DIPARTIMENTO DI PSICOLOGIA GENERALE

CORSO DI LAUREA MAGISTRALE IN
NEUROSCIENZE E RIABILITAZIONE NEUROPSICOLOGICA

TESI DI LAUREA MAGISTRALE

NON-INVASIVE BRAIN STIMULATION TECHNIQUES FOR THE TREATMENT OF FIBROMYALGIA: A SYSTEMATIC REVIEW AND META-ANALYISIS

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ANNO ACCADEMICO 2021/2022

TABLE OF CONTENTS

ABSTRACT:

BACKGROUND: FM is a complex chronic nervous system syndrome, in which pain represents the main symptom complained by patients. This condition is linked to a reduction in quality of life, involving multiple activities and domains, from the cognitive to the physical function. Non-invasive brain stimulation techniques (NIBS) are being increasingly used in rehabilitation as means of neurostimulation and neuromodulation. They include different techniques: transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS), transcranial alternating current stimulation (tACS) and reduced impedance non-invasive cortical electrostimulation (RINCE).

OBJECTIVE: to analyze the effectiveness of non-invasive brain stimulation techniques for the treatment of fibromyalgia.

DESIGN: A systematic review with meta-analysis

DATA SOURCES: We searched through the PubMed, Scopus, Web of Science, and Clinical Trials databases for relevant articles. Only randomized controlled trials and cross-over studies have been included, also investigating through the bibliography of the systematic reviews found in literature.

REVIEW METHODS: Articles were entirely read if they adhered to the inclusion criteria or if there was any uncertainty. A quality assessment of the included studies has been conducted with the application of the Jadad scale.

RESULTS: Positive therapeutic effect of rTMS on pain and quality of life (FIQ) was assessed, while tDCS resulted associated to a small effect on pain only. Adjustment for publication bias resulted in reduction of effect size and consequent cancellation of treatment effect. Application of rTMS maintains better FIQ scores after adjustment, particularly when left M1 in stimulated (Hedges' g = 0.74), compared to left DLPFC (Hedges' g = 0.22). Combined effect size after all subgroup analyzes demonstrates wide variability range and no statistical significancy, denoting inconsistency results.

CONCLUSIONS: No effect of rTMS or tDCS was found on pain when publication bias adjustment is conducted. FIQ scores demonstrate an improvement only after rTMS intervention, considering stimulation of left M1 as better performative. Inconsistency of data have been largely demonstrated.

1. INTRODUCTION

1.1 Fibromyalgia

Fibromyalgia (FM) is a complex chronic nervous system syndrome with a global prevalence of 2-4% and more prevalent in women compared to men (9:1) (Wolfe et al., 2018).

The American College of Rheumatology (ACR) describes FM as a condition characterized by a prominent widespread pain along with fatigue, stiffness, sleep disorders, allodynia, and hyperalgesia. Visceral symptoms as well as neuropsychiatric symptoms have also been recognized in FM. Some examples are digestion problems, irritable bowel syndrome, irritable or overactive bladder, depression, anxiety, and impaired memory. Many of these symptoms can be associated to FM psychological adaptation mechanisms which might be identified as the key factors in the fear-avoidance model od pain: catastrophizing, fear of movement, and activity avoidance (Vlaeyen et al., 2012).

Guillaume de Baillou described FM as a “muscular rheumatism” but the first author introducing the term Fibromyalgia was Hench P. K. in 1976. It was later accepted as a disease by the World Health Organization (WHO) in 1992 and thus included in the International Classification of Disease (ICD) as a non-joint type of rheumatism.

In 1990, the ACR published the first diagnostic criteria (Wolfe et al., 1990), which were then updated in 2010 (Wolfe et al., 2010), in 2011 (Wolfe et al., 2011) and in 2016 (Wolfe et al., 2016) (Galvez-Sanchez et al., 2020). Only the 1990 and the 2010 criteria have been officially recognized by the ACR.

The 2010 version considers two assessment scales: the Widespread Pain Index (WPI) and the Symptom Severity Scale (SS). The WPI recognizes 19 potentially painful areas and patients are asked if each point has hurt in the previous week (Figure 1). A max score of 19 can be attributed. The SS is comprised by two parts:

- SS2a assesses the intensity of 3 symptom categories identified in fatigue, waking unrefreshed, and cognitive symptoms using a 4-point Likert scale (0-3) within a range from 0 to 9.

- SS2b consists of a 41 symptoms list (irritable bowel syndrome, muscle weakness, etc.) and patients are asked to declare if they have suffered those symptoms in the previous week; SS2b can range from 0 to 3 (0, no symptoms; 1, 1-10 symptoms; 2, 11-24 symptoms; 3, 25-41 symptoms).

Diagnosis of FM can be made if WPI ≥ 7 and SS ≥ 5 or if WPI between 3 and 6 and SS ≥ 9 and symptoms must persist for a minimum of 3 months.

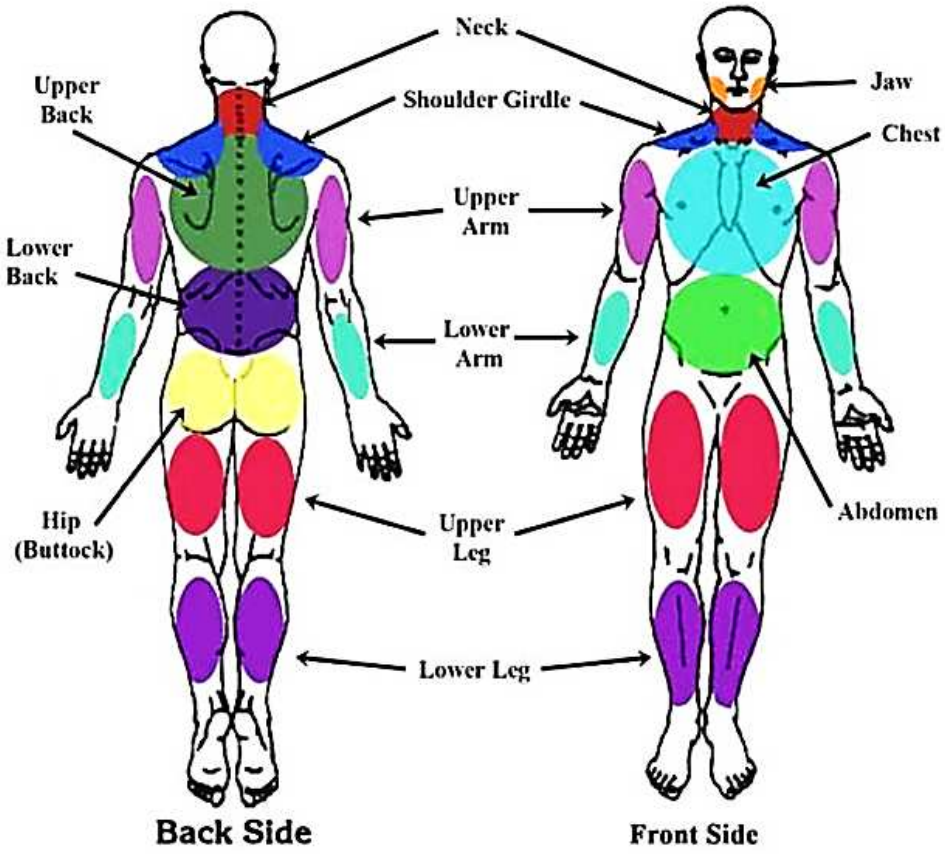

Figure 1. Body area included in the Widespread Pain Index scale of 2010 ACR diagnostic criteria.

