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Effects of non-invasive brain stimulation in multiple sclerosis: systematic review and meta-analysis

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Abstract

Objective: The objective of this meta-analysis was to summarize evidence on the therapeutic effects of non-invasive brain stimulation (NIBS) on core symptoms of multiple sclerosis (MS). Specifically, findings from studies deploying transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) protocols were summarized in this review.
Methods: We systematically searched articles published in four databases, until 31 May 2021, which compared the effects of active tDCS or rTMS with sham intervention in MS patients. We used a random-effects model for this meta-analysis. Meta-regression and subgroup meta-analysis were used to examine the effects of stimulation dose and different stimulation protocols, respectively.
Results: Twenty-five randomized controlled trials (RCTs) were included in this review, consisting of 19 tDCS and 6 rTMS studies. tDCS led to a significant and immediate reduction of fatigue with a large effect size (Hedges's $g = -0.870$, 95% confidence intervals (CI) = [−1.225 to −0.458], number needed to treat (NNT) = 2). Particularly, a subgroup analysis showed that applying tDCS over the left DLPFC and bilateral S1 led to fatigue reductions compared to sham stimulation. Furthermore, tDCS had favorable effects on fatigue in MS patients with low physical disability but not those with high physical disability, and additionally improved cognitive function. Finally, whereas rTMS was observed to reduce muscle spasticity, these NIBS protocols showed no further effect on MS-associated pain and mood symptoms.
Conclusion: tDCS in MS alleviates fatigue and improves cognitive function whereas rTMS reduces muscle spasticity. More high-quality studies are needed to substantiate the therapeutic effects of different NIBS protocols in MS.

Keywords: multiple sclerosis, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, fatigue, meta-analysis

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system (CNS).[1] The location, number, and size of lesions within the CNS determine the neurological symptoms and the burden of MS. The course of this disease is highly unpredictable and variable between patients. Characteristically, neurological deficits are initially reversible, followed by progressive neurological deterioration over time.[2] Symptoms include fatigue, vision problems, motor deficits, sensory disturbances, pain, spasticity, cognitive deficits, depression, bladder, and bowel dysfunction, all of which can occur in various combinations.[1] Furthermore, symptoms exacerbate each other, leading to accelerated deterioration. In one such case, spasmodic muscle contraction can cause secondary pain.[3] In another case, pain and fatigue can aggravate spasticity, movement problems, and cognitive problems.[3] Concerns about falling due to spasticity, paralysis, or postural instability often result in loss of activity. A decline

of mobility function, in turn, deteriorates fitness, gait function, and endurance.[4]

Multidisciplinary approaches are recommended to relieve symptoms and decrease the extent of MS exacerbation. Interventions include pharmacotherapy, exercise, and alternative or complementary approaches.[5,6] Whereas a milder course for MS has been realized following the 25 years since disease-modifying therapies (MDTs) became available, the incidence of MS has increased.[7] Despite recent and ongoing therapeutic pharmacologic advances in disease-modifying therapies (DMTs), MS remains a progressive disease in most cases, leading to disability and high socioeconomic costs.[8] Consequently, symptomatic therapies become necessary, especially in the later course of the disease. However, depending on the symptom, they considerably differ in their response to therapeutic interventions. A few symptoms like spasticity have a long and successful pharmaceutical history, starting with oral muscle-relaxants, intrathecal baclofen in severe cases, and, more recently, cannabinoids and botulinumtoxin Type-A. Other conditions including fatigue, muscle weakness, and postural instability are more challenging to treat pharmaceutically – instead, physical exercise programs and neuro-rehabilitation techniques are used to address these symptoms. Presupposing patient access, insurance coverage or the financial means to physical exercise programs, the therapeutic success highly varies between patients, depending on many variables such as regularity and patient's adherence. Therefore, auxiliary methods add therapeutic value. A potential set of methods are non-invasive brain stimulation (NIBS) techniques that include transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS). NIBS recommended as effective treatments for many neurological and chronic diseases include neuropathic pain, Parkinson disease, and fibromyalgia.[9,10] These techniques can be applied either as a single therapy or, potentially more promising, in combination with pharmaceutical intervention or physical exercise.

Lefaucheur and colleagues summarized the therapeutic effects of rTMS and tDCS on MS symptoms in their recent guidelines.[9,10] Based on three randomized controlled trials (RCTs), a probable efficacy (Level-B evidence) was concluded for intermittent theta-burst stimulation (iTBS), an rTMS protocol, to the leg motor cortex to treat lower-limb spasticity. However, no recommendations were made in the guideline for tDCS on MS due to the considerable variability in protocols and methodological heterogeneity. One recent meta-analysis demonstrated the favorable effects of tDCS on cognitive processing speed, pain, fatigue, and mood.[11] However, the effects of different NIBS protocols on MS need more attention as individual responses are disparate. Investigations into the differential effects and subgroup analyses (i.e. targets and types) of NIBS on MS are currently missing. Hence, the current review and meta-analysis aims to summarize the latest evidence on the therapeutic effects of NIBS on core symptoms of MS and compare the outcomes of different stimulation protocols. The NIBS in this review mainly focuses on tDCS and rTMS due to the limited use of other NIBS to treat and investigate MS. To elaborate, we included RCTs investigating the effects of tDCS and rTMS on symptoms of MS, including fatigue, pain, spasticity, mood, motor function, and cognitive deficits.

Material and methods

Data source and literature search
This review followed Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[12] We systematically searched four English bibliographic databases including PubMed, Medline, EMBASE, and Web of Science for articles published until 31 May 2021. The search was performed using the keywords (Multiple sclerosis OR Disseminated sclerosis OR Sclerosis) AND (non-invasive brain stimulation OR NIBS OR Transcranial direct current stimulation OR tDCS OR TMS OR transcranial magnetic stimulation) AND (randomized controlled trial OR randomly OR RCT OR randomized). In addition, reference lists of related published reviews and meta-analyses were screened for additional relevant studies. Three authors (GXJX, KTS, and RLDK) independently identified potential studies by reading study titles and abstracts, with disagreements settled through discussion with a fourth author (GSK).

Inclusion and exclusion criteria
Inclusion criteria were (1) studies defined MS diagnoses according to the standard McDonald's criteria; (2) studies used a form of tDCS or rTMS

intervention; (3) studies needed to include a sham stimulation control group; and (4) studies needed to be classified as an RCT and published in English. Exclusion criteria were studies published as conference abstracts, book chapters and dissertations, or if the stimulation target site was outside the brain.

Quality assessment and data extraction

Three authors (GXJX, KTS, and RLDK) extracted the relevant information and assessed the quality of each study independently after identifying eligible studies. Any disagreement between these authors was resolved by discussion. The Physiotherapy Evidence Database (PEDro) scale was used to assess the quality of included RCTs. A customized form was used for data extraction. Extracted information included the study design, sample size, characteristics of participants, stimulation protocols, time points of assessments, the measurement of outcomes, adverse effects, findings and whether the trial had been pre-registered. Studies were further classified into Class I–III studies as done by Lefaucheur *et al.*[13] A Class-I study is defined as an RCT with masked outcome assessments in an adequate population (enrolled population's size consistent with proper sample size estimate). Whereas a Class-II study is an RCT performed with a smaller sample size or an RCT that lacks at least one term listed in Class I, and a Class-III study included all other controlled trials (for details, see Lefaucheur *et al.*[13]).

Statistical analysis

Comprehensive meta-analysis version 3.0 for Windows was used for the statistical analyses. For studies with incomplete data, corresponding authors were contacted by email. Standard errors of the mean (SEM) were converted to standard deviations (SD) for studies reporting only SEM using the formula

$$SD = SEM \times \sqrt{n},$$

where n equals sample size. The formula,

$$SD = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \dfrac{N_1 N_2}{N_1 + N_2}\left(M_1^2 + M_2^2 - 2M_1 M_2\right)}{N_1 + N_2 - 1}}$$

was used to combine SD from subscales. Means and standard deviations were estimated according to Luo *et al.*[14] and Wan *et al.*[15] for studies that only provided median and interquartile ranges. GetData Graph digitizer 2.26 was used to extract data that were reported only as a graph.[16]

Individual study effect estimates

In our review, we define an immediate effect of stimulation treatment as the effect directly after the last stimulation treatment, that is, calculated as the change from baseline to the end of the last treatment. We define short-term durability as the effect observed at a follow-up visit (1–4 weeks after the last stimulation treatment), that is, calculated as the change from baseline to the follow-up visit. Individual effect sizes for immediate effects and short-term durability were estimated using absolute change scores (post-minus pre-stimulation scores) to correct for baseline differences between groups. The standardized mean difference, or Hedges's g (a variation of Cohen's d, but accounting for sample size[17]), and 95% confidence interval (CI) were computed for each trial by comparing patients undergoing active *versus* sham tDCS or rTMS.

