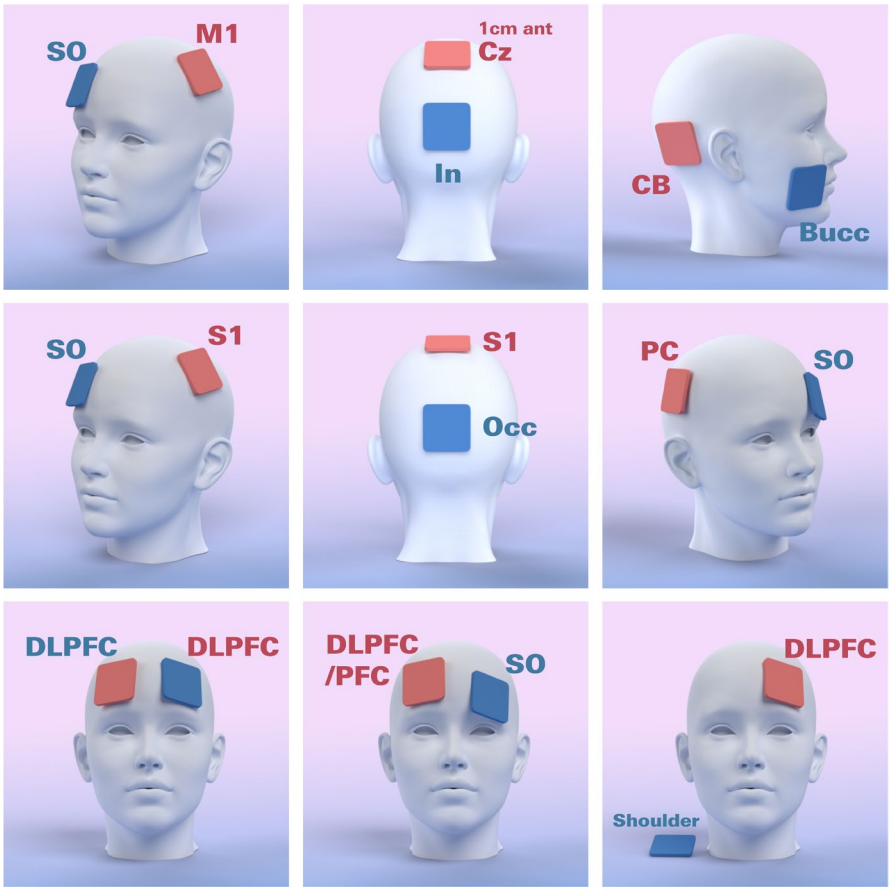

FIGURE 4 Electrode positions used in the studies analysed in the review. The red square represents the anodal electrode and the blue square corresponds to the cathodal electrode. Bucc, buccinator; CB, cerebellum; Cz, central reference point in the 10/20 electroencephalography system; DLPFC, dorsolateral prefrontal cortex; In, inion; M1, primary motor cortex; Occ, occipital cortex; PC, parietal cortex; PFC, prefrontal cortex; S1, primary somatosensory cortex; SO, supraorbital [Colour figure can be viewed at wileyonlinelibrary.com]

As previously observed with studies focusing on upper limb function, it appears difficult to compare studies that evaluated the influence of tDCS on gait function in PwMS because they differed in outcome measures and stimulation parameters used (Table 3). All those parameters can directly influence tDCS outcome in PwMS.

In order to improve comparability across studies, it would be ideal for each study to include at least one measure of short-distance walk (25FWT [51]), one measure of long-distance walk (2-min walking test/6MWT [52]) and one measure of postural control such as timed up and go [53] in the screening evaluation prior to the study and as outcome measures. As opposed to the three other studies examined, the results of both studies performed by Pilloni et al. [48,49] are encouraging. They underlined that PwMS with Expanded Disability Severity Scale above 4 are more likely to benefit from multiple sessions of atDCS. The results of Oveisgharan et al. [43] point out that an improvement on a walking scale following the stimulation might not transpose to a positive change in mobility and daily activities. The three above-mentioned points (clinically relevant outcomes, adequately chosen population, long-lasting effects in daily life) have serious implications for rehabilitation and the design of tDCS studies targeting gait improvement in PwMS. With this in mind, tDCS is still worth exploring as a means to improve training outcomes in relation to gait.