In 2011 Wolfe et al., revised the 2010 ACR criteria proposing a modification of the WPI and SS scales, with particular attention to the SS scale, in order to ease patient self-administration.

A systematic review of 2010 and 2011 criteria was conducted in 2016 by Wolfe, who tried to gather both previous versions together focusing the assessment on central pain perception and distress. According to this latest assessment set, a diagnosis of FM can be defined only if the following conditions are fulfilled:

- Presence of pain in four of five regions (four quadrants and axial).

- Presence of symptoms at a similar level for at least 3 months.
- WPI ≥ 7 and SS ≥ 5 or WPI between 4 and 6 and SS ≥ 9.
- Though other diagnosis are present, a diagnosis of FM is still possible. A diagnosis of FM does not exclude the presence of other illnesses.

In addition to diagnosis, the use of Polysymptomatic Distress Scale (PDS) was suggested (Wolfe et al., 2015) to assess FM severity and treatment effects.

In 2018 Davis and colleagues proposed a classification of FM based on pain and symptom severity, presence of specific comorbidities, and use of clinical procedures (Table 1). Four classes were identified:

- Class 1 (with 3 subclasses): Regional FM with classis symptoms.
- Class 2 (with 2 subclasses): Generalized FM with increasing widespread pain and additional symptoms.
- Class 3 (with 3 subclasses): Advanced FM with associated conditions, increasing widespread pain, increased sleep disturbance, and chemical sensitivity.
- Class 4 (no subclasses): Secondary FM reactive to disease.

Class	Description	Demographics: sex, %; age, mean (SD)	Main comorbidities	Body region prominence	Main secondary conditions	Main treatment focus
1. With three subclasses	Regional FM with classic symptoms	77.9% females, 55.3 (16.5) years; 22.1% males, 55.4 (16.5) years	Interstitial cystitis, muscle spasm, spinal arthritis	Knee, cervical, shoulder, arm, chest	GERD, osteoporosis, RLS	Facets and spinal cord stimulators
2. With two subclasses	Generalized FM with increasing widespread pain and additional symptoms	81.6% females, 61.4 (17.3) years; 18.4% males, 58.9 (17.2) years	Arthritis, upper body/limb pain, cervical conditions, migraine	Chest, lumbar/ hip, and significant increase in knee	GERD, RLS, polio	Epidurals, facets, spinal cord stimulators, bursa/trigger point injections, cervical/ thoracic injections
3. With three subclasses	Advanced FM with associated conditions, increasing widespread pain, increased sleep disturbance, and chemical sensitivity	74.2% females, 59.8 (18.0) years; 25.8% males, 61.4 (21.4) years	Arthritis, upper body/limb pain, cervical conditions, migraine	Chest, lumbar/ hip, and significant increase in knee	GERD, RLS, polio	Epidurals, facets, spinal cord stimulators, bursa/trigger point injections, cervical/ thoracic injections
4. With no subclasses	Secondary FM reactive to disease	80.5% females; 61.3 (17.8) years; 19.5% males, 49.4 (17.0) years	Chronic pain syndrome, joint/ limb pain	Chest	MS, lupus, TMJ, IBS	Joint and bursa injections

Abbreviations: FM, fibromyalgia; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; MS, multiple sclerosis; TMJ, temporomandibular joint disorder; RLS, restless leg syndrome.

Table 1. FM classes (Davis et al., 2018)

At follow-up a tendency was shown towards a progression from lower to higher classes associated with an increase in the number of comorbidities and secondary conditions.

The authors suggested FM as a condition continuum with an enhancement of pain centralization. The class differences in the centralization of pain could suggests that some treatments are more recommended than others (Davis et al., 2018).

1.2 Pathophysiology of fibromyalgia

Pathogenesis of FM is poorly understood but many are the factors which could be linked to the onset of this condition: genetic predisposition, peripheral and chronic sensitization processes, chronic system inflammation and environment/epigenetic factors.

Genetic predisposition to FM has been recognized as being associated with psychological symptoms in FM. About 30 genes seem to be linked with psychological disorders such as anxiety, depression, schizophrenia, and obsessive and compulsive disorder, along with pain sensitivity and/or migraine. Among the identified genes, some contribute to pain transmission pathways, thus they are supposed to be involved in the FM pathogenesis (Janssen et al., 2021).

FM, as a chronic pain syndrome, is characterized by peripheral sensitization (PS) and central sensitization (CS), which are respectively described as sensitization of nociceptors and increased responsiveness of the central nervous system to painful stimuli (Davis et al., 2018). CS indicates an alteration of the central nervous system (CNS) and its physiological state, which is thought to be linked to pathogenesis of chronic pain. A systematic review in 2014 showed a correlation between CS and gray matter volume decrease in specific brain regions, mainly anterior cingulate cortex and prefrontal cortex. In addition, other findings suggest a higher but similar pattern of activation of the neuromatrix (the neural substrate for pain perception - Melzack, 1999, 2001) in FM subjects compared to controls, associated with a decreased functional connectivity in the descending pain-modulation system (e.g.: dorsolateral prefrontal cortex, periaqueductal grey, posterior parietal cortex) (Cagnie et al., 2014). CS phenomena like temporal summation and lower pressure pain threshold reflect ascending facilitation of nociceptive signal in the CNS, while conditioned pain modulation assesses adequacy of descending modulatory pathways (Nir et al., 2015). They were all recently shown to be often present in FM (Bourke et al., 2021), suggesting an involvement of CS in both bottom-up and top-down directions.

In support to CS process in FM, two meta-analysis of voxel-based morphometry studies indicate a decrease gray matter volume in the anterior cingulate cortex (ACC), in the left medial prefrontal cortex (mPFC), the right dorsal posterior cingulate cortex (dPCC), the parahippocampal gyrus, and the cerebro-cerebellar circuits. These findings indicate that FM is associated to cognitive, affective, and non-affective components of pain processing, as well as an involvement of the Default Mode Network (Lin et al., 2016; Shi et al., 2016). In addition, in a recent article, Kim and colleagues (2021) described regional atrophy of the posterior thalamus (pulvinar/ventroposterior lateral nuclei) and disrupted structural and functional network with inferior parietal regions in FM subjects. The authors suggest that this dysfunction could be associated to an involvement of thalamo-inferior parietal lobule network and pain modulation and attentional processes, with interferences in pain sensitivity and pain levels (Kim et al., 2021).