Summary effect estimates

Random-effects meta-analysis was used to account for the clinical and methodological diversity among included trials, both for immediate effects and for short-term durability. Heterogeneity among the included studies was assessed by using Higgins' I^2 statistic.[18,19] Meta-regression was used to test the relationship between dose and effect size. Subgroup analysis was used to explore the effects of different tDCS and rTMS protocols (i.e. intensity and sites) on symptom reductions. Sensitivity analysis was performed using the leave-one-out method in cases where results were significant. Publication bias was assessed by visual inspection (of a funnel plot) and Egger's test in cases where there were more than 10 articles.[20,21] For significant meta-analytic results, we calculated the number needed to treat (NNT) using the following formula in MATLAB:

$$NNT = \frac{1}{2 \star \text{normcdf}\left(d / \text{sqrt}(2)\right) - 1},$$
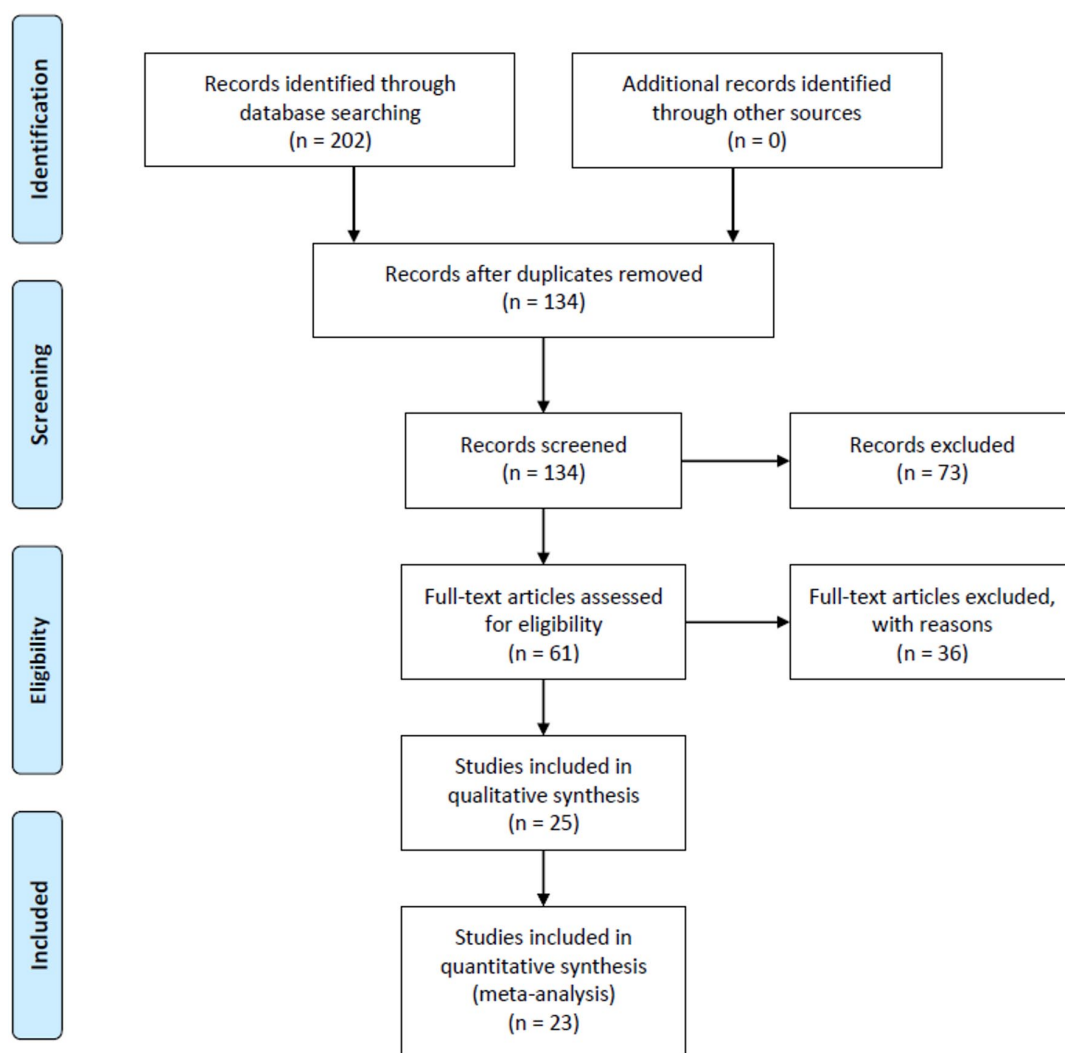
Figure 1. Flow diagram of the search strategy.

where *d* equals Hedges's *g*. The statistical threshold was set at $p < 0.05$ and $p < 0.1$ (two-tailed) for the main tests and the Egger's test, respectively.[20]

Results

Characteristics of included studies
Study selection. Twenty-five RCTs were identified as suitable for inclusion into the present review, and 23 RCTs were included in the meta-analysis (see Figure 1).[22–46] For details, see Supplementary Materials.

Participants. The demographic characteristics of the 25 RCTs included are presented in Table 1. These studies comprised a total of 491 patients.

Patients' diagnoses covered three types of MS including relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary-progressive MS (PPMS), with six studies including patients exclusively in the relapsing-remitting stage.[22,30,31,33,34,45] The mean score of the Expanded Disability Status Scale (EDSS) of included patients ranged from 2.3 to 6.5. Patients in three studies received no pharmacological treatment except for interferon-beta,[26,30,40] while patients in five other studies were on stable pharmacological treatment.[23,24,37,39,42] The remaining 17 studies did not provide information on pharmacological treatment.

Stimulation parameters. Table 2 depicts the stimulation parameters of included studies

Table 1. Demographic characteristics (*n* = 25 studies).

Author and year	Study design	Intervention	Sample size (M/F)	Age (years)	Participants condition	Clinicaltrials. gov or others (yes/no)	Disease type (RR/PP/SP)	Disease severity (EDSS)	Disease duration (years)
Mori et al.[33]	RCT	tDCS	19 (8/11)	44.8 ± 27.5	RRMS patients	–	19/0/0	–	–
Ferrucci et al.[26]	RCT, crossover	tDCS	23 (7/16)	44.54 ± 6.6	MS patients, MFIS > 45 EDSS (0, 6.5)	–	19/0/4	3.28 ± 0.24	13.23 ± 3.16
Meesen et al.[29]	Pseudo-RCT, crossover	tDCS	31 (9/22)	48.16 ± 10.13	MS patients, mild to moderate	–	20/2/9	3.15 ± 1.22	–
Saiote et al.[30]	Pseudo-RCT, crossover	tDCS	13 (3/10)	46.9 ± 6.8	MS patients, FSS ≥ 4	–	13/0/0	3.5 ± 4.0	9.0 ± 5.4
Tecchio et al.[32]	Crossover	tDCS	10 (3/7)	45.8 ± 7.6	MS patients, mild	–	7/2/1	1.5 (0–3.5)	7.1 ± 8.2
Iodice et al.[45]	RCT	tDCS	20 (5/15)	41.8 ± 6.213	RRMS patients	–	20/0/0	3.7 ± 0.88	7.4 ± 2.54
Tecchio et al.[31]	RCT, crossover	tDCS	E1:13 (4/9) E2: 8 (2/6)	E1:45.8 ± 7.6 E2:38.1 ± 9.8	E1: MS patients, MFIS > 15 E2: MS patients, MFIS > 16	–	E1: 13/0/0 E2: 8/0/0	E1: 1.5 (0–3.5) E2: 2 (1–2.5)	E1: 7.6 ± 8.2 E2: 13.5 ± 4.2
Mattioli et al.[44]	RCT	tDCS	20 (4/16)	/	MS patients	–	/	/	/
Ayache et al.[39]	RCT, crossover	tDCS	16 (3/13)	48.9 ± 10.0	MS with neuropathic pain	yes	11/1/4	4.25 ± 1.4	11.8 ± 9.4
Hanken et al.[28]	RCT	tDCS	40 (15/25)	49.25 ± 9.43	MS with cognitive fatigue	–	15/0/25	4.18 ± 1.55	12.19 ± 8.39
Cancelli et al.[22]	RCT, crossover	tDCS	10 (2/8)	43.2 ± 13.1	MS with MFIS > 35 BDI ≤ 19	–	10/0/0	0.9 (0–3.5)	6.6 ± 3.7
Chalah et al.[24]	RCT, crossover	tDCS	10 (6/4)	40.50 ± 11.18	MS with FSS > 5 BDI ≤ 19	–	9/0/1	2.3 ± 2.5	14 ± 9.9
Charvet et al.[25]	RCT	tDCS	27 (11/16)	44.18 ± 15.90	MS patients	–	13/14	E:6.0 (0.0–7.0) C:3.5 (0.0–8.5)	14.69 ± 10.16
Fiene et al.[40]	RCT, crossover	tDCS	15 (7/8)	43.20 ± 14.97	MS with WEIMuS ≥ 9 BDI ≤ 19	–	14/0/1	3.54 ± 1.94	9.63 ± 8.57

(Continued)

Table 1. (Continued)