Dysphagia

Dysphagia affects up to 30% of all PwMS and can lead to poor nutrition, lung infections and dehydration [54]. Therefore, interventions must also be developed to address this common symptom in MS. In a pilot study, improved scores on the penetration/aspiration scale (PAS) were found directly after five sessions on consecutive days of atDCS to the pharyngeal area of the motor cortex and at a 4-week follow-up [55]. Significant differences in pharyngeal motor evoked potentials (MEPs) were also found for real tDCS relative to sham directly after the five-session cycle. A single pilot study is not sufficient to deduce the effectiveness of tDCS in treating dysphagia. Future studies should compare the effect of tDCS on dysphagia to other common clinical therapies like traditional dysphagia therapy [56]. Combinational approaches using tDCS and validated therapies could also be considered. The implementation of validated measures of dysphagia like the Dysphagia in Multiple Sclerosis Questionnaire and the Mann Assessment of Swallowing Ability as outcome measures is mandatory to prevent discrepancy between protocols and results from various studies [57].

Spasticity

Spasticity affects between 40% and 80% of PwMS [58]. Only one study to date has investigated whether or not atDCS applied to the M1 might improve spasticity in PwMS. No improvement in the Multiple Sclerosis Spasticity Scale, Modified Ashworth Scale or the Multiple Sclerosis Walking Scale was found after five sessions of sham or atDCS [58]. However, in this study, tDCS was applied without an ongoing task. It has been hypothesized that tDCS in isolation is too weak or unspecific to enhance synaptic efficacy but may modulate excitability in active neurons and boost ongoing plasticity

TABLE 3 Heterogeneity of studies applying tDCS to modulate gait in PwMS

		Authors
Outcome measure	• 25FWT [43] • MSWS-12 [43] • 6MWT [47] • 2MWT [48] • 10-m walking test [48,49] • Locomotor adaptation on an SBT [50]	• Oveisgharan et al. (2019) • Oveisgharan et al. (2019) • Workman et al. (2019) • Pilloni et al. (2020) • Pilloni et al. (2020; 2020) • Nguemeni et al. (2020)
Stimulation timing	• Between examination [43] • Before task [47] • During task [47–49] • After task [50]	• Oveisgharan et al. (2019) • Workman et al. (2019) • Pilloni et al. (2020; 2020), Workman et al. (2019) • Nguemeni et al. (2020)
Stimulation site	• M1 [43,47–49] • CB [50]	• Oveisgharan et al. (2019), Pilloni et al. (2020; 2020), Workman et al. (2019) • Nguemeni et al. (2020)
Stimulation duration	• 6 min [47] • 13 min [47] • 15 min [50] • 20 min [48,49] • 30 min [43]	• Workman et al. (2019) • Workman et al. (2019) • Nguemeni et al. (2020) • Pilloni et al. (2020; 2020) • Oveisgharan et al. (2019)
Occurrence or absence of specific training	• Aerobic training [48,49] • Treadmill walking [50]	• Pilloni et al. (2020; 2020) • Nguemeni et al. (2020)

Abbreviations: 2MWT, 2-min walking test; 6MWT, 6-min walking test; 25FWT, 25-ft walking test; CB, cerebellum; M1, primary motor cortex; MSWS-12, Multiple Sclerosis Walking Scale 12; PwMS, people with multiple sclerosis; SBT, split-belt treadmill; tDCS, transcranial direct current stimulation.