A recent study suggests that pain-related gray matter volume (GMV) reductions in the anterior midcingulate cortex (aMCC) are common also in juvenile FM female patients and that affective, self-relevant memory, and language processes dysfunction are associated to inferior frontal regions alterations. There also seems to be a partial overlap, specifically for the anterior/posterior regions in juvenile FM and adult FM (Suñol et al., 2022).

Chronic systemic inflammation, and the consequent enhanced inflammatory state, seems to underlie chronic conditions such as FM. FM patients show an altered number of circulating inflammatory cytokines, even if literature is not consistent on the direction of this alteration (Sluka et al., 2016). The immune system and factors released from immune cells (e.g.: cytokines) appear to be somehow associated to a variety of acute and chronic pain conditions. Thus, they might play a role in the generation of fibromyalgia (Sluka et al., 2016).

Environment and epigenetic are also believed to play a role in the development of FM. Physical and/or psychosocial early-life events could influence gene expression and represent concurrent stressors in FM physiopathology (Polli et al., 2019). In addition, a controlled pilot study in 2019 demonstrated how DNA methylation is involved in FM pathogenesis as an alteration in methylation status in peripheral blood interfere with

neuron differentiation, and nervous, skeleton, and organ system development and chromatin compaction (Ciampi de Andrade et al., 2019).

1.3 Treatment of fibromyalgia

FM symptoms heterogeneity and the lack of understanding about its pathogenesis processes make the management of FM still a challenge. As suggested by the European League Against Rheumatism (EULAR), non-pharmacological treatment currently represent the first-choice intervention for FM (MacFarlane et al., 2017). Only some of non-pharmacological options will be discussed in this review as they are associated to a stronger impact on clinical manifestations, symptoms, and quality of life (Atzeni et al., 2019):

- Psychological therapies: psychological support can help FM patients, mainly through the activation of Basic Body Awareness Therapy (BBAT) or Cognitive-Behaviour Therapy (CBT) programs. These strategies are focused on movement awareness and coordination training (BBAT) and on coping strategies, emotional control, and cognitive psychology (CBT). They are demonstrated to have positive effects on pain and anxiety reduction and CBT seems also to have effect on insomnia (Atzeni et al., 2019).
- Physical exercise: a recent meta-analysis has analyzed the effect of different types of exercise in adults with FM. Results show that aerobic exercise seems to reduce pain perception and depression and improve quality of life, while resistance and stretching exercise are associated to a reduction in pain perception and quality of life but not on depression (Couto et al., 2022).
- Non-invasive brain stimulation: this topic will be discussed in the next chapter.

1.4 Non-invasive brain stimulation techniques

Non-invasive brain stimulation techniques (NIBS) have recently gained an important role in the field of rehabilitation as means of neurostimulation and neuromodulation. They are used in neurophysiology, in cognition, and in clinical practice. They have been employed in different disorders from psychiatric to neurological or musculoskeletal diseases (e.g., chronic pain syndromes).

NIBS includes different techniques: transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial random noise stimulation

(tRNS), transcranial alternating current stimulation (tACS) and reduced impedance non-invasive cortical electrostimulation (RINCE). They are all considered safe to apply, in particular if compared to invasive procedure.

TMS requires the application of a coil to the scalp with the aim of inducing electrical currents in the neurons by applying a magnetic field and, thus, stimulating the cerebral cortex. Repetitive TMS (rTMS) is obtained when TMS pulses are applied repetitively with the possibility to induce cortical excitability modulation – increasing or decreasing neurons depolarization – depending on the parameters of the stimulation (Rossi et al., 2009). When the motor cortex is stimulated, based on motor evoked potentials, high-frequency rTMS (≥5 Hz) seems to have excitatory responses, while low-frequency rTMS (≤1 Hz) seems to have inhibitory effects (Lefaucheur et al., 2019). Different patterned rTMS Theta Burst Stimulation (TBS) protocols imply the application of short bursts of 50 Hz rTMS repeated at a rate within the theta range (5 Hz), with either intermittent (iTBS) or continuous (cTBS) train (Rossi, 2009). Beside 1 Hz rTMS, inhibitory effects are associated to cTBS, while facilitatory effects follow iTBS, as previously stated for high-frequency rTMS.

As a recent technique, TMS is still not completely understood. For instance, it has been recently shown how high-frequency rTMS can modulate cortical areas which are distant from the site of application (Wang et al., 2020): this research study showed how a 10 Hz stimulation applied to the left motor cortex in healthy participants significantly activates also the right cerebellum ipsilateral to the induced finger movement. Moreover, TMS durable aftereffects have been reported in relation to a cortical excitability modulation on motor corticospinal output, but a high variability has been reported in relation to the properties of the brain network and the status of the population (Lefaucheur, 2019). Although overall NIBS impact seems to be short-lasting (Rossi 2019), in 2001 Lefaucheur demonstrated how motor cortex rTMS had analgesic effects on neuropathic pain, which lasted for up to 8 days.

Cortical inhibition and excitability effects are considered to be the consequence of different mechanisms, among which it is possible to list both long term depression (LTD) and long-term potentiation (LTP) as well as other forms of neuroplasticity (Rossi, 2009). The most recent expert guidelines for TMS safety and recommendations

highlight that TMS-induces seizure is to be considered the most serious risk, though very low (Rossi et al., 2021).

tDCS represents another non-invasive brain stimulation strategy. It requires the application of a large electrode (anode or cathode) on the scalp over the cortical area which is supposed to be reached by the current, and a return electrode of opposite polarity over the contralateral forehead, the chin, or the shoulder (Lefaucheur, 2019).

The tDCS primary effect on neurons can shift from depolarization to hyperpolarization of the neurons. As revealed by the amplitude of the motor evoked potential induced by TMS, anodal electrode yields to a facilitatory effect, while cathodal electrode induces an inhibitory effect of underlying cortical regions (Lefaucheur et al., 2017). LTD and LTP seem to be involved in the inhibition- or facilitation-induced processes through the key role played by the gamma-aminobutyric acid (GABA) neurotransmission or the calcium-dependent synaptic plasticity of glutaminergic neurons with engagement of N-methyl-D-aspartate receptors (NMDARs), respectively (Lefaucheur et al., 2017). Moreover, in 2017, Kronberg et al. suggested to apply tDCS during a task-specific activity (e.g., motor rehabilitation) in order to induce a frequency-dependent plasticity, which is the consequence of a modification of NMDARs activation levels. Indeed, if NMDARs are blocked, tDCS has no effect on synaptic strength. Therefore, according to the Beinenstock, Cooper and Munro (BMC)'s theory of synaptic plasticity (Cooper et al., 2012), tDCS can facilitate LTP and enhance LTD (Kronberg et al., 2017).