Author and year	Study design	Intervention	Sample size (M/F)	Age (years)	Participants condition	Clinicaltrials. gov or others (yes/no)	Disease type (RR/PP/SP)	Disease severity (EDSS)	Disease duration (years)
Oveisgharan et al.[43]	RCT	tDCS	13 (3/10)	38.9 ± 12.3	MS patients	–	3/10/0	3.8 ± 1.2	11.8 ± 8.9
Pilloni et al.[41]	RCT	tDCS	15 (4/11)	52.7 ± 11.3	MS patients, 1.0 < EDSS < 6.5	yes	5/0/10	4.98 ± 1.37	–
Young et al.[42]	RCT	tDCS	30 (15/15)	50.54 ± 11.07	MS patients	–	16/3/11	–	–
Mortezanejad et al.[38]	RCT	tDCS	36 (6/30)	–	MS patients, FSS > 4 EDSS < 4	yes	–	–	–
Chalah et al.[23]	RCT, crossover	tDCS	11 (3/8)	43.91 ± 9.69	MS patients	–	10/0/1	<6.5	6.30 ± 3.83
Mori et al.[34]	RCT	rTMS	20 (13/7)	38.4 ± 11.24	RRMS patients	–	20/0/0	3.7 ± 1.38	–
Boutiere et al.[35]	RCT	iTBS	17 (9/8)	51.59 ± 10.57	MS patients, 4 ≦ EDSS ≦ 7	–	4/0/13	–	15.26 ± 9.89
Gaede et al.[27]	RCT	dTMS	28 (6/22)	–	MS patients, FSS > 4 0 < EDSS < 6	yes	26/0/2	–	–
Korzhova et al.[36]	RCT	E1: rTMS E2: iTBS	34 (14/20)	–	MS patients	–	0/0/34	6.5	4–20
Şan et al.[37]	RCT	rTMS	16 (8/8)	49.93 ± 12.27	MS patients	–	–	–	16.5 ± 9.01
Tramontano et al.[46]	RCT	iTBS	16 (11/5)	51.75 ± 7.9	MS patients, 4.5 < EDSS < 6.5	–	0/7/9	5.75 ± 0.89	18.44 ± 8.66

BDI, Beck Depression Inventory; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; RCT, randomized controlled trials; RRMS, relapsing-remitting multiple sclerosis; WEIMuS, Würzburger Fatigue Inventory for MS.

Table 2. Treatment parameters of tDCS interventions for fatigue symptoms (*n* = 14).

Author and year	Intervention site	Intensity (mA)	Duration	Intervention	Control	Outcome measure	Assessment timepoint	Side affect	Findings
Ferrucci et al.[26]	C3, C4	1.5	15 min/session, 5 sessions	Active tDCS	Sham tDCS	FIS	Before, after, 1w after, 3w after	Two had skin reaction	A-tDCS applied at M1 improves fatigue when compared to sham stimulation
Meesen et al.[29]	C3, C4	1	20 min/session, 1 session	Active tDCS + motor training	Sham tDCS + motor training	VAS-fatigue	Before, during, 30 minutes after	/	A single session a-tDCS does not relieve fatigue when compared to sham stimulation
Saiote et al.[30]	Left DLPFC	1	20 min/session, 5 sessions	Active tDCS	Sham tDCS	FSS, MSFSS, MFIS	Day 0, day 5, 8, 10, 15, 30	/	A-tDCS of the DLPFC does not relieve fatigue when compared to sham stimulation
Tecchio et al.[32]	Bilateral S1	1.5	5 sessions	Active tDCS	Sham tDCS	MFIS	Before, after, 4w after, 8w after	/	A-tDCS of bilateral somatosensory areas improves fatigue when compared to sham stimulation
Tecchio et al.[31]	E1: Bilateral S1 E2: SM1	1.5	5 sessions	Active tDCS	Sham tDCS	MFIS	Before, after	No	A-tDCS of bilateral somatosensory areas improves fatigue when compared to sham stimulation
Ayache et al.[39]	Left DLPFC	2	3 sessions	Active tDCS	Sham tDCS	MFIS, BPI, VAS	Before, after	tDCS group: 3 headaches. sham group: 1 headache, 1 Phosphenes	A-tDCS significantly relieves pain; no effects on mood, fatigue, or attention when compared to sham stimulation.
Hanken et al.[28]	Right PC	1.5	20 min/session, 1 session	ActivetDCS	Sham tDCS	VAS-fatigue	Before, after	/	A-tDCS of the right parietal cortex shows positive effects on fatigue-associated performance but does not relieve fatigue when compared to sham stimulation
Chalah et al.[24]	E1: Left DLPFC E2: Right PPC	2	20 min/session, 5 sessions	Active tDCS	Sham tDCS	FSS, MFIS VAS-fatigue	Before, after	Active right PPC: Three insomnia, 2 headaches	A-tDCS of left DLPFC stimulation significantly ameliorates fatigue when compared to sham stimulation; a-tDCS of the right PPC improves anxiety and depression when compared to sham stimulation; no effect of any intervention on attention

(Continued)

Table 2. (Continued)

Author and year	Intervention site	Intensity (mA)	Duration	Intervention	Control	Outcome measure	Assessment timepoint	Side affect	Findings
Charvet et al.[25]	left DLPFC	2	20 min/ session, 20 sessions	Active tDCS	Sham tDCS	PROMIS-FS	Before, after	Two pain patients	A-tDCS significantly reduces fatigue when compared to sham stimulation, longer treatment periods and higher stimulation intensity are of greater benefit
Cancelli et al.[22]	Bilateral S1	1.5	15 min/ session, 5 sessions	Active tDCS	Sham tDCS	MFIS	Before, after	Weariness, tingling	A-tDCS leads to a significant reduction in fatigue when compared to sham stimulation
Fiene et al.[40]	left DLPFC	1.5	27.29 ± 1.15 30 min/ session, one session	Active tDCS + reaction time task	Sham tDCS + reaction time task	VAS-fatigue	Before, after	/	A-tDCS of the left DLPFC reduces fatigue when compared to sham stimulation
Chalah et al.[23]	left DLPFC	2	20 min/ session, 5 sessions	Active tDCS	Sham tDCS	FSS, MFIS	Before, after, 1w after	no	A-tDCS shows effects on fatigue and anxiety but not depression when compared to sham stimulation
Mortezanejad et al.[38]	E1: DLPFC E2: M1	1.5	20 min/ session, 6 sessions	Active tDCS	Sham tDCS	FSS	Before, after, 1 month after	Tingling, itching	Both M1 and DLPFC a-tDCS show effects on fatigue when compared to sham stimulation and effects of DLPFC a-tDCS. last up to four weeks.
Pilloni et al.[41]	C3	2.5	20 min/ session, 10 sessions	Active tDCS + physical training	Sham tDCS + physical training	MFIS-21	Before, after, 1 month after	/	A-tDCS has immediate and long-lasting effects on walking and endurance when compared to sham stimulation

BPI, Brief Pain Inventory; DLPFC, dorsolateral prefrontal cortex; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MSFSS, the MS-specific FSS; PC, parietal cortex; PPC, posterior parietal cortex; PROMIS-FS, the Patient-Reported Outcomes Measurement Information System-fatigue short form; SM1, hand sensorimotor areas; VAS, Visual Analog Scale.

regarding fatigue symptoms. For studies that focused on other symptoms, please see Supplemental Table S1. All 19 RCTs deploying tDCS used excitatory (anodal) stimulation with eight studies targeting the left dorsolateral prefrontal cortex (DLPFC),[23–25,30,38–40,44] three studies targeting bilateral primary somatosensory cortex (S1)[22,31,32] and four studies targeting primary motor cortex (M1).[26,29,38,41] The cathode was placed supraorbitally or over the contralateral hemisphere on the homologous brain region in most studies, except for two studies that used a monocephalic montage and placed the cathode on the contralateral shoulder and under the chin, respectively.[31,40] For studies that used anodal stimulation of bilateral S1, the cathode was positioned over the occipital cortex on electrode position Oz. The duration of each session ranged from 15 to 30 minutes, while the number of sessions ranged from 1 to 20, and the intensity of stimulation ranged from 1.0 to 2.5 mA. Table 3 depicts the stimulation characteristics of the seven RCTs utilizing rTMS. All RCTs used excitatory stimulation (frequency > 5 Hz). Treatment intensity ranged from 80% to 110% MT, and the number of intervention sessions ranged from 10 to 18. In nine studies, subjects received additional exercise or cognitive training in the experimental and control group.[29,34–37,40,41,44,46]

Quality assessment of included studies

The results of the quality assessment (PEDro) for the 25 RCTs can be found in the Supplementary Materials (Table S2). In short, four studies had a score of 9 on the PEDro scale, 11 studies had a score of 8, 8 studies had a score of 7, and 2 studies had a score of 6. Studies were designed as double-blind, except for four studies, for which patients were blinded but assessors were aware of the stimulation group.[25,37,40,42] With regards to Lefaucheur *et al*'.s criteria,[13] only one study could be classified as Class I,[36] whereas 24 studies were classified as Class II, and no study was classified as Class III.