activated by task performance [59,60]. The activity–specificity theory assumes that the enhanced activity of a network renders it preferentially sensitive to modulation by tDCS [59]. Hence, tDCS combined with physical therapy could improve spasticity. Although it seems unlikely that tDCS to the M1 will be able to improve spasticity in PwMS, with only one study published to date, the possible beneficial effects of tDCS on spasticity when paired with other forms of treatment cannot yet be ruled out. Additionally, motor processes are not purely modulated by M1; instead, other regions such as the cerebellum, basal ganglia, supplementary motor area and premotor cortex play a direct and indirect role in the different aspects of movement. Therefore, tDCS applied to other regions than M1 may improve spasticity in PwMS. Novel connectivity-based network mapping has helped identify not only symptom-specific but also stage-specific abnormalities in networks in other neurological diseases like Parkinson's [61]. This approach might also be valid in MS where the guidance of novel meta-analytic methods such as coordinate-based network mapping would identify target sites specific to our population and symptoms.

3.3 tDCS and non-motor outcomes in PwMS

Fatigue

Many PwMS report fatigue to be their most disabling symptom [62]. Subsequently, fatigue disrupts daily life, for instance by affecting attention, cognition and motor endurance. Hence, 12 of the articles discussed in this review reported on the application of tDCS to improve fatigue symptoms in MS. These studies used either self-reported measures [26,31–33,63–67], performance measures [64,68–70] or evoked potentials [33]. Fatigue can be reflected by a vigilance decrement, which can be measured by an increased response time and errors in a prolonged time task, as well as lower amplitudes and prolonged latencies of the P300 event related potential. Anodal tDCS to the left dorsolateral prefrontal cortex (DLPFC) increased P300 amplitudes and eliminated the fatigue related increase in response times [70]. Anodal tDCS to the right parietal cortex has also been shown to reduce vigilance decrement in PwMS [68]. However, self-reported subjective fatigue was not reduced, demonstrating a dissociation between the feeling of fatigue and cognitive fatigability which induces decline in performance. The topological part of these findings is supported by another study that found that atDCS to the left DLPFC but not the right parietal cortex was able to reduce the sensation of fatigue as measured using the MFIS and Fatigue Severity Scale (FSS), showing that tDCS to the right parietal cortex is unable to improve subjective fatigue [64]. Furthermore, bilateral tDCS to the frontal cortices significantly improved subjective fatigue and anxiety but not depression [66]. Interestingly, grip strength correlates with FSS [69], and atDCS to the M1 was able to improve subjective fatigue as measured by MFIS as well as sleep quality [65]. However, a lasting reduction in subjective fatigue as measured by the FSS was only achieved with tDCS to the DLPFC and not to the M1 [67]. In contrast to these findings, Saiote et al. [63] found no effect of atDCS to the left DLPFC for subjective fatigue. It is important to note that this study used only half the current intensity used by all other studies applying tDCS to the DLPFC. Indeed, there seems to be a minimum current density of about 0.06 mA/cm^2 required for improvements in fatigue. Details about the studies related to fatigue in MS are summarized in Table 1.

Given the high prevalence of fatigue in PwMS, easy access to treatment such as can be achieved by Rs-tDCS is important. Indeed, 10 sessions of Rs-tDCS at a current intensity of 1.5 mA to the left DLPFC were able to improve subjective fatigue as measured by the Patient Reported Outcomes Measurement Information System (PROMIS)—Fatigue Short Form [30]. However, more substantial fatigue reduction was demonstrated when the current intensity was increased to 2 mA and the number of sessions was doubled, suggesting that more intense and longer treatments will have more benefit.