In the treatment of pain syndromes, stimulation is usually delivered at an intensity of 2 mA (electrode size: 35 cm^2) on primary motor cortex (M1) or dorsolateral prefrontal cortex (DLPFC) with a daily session duration of 10 to 20 min repeated for up to 20 sessions. Concerning FM treatment, a Level B recommendation of probable efficacy was proposed by Lefaucheur (2017), who suggested the application of the anodal electrode on left M1 and cathodal electrode on right orbitofrontal region.

tRNS technique is similar to tDCS, but the stimulation current is varied randomly in a spectrum of 100-640 Hz, with the aim to enhance signal transmission to neural network (Paulus, 2011). A Cochrane review in 2018 quoted only 2 studies which used tRNS for fibromyalgia patients (Curatolo et al., 2017) and multiple sclerosis patients with related neuropathic pain (Palm et al., 2016). Both studies have been assessed with high risk

of bias, with no possible conclusions about the effectiveness or lack of effectiveness of tRNS for chronic pain (O'Connell, 2018).

tACS refers to the application of transcranial alternating current stimulation, which changes gradually from positive to negative every half-cycle. The tACS goal is to simulate the natural rhythmic pattern of electrophysiological activity of the brain. Specific brain oscillations have been identified to characterize diverse brain functions. In this context tACS is thought to represent a potential therapeutic mean to modify altered brain oscillations and connectivity patterns (Elyamany et al., 2021). In pain syndromes, tACS have been used at alpha frequency (10 Hz) to somatosensory cortex (Donna et al., 2020).

RINCE shares the same scalp application with the other electric stimulation techniques. Differently from them it uses specific stimulation frequencies, with the aim of reducing skin and skull impedance and therefore enable a deeper penetration and modulation of cortical activity (O'Connell, 2018).

1.5 Aim of this study

To our knowledge some systematic reviews rating the efficacy of tDCS or rTMS for the treatment of FM have been conducted in the past years. Only one Cochrane study considered all NIBS in 2018. The purpose of this study is to investigate and compare the effect of these therapeutic strategies for FM.

2. METHODS

2.1 Data source and search method

Guidelines from the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement and checklist (Page et al., 2021) were consulted to develop this systematic review. An extensive scientific literature search was performed in April 2022, with an update in September 2022, by two independent reviewers. Only Randomized Controlled Trials (RCT) and cross-over studies written in English or Italian were included with no limit on the period of publication. The online databases PubMed, Scopus, Web of Science, and Clinical Trials were consulted using the following keywords: "non-invasive brain stimulation", "transcranial magnetic stimulation", "current stimulation", “nibs”, “tacs”, “tdcs”, “trns”, “fibromyalgia”. Keywords were combined to obtain more specific results:

- PubMed: ("non-invasive brain stimulation"[Title/Abstract] OR "transcranial magnetic stimulation"[Title/Abstract] OR "current stimulation"[Title/Abstract] OR nibs[Title/Abstract] OR tacs[Title/Abstract] OR tdcs[Title/Abstract] OR trns[Title/Abstract] OR tms [Title/Abstract]) AND ("fibromyalgia"[Title/Abstract] OR "fibromyalgia")
- Scopus: (TITLE-ABS-KEY (fibromyalgia)) AND (TITLE-ABS-KEY (non-invasive AND brain AND stimulation) OR TITLE-ABS-KEY (nibs) OR TITLE-ABS-KEY (tdcs) OR TITLE-ABS-KEY (tms) OR TITLE-ABS-KEY (tacs) OR TITLE-ABS-KEY (trns)) AND (LIMIT-TO (LANGUAGE, "English"))
- Web of Science: ("non-invasive brain stimulation" OR "transcranial magnetic stimulation" OR "current stimulation" OR nibs OR tacs OR tdcs OR trns OR tms) AND ("fibromyalgia")
- Clinical Trials: single keywords

Titles and abstracts of the obtained articles were screened. Whenever an abstract or title seemed useful or not easily evaluable, the full text was retrieved. Using the formulated inclusion and exclusion criteria detailed below, it has been considered whether the collected full text sources were suitable for inclusion in this review (figure

2). A third senior reviewer acted as arbiter to resolve any discrepancies. Articles from the references of the retrieved trials and review articles were also analyzed and considered.

2.2 Inclusion and exclusion criteria

2.2.1 Type of participants

Included studies investigate FM patients of any age, whose diagnose was based on 1990, 2010, or 2016 American College of Rheumatology criteria. Only studies with subjects over 18 years suffering of chronic pain, lasting at least 3 months, have been included.

2.2.2 Type of interventions

Non-invasive brain stimulation techniques (tDCS, rTMS, tACS, tRNS, RINCE), aimed at reducing pain intensity and improving FM patients' quality of life. Only RCT and cross-over studies involving control groups stimulation were included.

2.2.3 Type of outcome measures

The outcomes considered in this study were pain intensity and quality of life. We included articles with validated scale, which are specified in the table below.

Outcome Measure	Validated Scales
Pain Intensity	Visual Analogic Scale (VAS), Numerical Rating Scale (NRS)
Quality of life	Fibromyalgia Impact Questionnaire (FIQ), 36-Item Short Form Survey (SF-36)

Table 2. Scales for Outcome Measures

Taking into account pain intensity, as the main and most common symptom in FM, the Numeric Rating Pain Scale (NRPS) was considered to assess the effect of NIBS techniques on FM subjects. Different self-reported numeric scales (eg. VAS, NRS) ranging from 0 (no pain) to 10 or 100 (worst pain) were examined. When no NRPS was contemplated in the included studies, pain intensity scales were extracted from specific items within other questionnaires (eg.: McGill Pain Questionnaire, Brief Pain Inventory, Fibromyalgia Impact Questionnaire).

Considering quality of life two indices were taken into consideration: Fibromyalgia Impact Questionnaire (FIQ) and 36-Item Short Form Survey (SF-36).

The FIQ is commonly used in FM patients to investigate quality of life, translated and validated in different languages. The first published version (Burckhardt et al., 1991) is comprised of 10 items: the first item contains 11 questions investigating physical activities, which are rated from 0 (always) to 3 (never) in a 4-points Likert type scale. Item 2 requires patients to mark the number of days they felt well, while item 3 refers to the number of days they were unable to work (including housework) because of fibromyalgia symptoms. Items 4 to10 are visual rating scales on which patients rate work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression. Higher FIQ score indicates a greater FM impact on patients' life. The maximum score is 100. A validated Revised FIQ (FIQR) was proposed in 2009 by Bennett and colleagues. The FIQR total maximal score is 100, as the previous version.

The SF-36 (Stewart et al., 1981) is a tool frequently used in scientific papers as a measure of health. It is composed of 36 items concerning limitations in physical and social activities, and in usual role activities because of physical or emotional problems, as well as bodily pain, general mental health, vitality, and general health perception. Items can be grouped in 2 main components: physical and mental.

2.3 Type of studies and quality assessment of included studies

Randomized Controlled Trials and cross-over studies were included. Studies have been excluded whenever they were not available in English or Italian. Studies quality assessment was performed using the Jadad's scoring: a score from 0 to 5 was assigned based on randomization method (0-2 points), blindness appropriateness (0-2 points), and dropouts and withdrawals (0-1 points). Higher scores indicate better reporting. Studies with a Jadad score of 2 or less are considered to have low quality and those with a Jadad score of 3 or more are considered to have high quality. (Tables 3, 4, 5, and 6).