Meta-analysis results for fatigue symptoms

Immediate effects. A total of 18 studies were included in this meta-analysis, with four RCTs involving two separate subgroups.[24,31,36,38] Thus, 22 data sets, including 17 tDCS data sets (Class II) and 5 rTMS data sets (Class I–II) with a total of 376 patients were subjected to meta-analysis. The

analysis of 17 tDCS studies (278 patients) revealed a positive effect on fatigue with a large effect size (Hedges's $g=-0.870$, (95%CI: -1.255, -0.485), NNT = 2), despite substantial heterogeneity between individual study estimates ($I^2=74.79\%$ for tDCS; see Figure 2(a)). Although this result was robust to leave-one-out sensitivity analysis, the Funnel plot indicated the possibility of a publication bias (see Figure 2(b)). Moreover, meta-regression indicated no significant effect of stimulation dose as defined tapped by the number of sessions. Performing the meta-analysis on the five rTMS data sets (98 patients) revealed no significant difference between active and sham stimulation (Hedges's $g=-0.336$, (95% CI: -0.720, 0.047), $p=0.086$); see Supplementary Figure S.1a).

Subgroup analysis. Subgroup analysis of tDCS on fatigue aimed at the differential effects of stimulation targets (bilateral S1, left DLPFC, M1), stimulation intensities (1.5 mA, 2 mA), and MS subtypes. In addition, in order to investigate the differential therapeutic efficacies of NIBS on different stages of MS, we divided the included studies into low physical disability (L-PD) and high physical disability (H-PD) groups based on the baseline EDSS score. The cut-off value was 3.5, with subgroups defined as L-PD (EDSS ≤ 3.5) and H-PD (EDSS > 3.5).[47] Moreover, the short-term durability of tDCS on fatigue in MS was also investigated (please refer to Supplementary 06 and Supplementary Table S.1b).

Targets. Among 17 tDCS studies (20 data sets), seven RCTs (Class II) targeted the left DLPFC,[23–25,30,38–40] whereas four RCTs (Class II) targeted M1[26,29,38,41] and three RCTs (Class II) targeted bilateral S1.[22,31,32] Left DLPFC stimulation produced a large effect size (Hedges's $g=-0.860$, (95%CI: -1.508, -0.213), NNT = 2) but also substantial heterogeneity among the included studies ($I^2=77.45\%$, see Figure 3(a)). Similarly, bilateral S1 stimulation showed a large effect size (Hedges's $g=-1.420$, (95% CI: -2.333, -0.507), NNT = 1) and substantial heterogeneity ($I^2=65.039\%$, see Figure 3(b)), whereas M1 stimulation indicated no significant effects (Hedges's $g=-0.528$, (95% CI: -1.214, 0.158), heterogeneity: $I^2=73.78\%$) (see Figure 3(c)).

Intensity. A total of nine data sets among seven RCTs (Class II) applied a current of 1.5 mA.[22,26,28,31,32,38,40] Results indicated a large effect

Table 3. Treatment parameters of rTMS interventions on fatigue symptoms (*n*=4).

Author and year	Brain target	Type of coil	Intensity (RMT)	Frequency (HZ)	Total pulses per session	Number of sessions	Experiment group	Control group	Assessment of time points	Outcome measures	Findings
Mori et al.[34]	Leg area of M1	/	80% of AMT	5/50	/	10	Active iTBS + exercise	Sham iTBS + exercise	Before, after	MAS, MSSS-88, FSS	iTBS significantly reduces spasticity and fatigue compared to sham stimulation
Korzhova et al.[36]	Both M1	Figure of eight	80%	E1: 20 E2: 5–35	E1: 1600 E2: 1200	10	E1: active HF-rTMS + physical therapy E2: active iTBS	E1: sham HF-rTMS + physical therapy E2: sham iTBS	Before, after, 2w after, 12w after	MAS, NAS, SESS; MFIS;	Both HF-rTMS and iTBS reduce spasticity, but only iTBS has long-term effects on spasticity compared to sham stimulation HF-rTMS also relieves pain and fatigue. compared to sham stimulation
Gaede et al.[27]	E1: LPFC E2: M1	E1: H6 E2: H10	E1: 120% of RMT E2: 90% of RMT	E1: 18 E2: 5	E1: 1800 E2: 800	18	Active rTMS	sham rTMS	Week1–6, 8, 10, 12	FSS	rTMS of M1 significantly reduces fatigue compared to sham stimulation
Tramontano et al.[46]	Active: left cerebellum Sham: right cerebellum	Figure of eight	/	/	/	10	Active iTBS + vestibular rehabilitation	Sham iTBS + vestibular rehabilitation	Before, after	FSS	C-iTBS shows significant improvement of lower limb function compared to sham stimulation

2MWT, Two-minute walking test; 5STS, Five repetition sit to stand test; AP, average power; A-tDCS, anodal tDCS; AMT, active motor threshold; BBS, Berg Balance Scale; BI, the Barthel Index; BPI, brief Pain Inventory; C-iTBS, cerebellar-iTBS; C3/C4, motor cortex; FDI, First dorsal interosseous; FSS, Fatigue Severity Scale; iTBS, intermittent transcranial magnetic theta burst stimulation; LPFC, lateral prefrontal cortex; MAS, modified Ashworth scale; MFIS, Modified Fatigue Impact Scale; MSSS-88, the 88 items Multiple Sclerosis Spasticity Score questionnaire; MSWS-12, Multiple sclerosis walking scale–12; NAS, numerical analog scale; NPS, Neuropathic Pain Scale; PLAS, pain level associated with spasticity; PT, peak torque; PT/BW, peak torque/ body weight; RDSS, the Rekand disability and spasticity score; RMT, rest motor threshold; S1, whole body somatosensory areas; SDMT, Symbol digit modalities test; SESS, the Subjective Evaluating Spasticity Scale; SPART, Spatial recall test; SRT, Select reminding test; T25-FW, Timed 25–foot walk; TBG, Tinetti Balance and Gait Scale; TPT, time to peak torque; TW, total work; WCST, Wisconsin card test; .

(a)

(b)
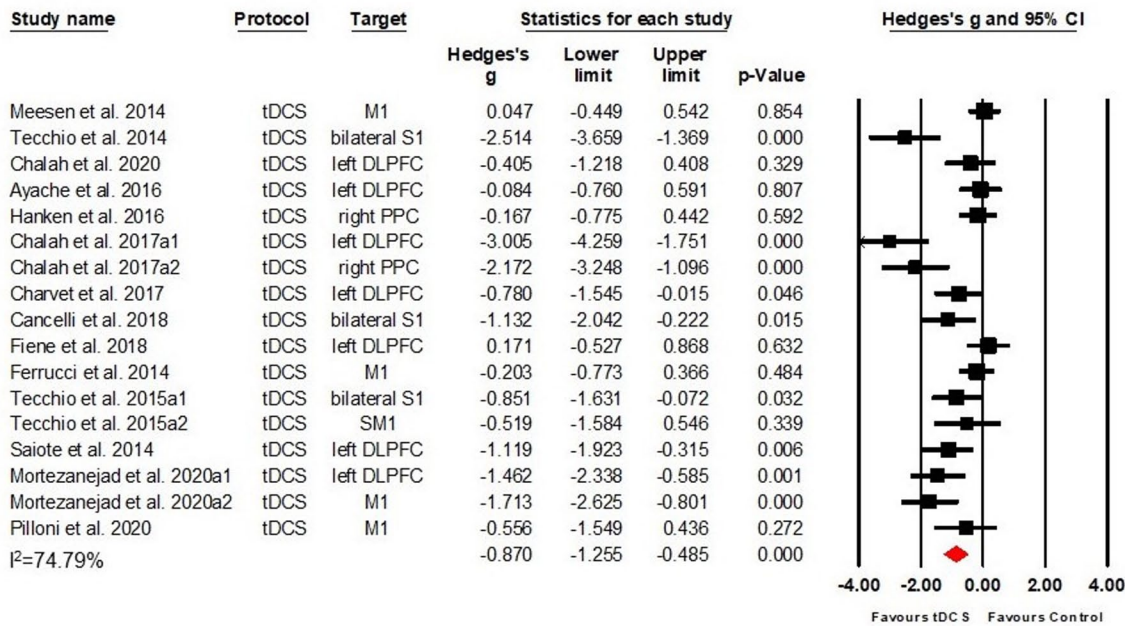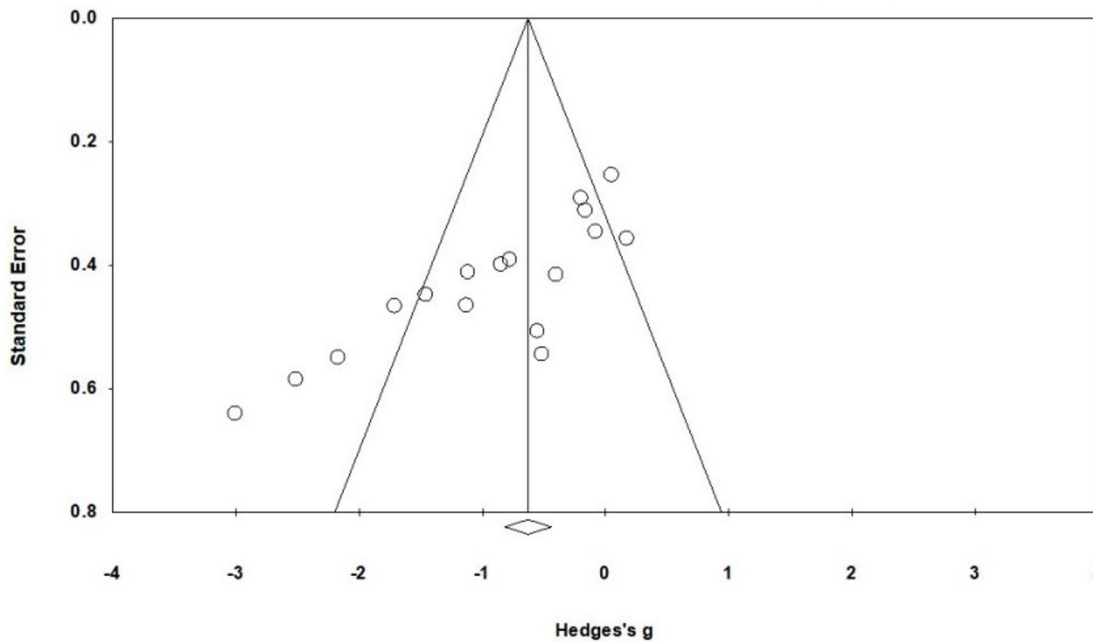
Figure 2. Effects of tDCS on fatigue in MS: (a) a forest plot showing studies that compare anodal tDCS with sham stimulation for fatigue symptoms on MS. (b) Examination of bias. The figure depicts an asymmetric funnel plot ($p < 0.001$). Possible sources of asymmetry are publication bias, poor methodological quality, true heterogeneity, and chance.