Inconsistent outcomes of tDCS have long been a problem in the field and these inconsistencies have been suggested to be due to interindividual anatomical variability [71]. Therefore, investigators have used personalized electrodes to attempt to account for these differences. Sessions of atDCS to the bilateral primary sensory cortex (S1) using personalized electrodes have been found to ameliorate subjective fatigue in individuals with mild MS as measured by the MFIS [31,32]. However, these effects were no longer present at a 4-week follow-up [31]. Only tDCS of the whole-body somatosensory area ($S1_{WB}$) was able to ameliorate fatigue, whilst tDCS of the hand sensorimotor area ($S1_{Hand}$) was not [33]. A more recent study applying personalized electrodes to treat MS subjective fatigue found a more pathological neuronal electrical activity in the S1 than in the M1 that was normalized after treatment [26]. Whilst the $S1_{WB}$ and DLPFC may be preferred targets, the wide range of brain regions found to be effective in reducing fatigue suggest that fatigue in MS may better localize to a network than to single regions. Recent work by Wylie et al. [72] has provided further evidence of a functionally connected 'fatigue network' in the brain. This network might include the striatum of the basal ganglia, the DLPFC, the ventro-medial prefrontal cortex (vmPFC) and the anterior insula. fMRI analysis during the performance of an N-Back working memory task indicated reciprocal functional connectivity between three pairs of regions: the striatum insula, the vmPFC insula and the vmPFC DLPFC. The connectivity between these regions and other frontal regions largely decreased as cognitive fatigability increased whilst connectivity between these seeds and more posterior regions increased. This work suggests that novel connectivity-based network mapping methods might help identify symptom-specific abnormalities in networks that will enable the researchers to select better target regions. Summarizing the above-mentioned studies, the efficacy of tDCS, especially to the left DLPFC, in ameliorating fatigue symptoms is convincing. An Rs-tDCS protocol applying higher current intensities, for instance 2 mA, and using personalized electrodes could therefore be a viable treatment option for MS related fatigue and should definitely be looked into. Based on the recent data

regarding fatigability network, the systematic implementation of objective measures of fatigue like simple reaction time and accuracy or P300 event related potential paradigms to complement the subjective nature of fatigue diagnostics is suggested [73]. This step is important for the development of new approaches using network mapping supported tDCS.

Cognition

Cognitive impairment affects between 35% and 70% of PwMS [74] and leads subsequently to significant individual disease burden, premature retirement and, as a consequence, poor quality of life for PwMS [75]. Anodal tDCS to the left DLPFC significantly improved performance on the Symbol Digit Modality Task, the Wisconsin Card Sorting Task as well as the Paced Auditory Serial Addition Task [24]. More recently, however, Grigorescu et al. [76] found that bifrontal tDCS to the prefrontal cortex impaired performance on the 1-Back test and had no effects on the Symbol Digit Modality Task and social cognitive measures. This may highlight the impact of electrode montages on the effect of tDCS. Whilst left DLPFC tDCS may improve cognition, bilateral prefrontal cortex tDCS may impair cognition. These studies demonstrate that much more groundwork needs to be done before applying a technique such as tDCS to improve cognition in PwMS. There is a need to better understand the networks involved in these processes as well as the MS-specific network abnormalities to aid the selection of target sites.

Tactile

Sensory deficits affect up to 69% of PwMS [77] and are a possible cause of disability. Sensation, including proprioception, is key for the correct execution of movements as well as for motor learning which heavily relies on sensory feedback. Thus, interventions should also target tactile sensory deficits whenever they are recognized to be a problem and are hindering rehabilitation. Anodal tDCS to the primary somatosensory cortex S1 was found to significantly improve tactile discrimination thresholds [77]. Nevertheless, with only one such published study, the efficacy of tDCS in improving tactile sensations and its functional relevance in PwMS cannot yet be confirmed. First, investigations into the abnormalities in the somatosensory system of PwMS are needed. Further research regarding the efficacy of tDCS in improving tactile discrimination together with investigations of its resulting effect on motor rehabilitation need to be carried out.

Pain

Although once considered a painless disease, in recent years it has been estimated that 75% of PwMS experience pain [78]. Treatment for pain accounts for nearly 30% of drug use in MS, yet patients are generally unsatisfied with these treatments. Hence, adjuncts to pharmacological treatment for pain in MS are much needed, and tDCS shows promise to be one such therapy. Five daily sessions of atDCS to the M1 was able to significantly reduce pain up to 3 weeks after treatment [78,79], whilst three daily sessions of atDCS to the left DLPFC was also effective for ameliorating neuropathic pain [25]. Additional studies are needed to confirm these results and to compare the two sites of stimulation with respect to their efficacy in alleviating pain. Considering the current limits of pharmacological treatment for pain, tDCS remains a promising adjunct therapy.