2.4 Data Extraction and Synthesis

After inclusion in the present review, the following data were retrieved from the articles: title, year of publication, country of publication, first author, population characteristics (mean age and sex, expressed in percentual of females), intervention features and

protocol, pain and quality of life outcomes in line with the above expressed inclusion criteria, and assessment timings after intervention. Data, such as mean, standard deviation, standard error and confidence intervals were extracted. When not available data were collected from previous systematic reviews and meta-analysis (Sun et al., 2022, Toh et al., 2022, Lloyd et al., 2020). Studies features are summarized in Tables 3, 4, 5, and 6).

TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

FIRST AUTHOR, YEAR, LOCATION, DESIGN	INTERVENTION	CONTROL	NR		Age (y), Mean (SD)		Sex (% Women)		PROTOCOL	OUTCOME CONSIDERED	OBSERVATION TIME		JADAD SCORE
			EXP.	CONT.	EXP.	CONTR.	EXP.	CONTR.			POST-INTERVENTION	FOLLOW-UP	
Atlas et al., 2019, Turkey - RCT	10 Hz TMS over left DLPFC 10 Hz rTMS over left M1	Sham	10 10	10	47.8 (9.38) 46.3 (9.01)	48.2 (9.38)	100 100	100	15 sess/3 w	VAS, FIQ, SF-36	After intervention	/	5
Avery et al., 2015, United States - RCT	10 Hz rTMS over left DLPFC	Sham	7	11	54.9 (7.65)	52.1 (10.02)	100	100	15 sess/4 w	VAS, NRS, SF-36	After 5, 10 and 15 sess	1 w, 1 m, 3 m after treatment	5
Bilir et al., 2021, Turkey - RCT	10 Hz rTMS over left DLPFC	Sham	10	10	46.7 (9.06)	43.8 (9.37)	100	100	14 sess/6 w	VAS, FIQ	After intervention	/	5
Boyer et al., 2014, France - RCT	10 Hz rTMS over left M1	Sham	19	19	49.1 (10.6)	47.7 (10.4)	100	100	14 sess /10 w	Average daily pain, FIQ	1 week after treatment	/	5
Carretero et al., 2009, Spain - RCT	1 Hz rTMS over right DLPFC	Sham	14	12	47.5 (5.7)	54.9 (4.9)	100	83.3	20 sess/4 w	Likert pain scale 0-10	After intervention	4 w after treatment	3
Cheng et al., 2018, Taiwan - RCT	10 Hz rTMS over left DLPFC	Sham	9	11	48.0 (14.5)	51.5 (13.6)	77.8	70.0	10 sess/2 w	VAS	After intervention	/	4
Fitzgibbon et al., 2018, Australia - RCT	10 Hz rTMS over left DLPFC	Sham	14	12	45.1 (11.2)	46.3 (15.0)	92.9	91.7	20 sess/4 w	VAS, NRS, FIQ, SF-36	After intervention	1 m after treatment	5
Guinot et al., 2019, France - RCT	10 Hz rTMS over right M1 + multicomp. therapy	Sham + multicomp. therapy	18	19	46.5 (10.4)	42.8 (8.8)	100	79	16 sess/14 w	FIQ, VAS	After intervention	40 w after first treatment	4
Izquierdo-Alventosa, 2021, Spain - RCT	10 Hz rTMS over left M1 Low-intensity physical exercise	Sham	17 16	16	50.47 (8.90) 53.06 (8.40)	55.13 (7.35)	100	100	10 sess/2 w 16 sess/8 w in groups	VAS, FIQ-R	After intervention	/	5
Lacroix et al., 2021, France - RCT	10 Hz rTMS over left M1	Sham	41	37	47.9 (7.7)	47.2 (8.5)	95.1	91.9	15 sess/3 w	VAS, FIQ	After intervention	3 weeks	5
Lee et al., 2012, Korea - RCT	1 Hz rTMS over right DLPFC 10 Hz rTMS over left M1	Sham	5 5	5	45.6 (9.6) 53.0 (4.2)	51.3 (6.2)	100 100	100	10 sess/2 w	VAS, FIQ	After intervention	1 month after treatment	3

Mhalla et al., 2011, France - RCT	10 Hz rTMS over left M1	Sham	16	14	51.8 (11.6)	49.6 (10.0)	100	199	14 sess/21 w	NRS, FIQ	After 5 sess, 21 w after first treatment	1m after treatment	5
Pareja et al., 2022, Spain - RCT	8 Hz rTMS + pharm. treatment	Pharm. treatment	280	280	NR	NR	100	100	8 sess/8 w	FIQ	After intervention	2, 12, 24 w after treatment	2
Passard et al., 2007, France - RCT	10 Hz rTMS over left M1	Sham	15	15	52.6 (7.9)	55.5 (8.9)	96.7	96.7	10 sess/2 w	NRS, FIQ	After intervention	30 and 60 d after first treatment	5
Short et al., 2011, United States - RCT	10 Hz rTMS over left DLPFC	Sham	10	10	54.2 (8.2)	51.67 (18.19)	90	78	10 sess/2 w	Average daily pain (NRS)	Day 5 and 10	1/w for 2 w after treatment	3
Tanwar et al., 2020, India - RCT	1 Hz rTMS over right DLPFC	Sham	9	11	41,54 (8,58)	39,05 (7,12	100	100	20 sess/4 w	NRS	After intervention	15 d, 3 m, and 6 m after treatment	5
Tekin et al., 2014, Turkey - RCT	1 Hz rTMS over left M1	Sham	27	24	42.4 (7.63)	46.5 (8.36)	88.9	95.8	10 sess (consecutive)	VAS	After 5 and 10 sess	/	5
Yağci et al., 2014, Turkey - RCT	10 Hz rTMS over left M1	Sham	12	13	45.25 (9.33)	43.0 (7.73)	100	100	10 sess/2 w	VAS, FIQ	After intervention	1 m and 3 m after session	5

rTMS: repetitive transcranial magnetic stimulation; DLPCF: Dorsolateral Prefrontal Cortex; M1: primary motor cortex; VAS: Visual Analogic Scale; NRS: Numerical Rating Scale; FIQ: Fibromyalgia Impact Questionnaire; FIQ-R: Revised Fibromyalgia Impact Questionnaire; SF-36: Short Form 36 General Health Survey; NR: Not Reported; RCT: Randomized Controlled Trial; SD: Standard Deviation

Table 3. The description of rTMS included studies

TRANSCRANIAL DIRECT ELECTRIC STIMULATION (tDCS)