size (Hedges's $g = -0.856$, (95%CI: -1.376, -0.337), NNT = 2) despite substantial heterogeneity ($I^2 = 70.49\%$; see Figure 4(a)). Five data sets among four RCTs (Class II) applied a current of 2 mA[23–25,39] and revealed a large effect size (Hedges's $g = -1.193$, (95%CI: -2.140, -0.246), NNT = 2) despite substantial heterogeneity ($I^2 = 82.81\%$; see Figure 4(b)).

(a)

Study name	Protocol	Target	Statistics for each study				Hedges's g and 95% CI
			Hedges's g	Lower limit	Upper limit	p-Value	
Chalah et al. 2020	tDCS	left DLPFC	-0.405	-1.218	0.408	0.329	
Ayache et al. 2016	tDCS	left DLPFC	-0.084	-0.760	0.591	0.807	
Chalah et al. 2017a1	tDCS	left DLPFC	-3.005	-4.259	-1.751	0.000	
Charvet et al. 2017	tDCS	left DLPFC	-0.780	-1.545	-0.015	0.046	
Fiene et al. 2018	tDCS	left DLPFC	0.171	-0.527	0.868	0.632	
Saiote et al. 2014	tDCS	left DLPFC	-1.119	-1.923	-0.315	0.006	
Mortezanejad et al. 2020a1	tDCS	left DLPFC	-1.462	-2.338	-0.585	0.001	
I^2=77.45%			-0.860	-1.508	-0.213	0.009	

-4.00 -2.00 0.00 2.00 4.00

Favours tDCS   Favours Control

(b)

Study name	Protocol	Target	Statistics for each study				Hedges's g and 95% CI
			Hedges's g	Lower limit	Upper limit	p-Value	
Tecchio et al. 2014	tDCS	bilateral S1	-2.514	-3.659	-1.369	0.000	
Cancelli et al. 2018	tDCS	bilateral S1	-1.132	-2.042	-0.222	0.015	
Tecchio et al. 2015a1	tDCS	bilateral S1	-0.851	-1.631	-0.072	0.032	
I^2=65.04%			-1.420	-2.333	-0.507	0.002	

-4.00 -2.00 0.00 2.00 4.00

Favours tDCS   Favours Control

(c)

Study name	Protocol	Target	Statistics for each study				Hedges's g and 95% CI
			Hedges's g	Lower limit	Upper limit	p-Value	
Meesen et al. 2014	tDCS	M1	0.047	-0.449	0.542	0.854	
Ferrucci et al. 2014	tDCS	M1	-0.203	-0.773	0.366	0.484	
Mortezanejad et al. 2020a2	tDCS	M1	-1.713	-2.625	-0.801	0.000	
Pilloni et al. 2020	tDCS	M1	-0.556	-1.549	0.436	0.272	
I^2=73.78%			-0.528	-1.214	0.158	0.131	

-4.00 -2.00 0.00 2.00 4.00

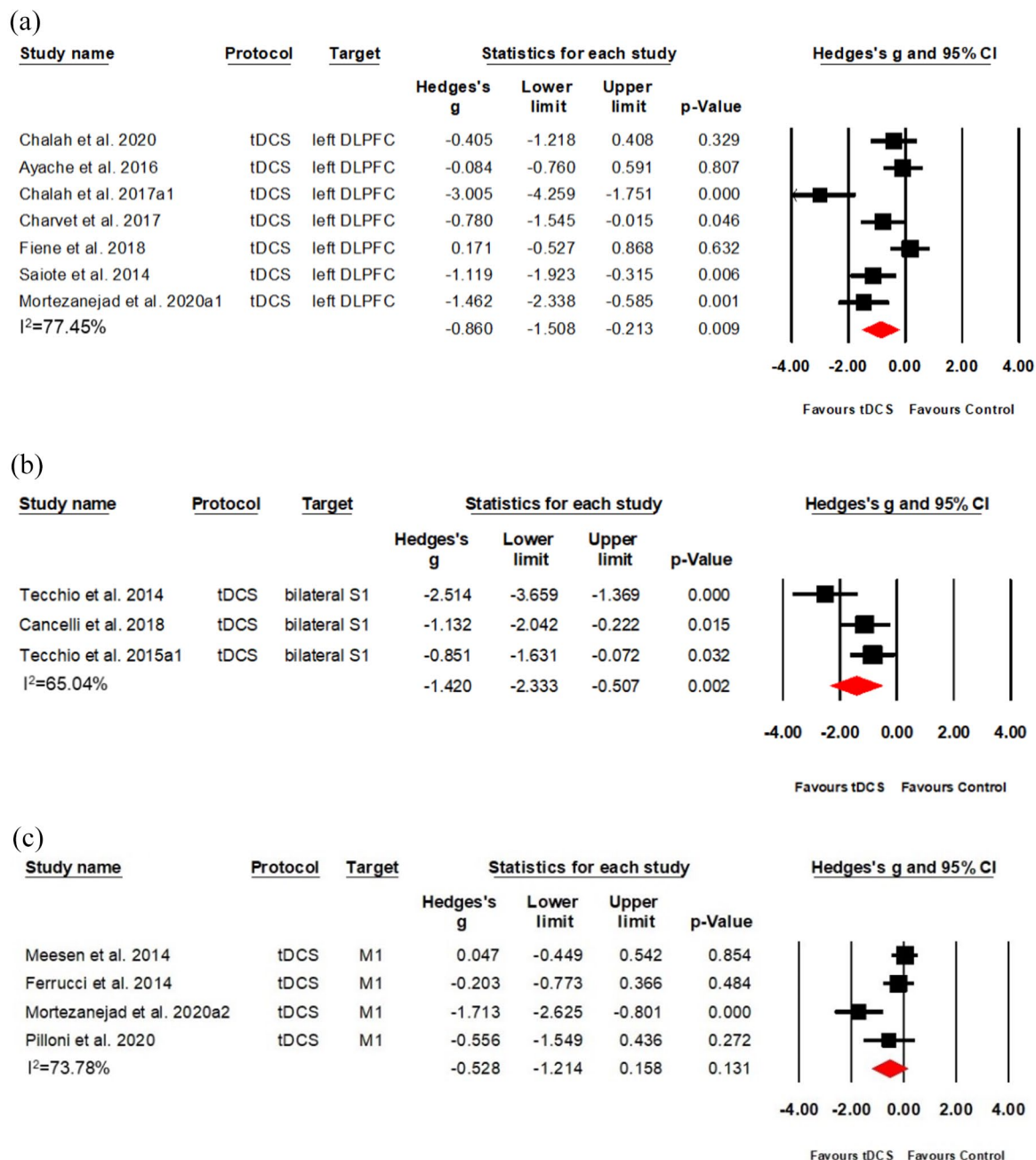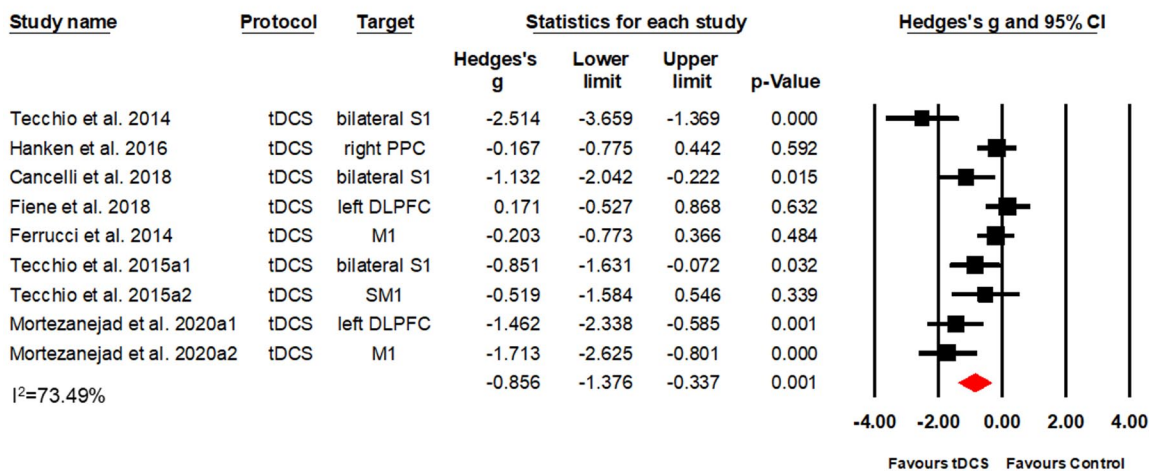Favours tDCS   Favours Control