AN OVERALL VIEW

The studies reviewed showed that the most common sites in PwMS for modulation by tDCS are the M1 for motor related symptoms, left DLPFC, $S1_{WB}$, M1 and the right parietal cortex for fatigue, and the left DLPFC for cognitive impairment and pain. Whilst multiple sessions with current intensities of at least 2 mA seem to be required for effects on motor symptoms to be observed, fewer sessions and lower current intensities (1.5 mA) seem sufficient for observable effects on fatigue, cognition and pain. Nevertheless, more sessions at higher current intensities result in generally greater and longer lasting effects. The effects of tDCS on the motor symptoms of MS are inconsistent and modest at best. However, tDCS shows promise in ameliorating fatigue and pain as well as improving cognition, which generally improves the quality of life for PwMS. Ameliorating these symptoms could also ultimately translate into slowing down disease progression by freeing up resources for physical rehabilitation. Yet, only a limited number of studies have so far investigated the effects of tDCS in PwMS and several studies failed to report in detail their stimulation protocols. More target sites need to be investigated to validate the efficacy of tDCS as well as the hypothesis that more treatment sessions combined with higher current intensities will result in greater and longer lasting effects. Detailed reporting of stimulation protocols and parameters are greatly needed at this stage to allow a better understanding of this complex system as well as to help identify optimum protocols and parameters to move forward research in the application of tDCS in MS.

Approximately half of the studies done to date included fairly small sample sizes, often requiring a within-subjects sham control. Sham-blinding at low intensities has been demonstrated to be ineffective with participants showing above chance accuracy when asked to guess their stimulation condition [80]. This makes the effects of the intervention more difficult to evaluate objectively. As such, multi-centre and collaborative studies could be a good option for future research. Moreover, a dissociation between subjective ratings and objective measures of symptoms have been found in several studies. This highlights the need to evaluate whether the chosen outcome measure meaningfully reflects the symptom that

was intended to be ameliorated. In addition, it also remains possible that certain outcome measures may lack the sensitivity to detect small changes.

The disease course of MS varies considerably, yet many studies using tDCS treatment in PwMS do not report the lesion load or other measures of corticospinal tract integrity such as MEPs. Out of the 30 publications included in this review, only a third assessed these parameters in various ways. One study reported whole brain lesion volumes [24], and another one indicated whether the subjects had cerebral or spinal lesions [78]. The lesion location was reported in one study [56] and four studies evaluated lesion volume in the grey matter and white matter [33,51,56,63]. The integrity of corticospinal tracts was assessed using MEPs in one report [56] and two studies evaluated the central motor conduction times in the patients [33,51]. However, the interpretation of the tDCS effect in those studies was usually not put in perspective with the lesion load or the central motor conduction time. In only one study evaluating the effect of tDCS on fatigue in PwMS was a correlation found between response to the stimulation regarding subjectively perceived fatigue and lesion load in the left frontal cortex. PwMS who responded positively to atDCS had higher lesion load compared to non-responding patients [63]. This result indicates that evaluation of the lesion load could help to identify responders and non-responders to tDCS. Further, abnormal upper extremity MEPs have been found to be predictive of worse performance on measures such as the 9HPT. The latency in MEPs correlated with a reduction of the distance walked in the 6MWT and an increase of the time spent performing the 10-m walk test [81]. Therefore, it is crucial to report MEPs before the stimulation in order to ensure the comparability between real and sham stimulation groups as well as to distinguish the real effect of tDCS from outcomes related to the difference in baseline disease conditions.