FIRST AUTHOR, YEAR, LOCATION, DESIGN	INTERVENTION	CONTROL	NR		Age (y), Mean (SD)		Sex (% Women)		PROTOCOL	OUTCOME CONSIDERED	OBSERVATION TIME		JADAD SCORE
			EXP.	CONT.	EXP.	CONT.	EXP.	CONT.			POST-INTERVENTION	FOLLOW-UP	
Arroyo-Fernandez, 2021, Spain - RCT	2mA atDCS over left M1 and cathode over left SO	Sham	40	40	50.6 (7.0)	49.5 (8.7)	95	97.5	8 sessions (5 in first week and 3 in second week)/2 weeks	VAS, FIQ	After intervention	/	5
Arroyo-Fernandez, 2022, Spain - RCT	2 mA atDCS over left M1 and cathode over right SO + exercise	Sham + exercise	40	40	50.6 (7.01)	49.53 (8.74)	95	97.5	5 sessions (20 mins) (every second day) (1 hr: 20 mins stim + exercise)/2 weeks	VAS, FIQ	After intervention	1 month	5
		No intervention		40		50.75 (5.94)		90			After intervention		
Bin Yoo et al., 2018, United States - RCT	1,5 mA ONS: anode over right occipital region (right C2) and cathode over left occipital region (left C2)	Sham	21	16	47.81 (8.23)	47.19 (8.14)	95,24	93.75	8 consecutive sessions (20 mins) twice a week/4 weeks	NRS, FIQ	After intervention	/	2
	2 mA atDCS over right DLPFC + 1,5 mA ONS: anode over right occipital region (right C2) and cathode over left occipital region (left C2)		21		45.76 (10.80)		95,24		8 consecutive sessions (40 mins) twice a week/4 weeks		After intervention		
Borckardt et al., 2018, United States - RCT	2 mA atDCS left DLPFC + CBT	Sham + CBT	7	8	48 (14.69)	50.75 (10.25)	86	87.5	30 mins + 6 CBT sessions	BPI – Average Pain	/	1 month	4
Brietzke et al., 2020, Brazil - RCT	2mA atDCS over left DLPFC and cathode over right DLPFC	Sham	10	10	48.6 (NR)	49.7 (NR)	100	100	5 sessions a week (30 mins)/12 weeks	VAS	After intervention	/	5
De Ridder et al, 2017, Belgium - CROSS OVER	1.5 mA a tDCS over right C2	Sham	19		46.11 (7.85)		78,95%		3 sessions in 1 week (20 mins)	NRS, FIQ	After intervention	/	3
De Melo et al., 2020, Spain - RCT	2mA atDCS over left M1 and cathode over right SO	Sham	11	11	44.81 (8.8)		100	100	5 sessions/5days	VAS	After intervention	/	5
	2mA atDCS over left M1 and cathode over right SO		9				100		10 sessions/2 weeks				
Fagerlund et al., 2015, Norway - RCT	2 mA atDCS over left M1 and cathode over right SO	Sham	24	24	49.04 (8.63)	48.17 (10.56)	100	87.5	5 consecutive sessions (20 mins daily)	NRS, FIQ, SF-36	After intervention	/	4

Foerster et al., 2015, United States - CROSS-OVER	2 mA atDCS over left M1	Sham	13		47.6 (10.6)		100		5 consecutive sessions (20 mins)	VAS	After intervention	/	1
Fregni et al., 2006, United States - RCT	2 mA atDCS over M1 and cathode over controlateral SO	Sham	10	10	54.8 (9.3)	50.8 (10.2)	100	100	5 consecutive sessions (20 mins daily)	VAS, FIQ, SF-36	After intervention	21 days	5
	2 mA atDCS over left DLPFC and cathode over controlateral SO		11		54.2 (7.4)		100						
Gomez-Alvaro et al., 2022, Spain - CROSS-OVER	1mA atDCS over left DLPFC	Sham	13		30-75		100		20 mins	FIQ-R	After intervention	/	4
	2mA atDCS over left DLPFC												
Jales Junior et al. 2015, Brazil - RCT	2 mA atDCS over left M1 and cathode on controlateral SO	Sham	10	10	46.4 (10.62)		100	100	1 session per week (20 mins each)/10 weeks	VAS, FIQ, SF-36	After intervention	/	3
Khedr et al., 2017, Egypt - RCT	2 mA atDCS over left M1 and cathode over controlateral arm	Sham	18	18	31.3 (10.99)	33.89 (11.18)	94.44	94.44	10 sessions (20 mins)/2 weeks	VAS	After intervention	1 month	4
Matias et al., 2022, Brazil - RCT	2 mA tDCS over left M1 and cathode over controlateral SO + functional exercise	Sham + functional exercise	17	14	48.94 (13.83)	49.43 (15.14)	100	100	5 consecutive sessions tDCS/ + 24 exercise sessions (3 times per week) (40 mins)/8 weeks	VAS. FIQ	After intervention	4 weeks 8 weeks	5
Mendonca et al., 2011, Brazil/United States - RCT	CAT-M1: 2 mA ctDCS over left M1	Sham	6	6	41.8 (12.9)	43.5 (10.4)	83.4	100	1 session (20 mins)	NRS	After intervention	/	4
	CAT-SO: 2 mA ctDCS over right SO		6		43.5 (8.5)		100				After intervention		
	ANO-M1: 2 mA atDCS over left M1		6		44.5 (10.5)		83.4				After intervention		
	ANO-SO: 2 mA atDCS over right SO		6		42.6 (9.2)		100				After intervention		
Mendonca et al., 2016, Brazil - RCT	2 mA atDCS over left M1 and cathode over right SO	Sham + Aerobic exercise	15	15	49.9 (10.6)	46 (11.8)	100	100	5 daily sessions (20 mins)/1 week	VAS, SF-36	After intervention	1 and 3 months	4
	2 mA atDCS over left M1 and cathode over right SO + Aerobic exercise		15		44.5 (14)		93.33						
Plazier et al. 2015, Belgium - CROSS OVER	1.5 mA atDCS over left C2	Sham	9		42 /4.23)		100		3 sessions in 1 week (20 mins)	NRS	After intervention	6 months	2
Riberto et al., 2011, Brazil - RCT	2 mA atDCS over M1 controlateral to most painful side or dominant hand	Sham	11	12	58.3 (12.1)	52.4 (11.5)	100	100	1 session per week (20 mins)/10 weeks	VAS, SF-36, FIQ	After intervention	4 months	4