Figure 3. Effects of tDCS on fatigue in MS, separated for different stimulation targets: (a) A forest plot showing studies comparing anodal tDCS of the left DLPFC with sham stimulation. (b) A forest plot showing studies comparing anodal tDCS of bilateral S1 with sham stimulation. (c) A forest plot showing studies comparing anodal tDCS of M1 with sham stimulation.

RR-MS patients. Four data sets (three RCTs, Class II) only included RRMS subtype patients.[30,37,46] Other studies included all MS subtypes or did not mention the MS type of their participants. When only including studies with the RR subtype in the meta-analysis, which was the most frequently diagnosed subtype of MS, we found a large effect size (Hedges's $g = -0.938$, (95%CI: -1.373, -0.503), NNT = 2) without heterogeneity ($I^2 = 0$%) (see Supplementary Figure S.1c). Results were robust to leave-one-out sensitivity analysis.

(a)

Study name	Protocol	Target	Statistics for each study				Hedges's g and 95% CI
			Hedges's g	Lower limit	Upper limit	p-Value	
Tecchio et al. 2014	tDCS	bilateral S1	-2.514	-3.659	-1.369	0.000	
Hanken et al. 2016	tDCS	right PPC	-0.167	-0.775	0.442	0.592	
Cancelli et al. 2018	tDCS	bilateral S1	-1.132	-2.042	-0.222	0.015	
Fiene et al. 2018	tDCS	left DLPFC	0.171	-0.527	0.868	0.632	
Ferrucci et al. 2014	tDCS	M1	-0.203	-0.773	0.366	0.484	
Tecchio et al. 2015a1	tDCS	bilateral S1	-0.851	-1.631	-0.072	0.032	
Tecchio et al. 2015a2	tDCS	SM1	-0.519	-1.584	0.546	0.339	
Mortezanejad et al. 2020a1	tDCS	left DLPFC	-1.462	-2.338	-0.585	0.001	
Mortezanejad et al. 2020a2	tDCS	M1	-1.713	-2.625	-0.801	0.000	
I^2=73.49%			-0.856	-1.376	-0.337	0.001	

(b)

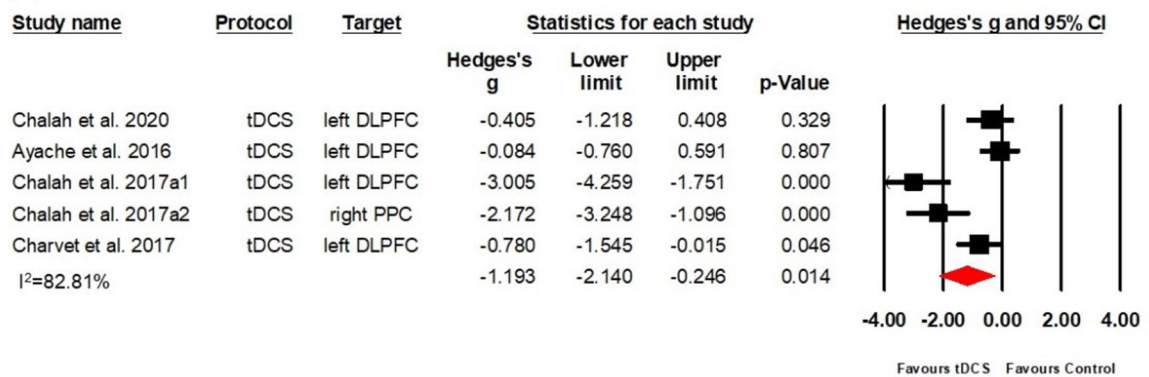| Study name	Protocol	Target	Statistics for each study				Hedges's g and 95% CI
			Hedges's g	Lower limit	Upper limit	p-Value	
Chalah et al. 2020	tDCS	left DLPFC	-0.405	-1.218	0.408	0.329	
Ayache et al. 2016	tDCS	left DLPFC	-0.084	-0.760	0.591	0.807	
Chalah et al. 2017a1	tDCS	left DLPFC	-3.005	-4.259	-1.751	0.000	
Chalah et al. 2017a2	tDCS	right PPC	-2.172	-3.248	-1.096	0.000	
Charvet et al. 2017	tDCS	left DLPFC	-0.780	-1.545	-0.015	0.046	
I^2=82.81%			-1.193	-2.140	-0.246	0.014	

Figure 4. Effects of different intensities of anodal tDCS on MS-associated fatigue: (a) a forest plot showing studies comparing 1.5 mA anodal tDCS with sham stimulation and (b) a forest plot showing studies comparing 2.0 mA anodal tDCS with sham stimulation.

Baseline EDSS score. Nine RCTs (12 data sets) in total with 165 participants were in the L-PD group.[22–24,26,29–32,38] Results show a large effect size (Hedges's g=−1.165, (95% CI: −1.680, −0.650), NNT=2) despite substantial heterogeneity (I^2=78.18%; see Figure 5(a)). This result was robust to leave-one-out sensitivity analysis, although the Funnel plot indicated the possibility of a publication bias (see Figure 5(b)). Meta-analysis of five RCTs that were in the H-PD group with 113 participants[25,28,39–41] revealed no significant results (Hedges's g=−0.226, (95%CI: −0.547, 0.096), p=0.169) (see Figure 5(c)).

Meta-analysis results for pain symptoms
Immediate effects. Five RCTs (Class I–II, four tDCS studies, one rTMS study) with 130 patients investigated the effects of NIBS on pain symptoms.[29,33,36,39,42] Results of the four tDCS (Class II) studies with 96 patients showed no significant effect, albeit a clear trend (Hedges's g=−0.994, (95%CI: −2.000, 0.013), p=0.053) (see Figure 6(a)). The only rTMS study (Class I), with 34 patients, indicated that high-frequency rTMS significantly improved MS pain, with effects lasting over 2 weeks posttreatment.[36] However, no significant effect was found in the iTBS group.[36]