A limitation of this review is the small number of studies available to be included. Additionally, no statistical analysis could be done due to the range of tasks and stimulation parameters used. Furthermore, a publication bias could exist whereby studies reporting a lack of effect of tDCS were not published and hence this review is unable to consider these studies. Transcranial DCS modulates regions that are both functionally and structurally connected [59]. Therefore, tDCS could influence whole networks. Network mapping allows the identification of whole brain networks, regions functionally connected and interacting with one another, during a task or at rest in relation to a symptom [82,83]. In recent years, novel meta-analytic methods have allowed for the mapping of specific symptoms to a common network [61,81]. Using graph theory approaches, abnormalities in global network properties have been found in PwMS, such that PwMS show a loss of hubs in areas such as the superior frontal gyrus, precuneus and anterior cingulum, as well as different lateralization in areas such as the cerebellum [84]. Yet, there remains a lack of research on symptom-specific network abnormalities in MS. Applying these novel meta-analytic network mapping methods such as the coordinate-based network mapping used by Weil et al. [61] will allow us to use existing data from fMRI research to identify potential target sites for treating specific symptoms in MS, in particular fatigue where a wide range of brain regions seem to be involved as mentioned earlier. Identifying common networks for tasks would also allow us to identify the abnormalities that lead to an impairment on the task in PwMS and therefore potential stimulation sites to modulate performance on the task. The heterogeneity of symptoms in MS, the variable brain regions involved in a single symptom as well as the effects of a single brain region on several different symptoms, as demonstrated in this review, suggests that perhaps tDCS interventions for MS should take a more holistic approach. This is not unreasonable to say as symptoms impact one another. Individual differences in neuroanatomy could also influence the outcome of tDCS. As such, modelling the effects of tDCS on an individual basis and running optimization protocols could reduce individual variability and also maximize the beneficial effects of tDCS.

FUTURE DIRECTIONS

To summarize, this review paints a picture of the current state of tDCS research in MS; however, the work that has been published so far is insufficient to allow for any final conclusions. Therefore, this review aims to guide future research in selecting target sites as well as stimulation parameters that are most likely to be effective whilst limiting the reproduction of unsuccessful protocols. First, a single session of tDCS is unlikely to produce any benefit and, whilst low current intensities (1.5 mA) are able to produce some improvements in fatigue, the most beneficial outcomes resulted from multiple sessions at higher current intensities (2 mA). Secondly, to reap the most benefit from treatment with tDCS, tDCS should not be applied as a treatment in isolation but in combination with other forms of treatment. The interpretation of the benefits should be based on clinically meaningful scales in order to infer the impact on the quality of life of the patients. Thirdly, tDCS parameters such as target sites and electrode montages should also not be taken straight out of research on healthy controls. Instead, careful investigations of the structural and functional differences in PwMS should guide the selection of MS-specific tDCS protocols. Network mapping of MS-specific symptoms could provide us with a wealth of information regarding electrode sizes and montages, current intensities, timing and schedule of stimulation. Finally, to ensure that each individual with MS reaps the best possible outcome with tDCS, tDCS protocols should be tailored to the individual's own neuroanatomy, shape of head and conductivities of the individual's scalp and skull using existing optimization protocols. Although much more work needs to be done, tDCS shows promise as a non-drug approach in ameliorating MS symptoms, where other treatment options remain limited, and promises to continue to inform and update our current understanding of MS.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Carine Nguemeni: Conceptualization (lead); data curation (supporting); formal analysis (lead); funding acquisition (lead); methodology (lead); project administration (equal); supervision (equal); validation (equal); writing—original draft (equal); writing—review and editing (lead). Shawn Hiew: Conceptualization (supporting); data curation (lead); formal analysis (equal); investigation (equal); methodology (equal); writing—original draft (equal); writing—review and editing (supporting). Daniel Zeller: Conceptualization (equal); funding acquisition (lead); project administration (lead); resources (lead); supervision (lead); writing—original draft (equal); writing—review and editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no new datasets were generated during the current study. This review describes and discusses data originating from already published original research.

ORCID

Carine Nguemeni https://orcid.org/0000-0002-5930-7360
Daniel Zeller https://orcid.org/0000-0003-3393-5657

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