Samartin-Veiga et al., 2022 (b), Spain - RCT	2 mA atDCS over left M1	Sham	32	29	49.38 (8.83)	50.67 (8.88)	100	100	15 sessions (20 mins)/3 weeks	SF-36, FIQ-R	After intervention	6 months	5
	2 mA atDCS over left DLPFC		33		51.00 (9.15)								
	atDCS over left OIC		33		50.21 (8.20)								
Samartin-Veiga et al., 2022 (a), Spain - RCT	2 mA atDCS over left M1	Sham	29	25	49.38 (8.83)	50.67 (8.88)	100	100	15 sessions (20 mins)/3 weeks	FIQ-R	After intervention	6 and 12 months	5
	2 mA atDCS over left DLPFC		26		51.00 (9.15)								
	atDCS over left OIC		28		50.21 (8.20)								
To et al., 2017, Belgium - RCT	1.5 mA bifrontal tDCS: anode over left DLPFC and cathode over right DLPFC	Sham	11	16	47.81 (10.17)	46.19 (49)	90.9	87.5	8 sessions/4 weeks	NRS	After intervention	/	4
	1.5 mA occipital tDCS: anode over left C2 and cathode over right C2		15		47.12 (10.01)		80						
Valle et al., 2009, Brazil - RCT	2 mA atDCS over left DLPFC (F3)	Sham	13	14	NR	NR	100	100	10 sessions (20 mins)/2 weeks	VAS, FIQ	After intervention	30 and 60 days	5
	2 mA atDCS over left M1 (C3)		14		NR		100						
Villamar, 2013, United States – CROSS-OVER	2 mA HD-atDCS over left M1	Sham	18		50.3 (8.5)		83.3		1 session (20 mins) per intervention (1 session every 7 days)	NRS	After intervention	/	5
	2 mA HD-ctDCS over left M1												

atDCS: anodal transcranial Direct Current Stimulation; ctDCS: cathodal transcranial Direct Current Stimulation; HD-atDCS: High Definition-anodal transcranial Direct Current Stimulation; ONS: Occipital Nerve Stimulation; DLPCF: Dorsolateral Prefrontal Cortex; M1: primary motor cortex; SO: supraorbital cortex; OIC: operculo-insular cortex; VAS: Visual Analogic Scale; NRS: Numerical Rating Scale; FIQ: Fibromyalgia Impact Questionnaire; FIQ-R: Revised Fibromyalgia Impact Questionnaire; SF-36: Short Form 36 General Health Survey; NR: Not Reported; RCT: Randomized Controlled Trial; SD: Standard Deviation

Table 4. The description of tDCS included studies

TRANSCRANIAL MAGNETIC STIMULATION (rTMS) vs TRANSCRANIAL DIRECT ELECTRIC STIMULATION (tDCS)									
FIRST AUTHOR, YEAR, LOCATION	**INTERVENTION**	**NR**	**Age (y), Mean (SD)**	**Sex (% Women)**	**PROTOCOL**	**OUTCOME CONSIDERED**	**OBSERVATION TIME**		**JADAD SCORE**
							POST-INTERVENTION	**FOLLOW-UP**	
Forogh et al., 2021, Iran - RCT	10 Hz rTMS over left DLPFC (F3)	15	45.73 (9.32)	100	3 sessions	VAS, FIQ-R	After intervention	/	5
	2 mA atDCS over left DLPFC	15	46.07 (11.73)	100	3 sessions		After intervention	/	
El-Badawy et al., 2021, Egypt - RCT	10 Hz rTMS over left M1 (C3)	15	32.73 (5.65)	73.33	2 sessions per week/4 weeks	VAS, FIQ-R	After intervention	/	3
	2 mA atDCS over left M1 (C3)	15	31.8 (6.30)	60	2 sessions per week (20 mins)/4 weeks		After intervention	/	
rTMS: repetitive transcranial magnetic stimulation; atDCS: anodal transcranial Direct Current Stimulation; DLPCF: Dorsolateral Prefrontal Cortex; M1: primary motor cortex; VAS: Visual Analogic Scale; FIQ-R: Revised Fibromyalgia Impact Questionnaire; NR: Not Reported; SD: Standard Deviation; RCT: Randomized Controlled Trial.									

Table 5. The description of rTMS vs tDCS included studies

TRANSCRANIAL RANDOM NOISE STIMULATION (tRNS), TRANSCRANIAL ALTERNATING CURRENT STIMULATION (tACS), REDUCED IMPEDANCE NON-INVASIVE CORTICAL ELECTROSTIMULATION (RINCE)												
FIRST AUTHOR, YEAR, LOCATION, DESIGN	**INTERVENTION**	**CONTROL**	**NR**		**Age (y), Mean (SD)**		**Sex (% Women)**		**PROTOCOL**	**OUTCOME CONSIDERED**	**RESULTS**		**JADAD SCORE**
			EXP.	**CONT.**	**EXP.**	**CONT.**	**EXP.**	**CONT.**			**POST-INTERVENTION**	**FOLLOW-UP**	
Bernardi, 2021, Italy – CROSS-OVER	Beta-tACS at 30 Hz or theta-tACS at 4 Hz + physical rehabilitation	1 or 2 mA tRNS (active sham) with anode over the region with higher power spectral difference and cathode over the ipsilateral mastoid + physical rehabilitation	15 (1:1)		53.07 (4.18)		86.7		10 sessions (30 mins) + 60 mins physical rehabilitation/2 weeks	VAS, SF-36	After intervention	4 weeks after last session before crossing-over	3
Curatolo, 2017, Italy - RCT	1.5 mA tRNS over M1 (side not reported)	Sham	10	10	44.4 (10.25)	44.2 (9.81)	100	100	10 sessions/2 weeks	NRS, FIQ	After intervention	Not planned	3
Gardoki-Souto, 2021, Spain - RCT	EMDR + active-MtCS	EMDR + sham-MtCS	45		NR	NR	100	100	20 sessions	VAS, FIQ	After intervention	6 months	5
		Waiting list						100					
Hargrove et al., 2012, United States - RCT	RINCE: 10kHz at 40Hz over parietal region (PZ) and ground on earlobes	Sham	39	38	51.3 (NR)	54.0 (NR)	94.9	89.5	22 sessions (11 mins)/11 weeks (2 sessions per week)	VAS, FIQ	After intervention	/	5
tRNS: Transcranial Random Noise Stimulation; tACS: Transcranial Alternating Current Stimulation; RINCE: Reduced Impedance Non-Invasive Cortical Electrostimulation; EMDR: Eye Movement Desensitization and Reprocessing; DLPCF: Dorsolateral Prefrontal Cortex; M1: primary motor cortex; VAS: Visual Analogic Scale; NRS: Numerical Rating Scale; FIQ: Fibromyalgia Impact Questionnaire; SF-36: Short Form 36 General Health Survey; NR: Not Reported; RCT: Randomized Controlled Trial; SD: Standard Deviation												

Table 6. The description of tRNS, tACS, RINCE included studies

2.5 Statistical analyses

Random-effect meta-analyses were conducted separately for the included studies using rTMS and tDCS interventions. Effect size measures were computed based on the reported sample sizes and statistics (e.g., t- and F-values), when available. When the statistics were not reported, they were estimated conservatively based on the reported p-values and/or the descriptive statistics (i.e., mean values and the corresponding standard deviations).

We used all the meaningful comparisons reflecting the specific effect of the therapy. Whenever possible, we computed an estimation of the treatment effect for each fibromyalgia-related measure reported in the included studies. According to the previously specified outcomes, only treatment effect estimations that were comparable across studies were included. Post-treatment follow-up were not analyzed because of the restricted therapeutic effect found through the analysis and the limited reported statistics.

Meta-Essentials workbooks were used to run the present meta-analysis (Suurmond et al., 2017).

The Hedges' g was then computed as a measure of the effect size for each of the included estimations of the treatment effect. Different weights were assigned to each measure based on the sample size of the corresponding study. Finally, a combined effect size measure (Hedges' g) was derived to estimate the general effect of the treatment. Hedges' $g > 0.20$ indicates small effect, $g > 0.5$ medium effect, and $g > 0.8$ states large effect.