Meta-analysis results for spasticity symptoms
Immediate effects. Five studies (Class I–II) assessed spasticity in MS patients, with one using tDCS as intervention and four using rTMS.[34–37,45] Performing the meta-analysis on the five rTMS (Class I–II) data sets with a total of 87
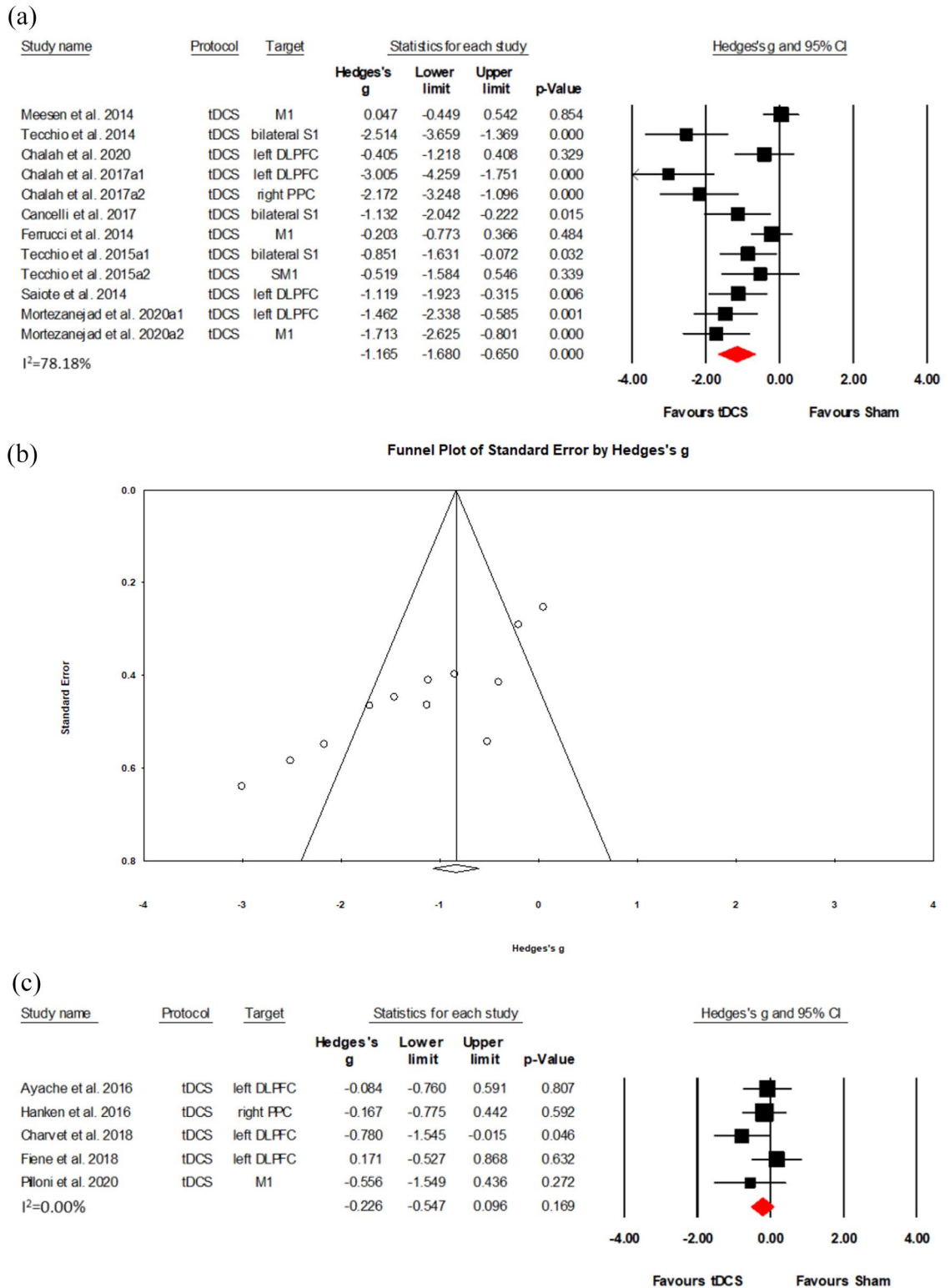
(a)

(b)

(c)

Figure 5. Effects of tDCS on fatigue in low physical disability and high physical disability MS: (a) a forest plot showing studies that compare anodal tDCS with sham stimulation for fatigue symptoms on low physical disability MS. (b) Examination of bias. The figure depicts an asymmetric funnel plot ($p < 0.001$). Possible sources of asymmetry are publication bias, poor methodological quality, true heterogeneity and chance. (c) A forest plot showing studies that compare anodal tDCS with sham stimulation for fatigue symptoms on high physical disability MS.

patients revealed a large effect size (Hedges's $g = -1.126$, (95% CI: -1.543, -0.710), NNT = 2); (see Figure 6(b)). However, the result of the tDCS study showed that five sessions of stimulation did not improve the lower spasticity limb in MS.[45] Only one of these studies (Class I) investigated the short-term durability of NIBS effects on spasticity, revealing that both HF-rTMS and iTBS significantly reduced spasticity. Notably, these effects lasted 2 weeks after HF-rTMS, while effects of iTBS lasted for 12 weeks.[36]

Review results for motor function
Immediate effects. Six studies investigated the effects of NIBS on motor function, including lower limb function (i.e. walking; 3 tDCS and 1 rTMS)[41,43,45,46] and fine hand motor function (2 tDCS studies).[29,31] No meta-analysis was conducted on these studies due to the low count and variety of stimulation protocols and outcomes. In terms of the effects of tDCS on lower-limb function, patient walking speed increased significantly when the target site was M1,[41,43] but no significant change on the MS Walking Scale (MSWS-12) was observed.[43,45] Only one rTMS study showed a positive effect on lower limb function after stimulation was applied to the cerebullaem.[46] As for two studies that investigated the effects of tDCS on fine hand motor function, the first study observed no significant differences between active and sham tDCS when the target site was M1,[43] whereas the second study found positive effects of tDCS on the fine motor function when bilateral S1 was stimulated.[31] Only one study investigated the short-term durability of effects, revealing improved of lower limb function that lasted for 4 weeks after active tDCS stimulation.[41]

Review and meta-analysis results for depression and anxiety
Immediate effects. Five Class II studies investigated depression and anxiety symptoms. Meta-analysis including four tDCS studies (five data sets totaling 75 patients)[24,33,39,42] showed no effects of active tDCS on depression when compared to sham stimulation (Hedges's $g = -0.814$, (95% CI: -1.737, 0.109)); (see Supplementary Figure S.2a).[24,33,39,42] Three of these studies (four data sets including 56 patients) also investigated anxiety symptoms.[24,39,42] As with the depression set of studies, meta-analysis indicated no significant effects of active tDCS when compared with

sham stimulation (Hedges's $g = -0.954$, (95% CI: -2.030, 0.122)); (see Supplementary Figure S2b). One study without valid data for quantitative analysis was not subjected to meta-analysis,[23] but suggested an anxiolytic effect of tDCS 1 week poststimulation and no immediate effect. However, the study did not report a comparison between active and sham stimulation groups.

Meta-analysis results for cognitive function
Immediate effects. Four Class II studies with 107 patients investigated the effects of tDCS on attention (three studies) or executive function (one study).[28,29,39,44] Meta-analysis revealed a positive effect of active tDCS on attention and executive function with a medium effect size compared to sham stimulation (Hedges's $g = -0.447$, (95% CI: -0.858, -0.036), NNT = 4); (see Figure 6(c)).

Discussion
Patients with MS show multiple neurological dysfunctions or disease-related complications due to chronic inflammatory demyelinating of the CNS and focal or diffuse neurodegeneration. Both rTMS and tDCS are presumed to modify neural and cortical activity, and may further elicit changes to non-neuronal tissues (i.e. glial cells) in the brain as all tissues and cells in the CNS are sensitive to electromagnetic fields.[9,10] As such, these NIBS devices are promising therapeutic options for MS in regards to the change in neuronal excitability and influence on inflammation.

In this review with 25 RCTs including 491 patients, we investigated the effects of NIBS on core symptoms of MS. First, we found that anodal tDCS but not rTMS can significantly relieve fatigue compared to sham stimulation. The effect was observed immediately after the end of treatment and remained significant during a follow-up visit 1–4 weeks posttreatment in a subset of studies. Second, our analysis further revealed a spasticity relieving effect of rTMS and cognitive improvement upon tDCS. Third, studies indicated no effect of tDCS on pain and mood. Finally, no conclusion could be made about the effects of NIBS on motor function because of the variety of the relevant studies.

With regards to the stimulation parameters and type, significantly positive effects of anodal tDCS on fatigue were found when bilateral S1 and left
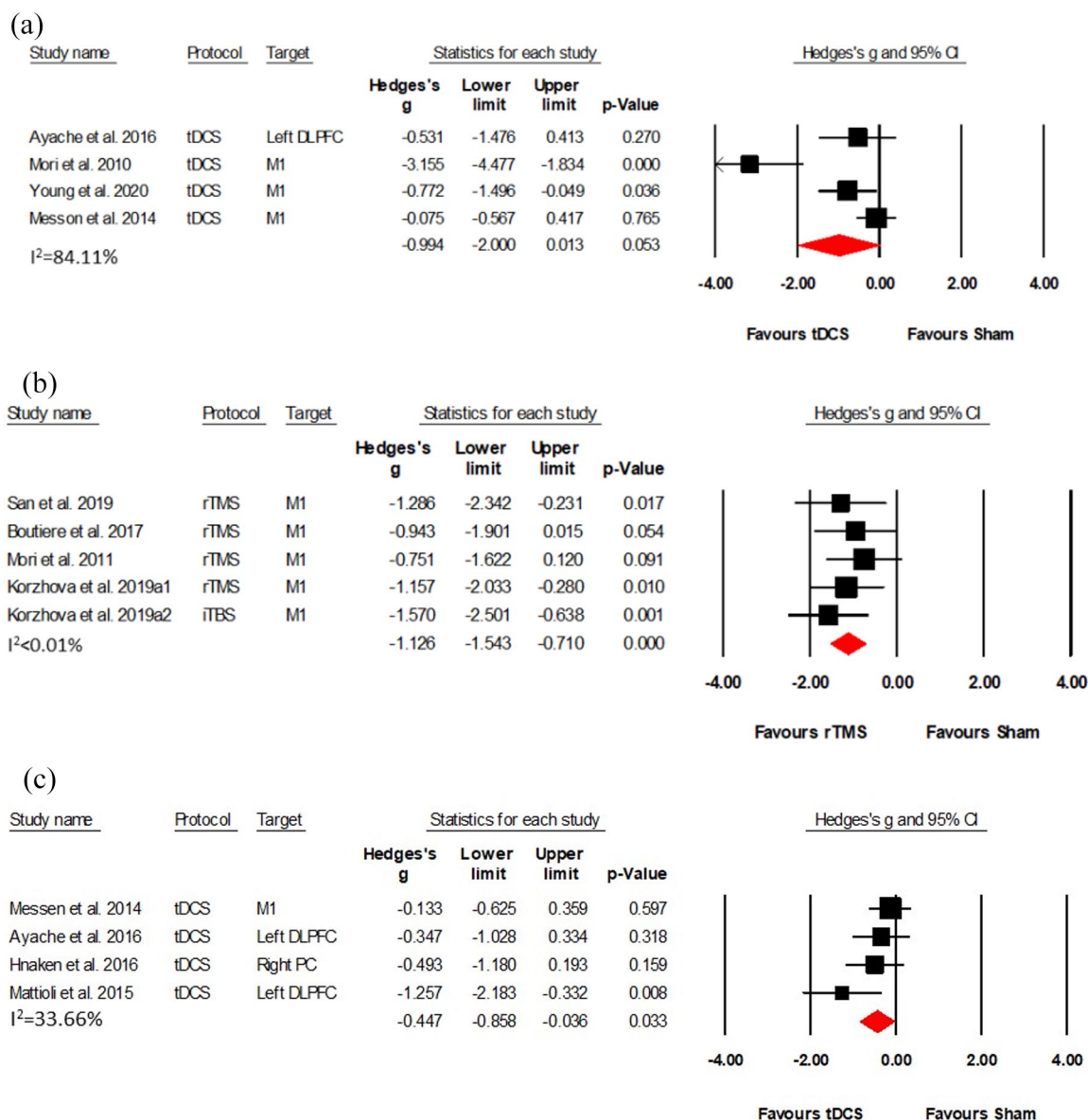
(a)

(b)

(c)

Figure 6. Effects of NIBS on pain, spasticity and cognitive function in MS: (a) a forest plot showing studies comparing effects of NIBS with sham stimulation on pain in MS, (b) a forest plot showing studies comparing NIBS with sham NIBS stimulation for spasticity on MS, and (c) a forest plot showing studies comparing NIBS with sham NIBS stimulation for cognitive function on MS.

DLPFC were stimulated but not M1. Notably, both 1.5 mA and 2 mA tDCS current intensities produced improvements. Patients with RRMS seemed to benefit from tDCS treatment, whereas no conclusions could be made about tDCS effects on other subtypes of MS due to a lack of data. tDCS showed favorable effects on fatigue for low compared to high physical disability patients.

When interpreting these results, it is important to note that fatigue in MS patients may be the result of multiple factors related to structural or functional brain network impairments. For instance, impaired functional connectivity between the striatum and sensorimotor cortex has been linked to fatigue in MS, which may be restored by NIBS.[48,49] Another study has shown that anodal tDCS can enhance axonal conduction through a subthreshold polarizing effect, mitigating MS fatigue.[49] In addition, while fatigue symptoms of MS have been associated with inflammatory cytokines and synaptic changes, tDCS has been

observed to promote beneficial synaptic changes and counteract the harmful effects of MS on neurotransmission, resulting in reduced fatigue.[49] However, to what extent tDCS can relieve the motor or cognitive components of fatigue remains to be investigated.

Anodal tDCS targeted at bilateral S1 and left DLPFC showed a large effect size in our review, whereas stimulation of M1 produced no effects. Previous studies indicated that increased connectivity between DLPFC and sensory cortical regions may contribute to the pathophysiology of MS-related fatigue.[48] Hence, the large positive effect of anodal tDCS over bilateral S1 and left DLPFC observed in our analysis may be associated with normalization of S1 and DLPFC connectivity. In addition, Jaegar *et al.*[48] suggested a bi-directional relationship between fatigue and mood characteristics, with several lines of evidence indicating that tDCS of the left DLPFC has positive effects on depression and anxiety.[50–52] Hence, we hypothesize that changes in fatigue after stimulation are related to the positive effects of left DLPFC stimulation on mood symptoms. However, our meta-analysis indicated no effects of NIBS on mood and anxiety symptoms in MS, which speaks against our view.

As for the intensity of tDCS, our review suggested that both 2 mA (Hedges's $g = 1.193$) and 1.5 mA (Hedges's $g = 0.856$) significantly improved fatigue symptoms. There are inconsistencies among electrophysiological studies, such as one study finding stronger cortical excitability with higher current intensities,[53] while another study did not find such a relationship.[54] We conclude that a dose-response relationship between tDCS intensity and treatment efficacy remains an open question, with preliminary evidence indicating both 1.5 mA and 2.0 mA intensities show promising effects on fatigue relief.

Our preliminary analysis on tDCS in RRMS (four data sets) indicated a similar effect size compared to the overall effect size that included all studies, yet, no conclusions can be drawn for other types of MS given a lack of data and future studies need to further explore a possible differential effect of tDCS on different MS types.

One study showed that both cortical demyelinating lesions and inflammation were frequent in early-stage MS,[55] which may theoretically be modulated by tDCS.[9] The progression of MS in this review is determined by baseline EDSS scores, and our study indicated that applying tDCS to MS in early stages lead to promising results on fatigue.

Our meta-analysis revealed that tDCS did not ameliorate chronic neuropathic pain, contradicting a recent review's claim that tDCS in MS may have positive effects on pain[56] – though it should be noted that their conclusion was based on one study. In healthy subjects, tDCS applied over M1 or DLPFC alleviated pain and increased pain thresholds.[57,58] Incidentally, rTMS has also been shown to have positive effects on chronic pain.[59] More high-quality studies are necessary to reach a conclusion.

Our meta-analysis further revealed that rTMS can significantly improve MS-associated spasticity. Our proposed mechanism for this antispastic effect is that MS spasticity may be due to excessive excitation of the neural stretch reflex caused by lesions of the corticospinal tract, so the application of rTMS may improve corticospinal tract excitability and thus reduce the activation of the stretch reflex.[60,61] Indeed, the antispastic effect of rTMS has also been shown in patients with spinal cord injuries, cerebral palsy, and stroke.[62,63] However, the longevity of the antispastic effect of rTMS observed in our meta-analysis after treatment is unknown and subject to future research.

No conclusion was reached on the effects of NIBS on motor function. Studies indicated that multiple sessions of anodal tDCS stimulation of M1 had a cumulative effect on motor function,[29,41] but further investigation is needed.

Finally, our meta-analysis indicated a positive short-term effect of tDCS on cognitive function. But more well-powered studies are needed to substantiate the therapeutic effects of NIBS on cognitive function in MS.

Limitations
Our meta-analysis has multiple limitations: (1) several included studies had a cross-over design but did not mention details about the length of the washout period, so potential carry-over effects in these studies may affect the overall result of our meta-analysis; (2) the meta-analysis results were

based on self- and observer-rating outcome measures, with self-rating scales being especially susceptible to subjective factors that may bias these results; (3) results indicated a potential publication bias and so should be interpreted with caution; (4) medication effects likely confound NIBS effects; (5) most patients in the included studies belonged to the RRMS subtype, so our findings may not generalize to other forms of MS; (6) our review and meta-analysis include several low-quality studies with small sample sizes and heterogeneous study designs, therefore, future reviews should include higher-quality studies with sufficient sample sizes to substantiate the therapeutic effects of NIBS in MS; (7) finally, our study was not registered on PROSPERO and a protocol for this study was not prepared.

Conclusion
In conclusion, this systematic review and meta-analysis showed that anodal tDCS of bilateral S1 or left DLPFC can significantly reduce fatigue in patients with MS. Importantly, tDCS relieves fatigue in low physical disability but not high physical disability MS. Furthermore, rTMS relieves MS-associated spasticity and tDCS improves MS-associated cognitive function, but tDCS has no effects on MS-associated mood and pain. No conclusion can be made regarding motor function effects of NIBS due to the variety of protocols. Open questions pertain to the longevity of effects, the differential outcomes following different stimulation intensities and whether specific subtypes of MS benefit more from stimulation treatments than others.

Author contributions
Rebecca L. D. Kan: Conceptualization; Methodology; Software; Writing-original draft; Writing-review & editing.
Grace X. J. Xu: Conceptualization; Methodology; Software; Writing-original draft.
Kate T. Shu: Conceptualization; Methodology; Software; Writing-original draft.
Frank H. Y. Lai: Resources; Writing-review & editing.
Gottfried Kranz: Resources; Writing-review & editing.
Georg S. Kranz: Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Funding acquisition; Writing-review & editing.

Conflict of interest statement
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material
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