I^2 statistic was conducted to evaluate heterogeneity. It ranges from 0% to 100%: 0% indicates no observed heterogeneity, while values > 50% state moderate heterogeneity.

Publication bias was assessed through the creation of funnel plots, which allow to visually assess the symmetry of the reported effect sizes, along with Trim-and-Fill method (Duval et al., 2000) to adjust the combined effect size in case of asymmetry or small sample bias.

3. RESULTS

3.1 Study Selection

In the preliminary search 646 studies were identified. 576 of them were excluded by title and abstract criteria, based on inclusion and exclusion criteria. The main reasons for exclusion were: duplicates, study design, population characteristics, treatment strategies. Considering results from clinicaltrial.org, 123 out of 138 were non concluded or did not report results. 24 studies were excluded after full-text reading primarily because no results were reported, they were not RCT or cross-over studies and outcome was not consistent with inclusion criteria. One full text could not be retrieved (Caumo et al., 2022). A total of 46 studies were judged to be aligned with the purpose of this study and reviewed. Among selected papers 18 were related to rTMS, 22 to tDCS, 2 considered both these techniques and 4 were dealing with other NIBS techniques. Flow chart of research is displayed in figure 2.

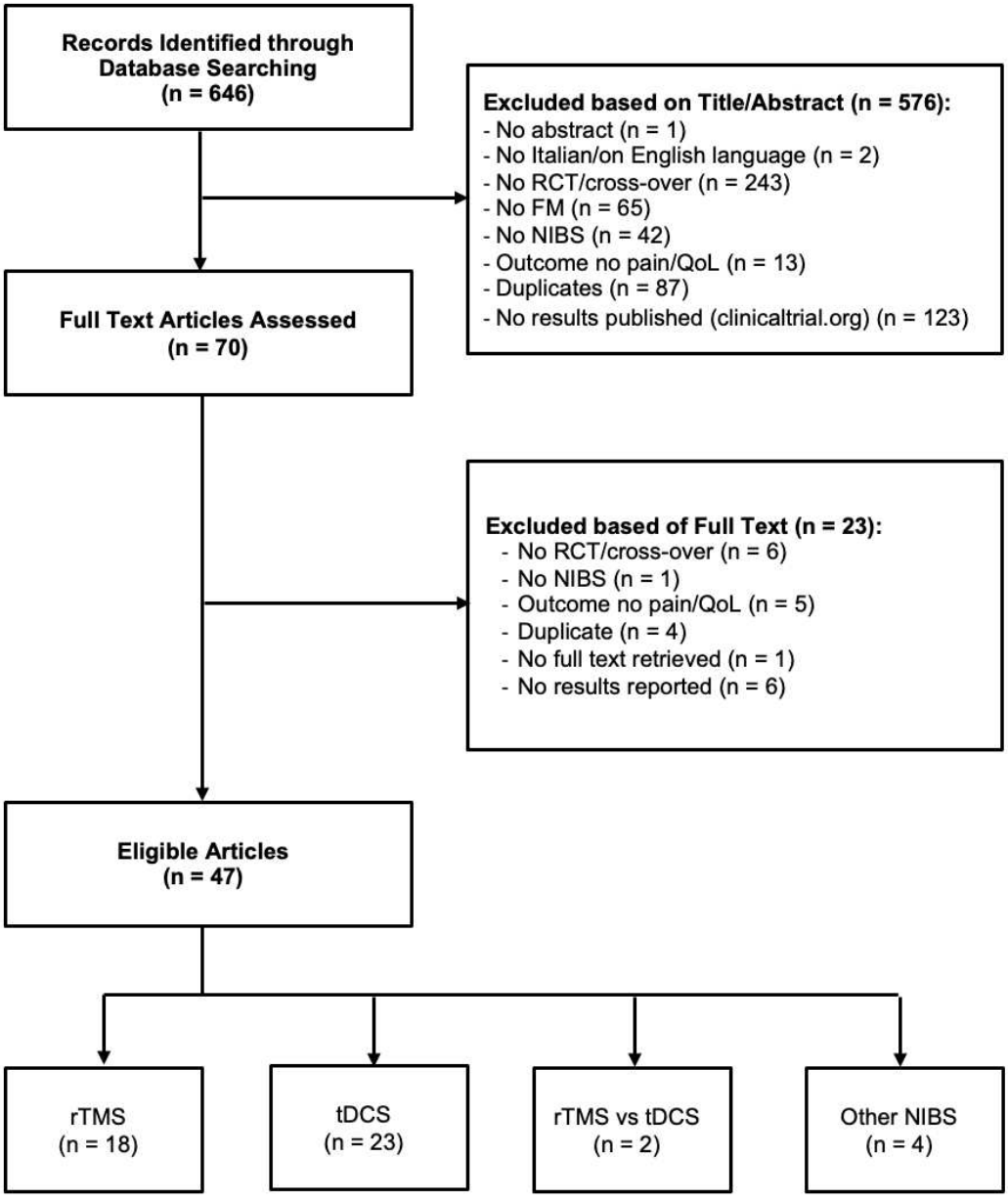

Figure 2. Flow chart of the literature screening process and results as per PRISMA 2020.

3.2 Characteristics of Included Studies

After selection 41 studies were RCT and 6 cross-over studies.

rTMS articles were all RCTs with Jadad score 3 or over for all studies except one (Pareja et al., 2022). rTMS selected papers involved 1083 subjects, although the study by Pareja and colleagues included 560 FM patients. The number of subjects varied from 15 (Lee et al., 2012) to 560 (Pareja et al., 2022). High percentages of female have been enrolled, frequently over 90% but never under 70% (Lee et al., 2021).

Included studies were conducted in Turkey (Atlas et al., 2019; Bilir et al, 2021; Tekin et al., 2014; Yağci et al., 2014), in the United States of America (Avery e al., 2015; Short et al., 2011), in France (Boyer et al., 2014; Guinot et al., 2018; Lacroix et al., 2021; Mhalla et al., 2011; Passard et al., 2007), in Spain (Carretero et al., 2009; Izquierdo-Alventosa et al., 2021; Pareja et al., 2022), in Taiwan (Cheng et a., 2018), in Korea (Lee et al., 2011) in India (Tanwar et al., 2020) and in Australia (Fitzgibbon et al., 2018). All selected studies were written in English.

Control groups were mainly sham rTMS, except for two articles: Guinot and colleagues added multicomponent therapy for both rTMS and control groups, while pharmacological treatment was planned for the control group and added to the rTMS group in Pareja and colleagues' study.

Among the 18 studies 9 investigated the effect of rTMS over left M1 (Atlas et al., 2019; Boyer et al., 2014; Izquierdo-Alventosa et al., 2021; Lacroix et al., 2021, Lee et al., 2012; Mhalla et al., 2011; Passard et al., 2007; Tekin et al., 2014; Yağci et al., 2014), 1 over right M1 (Guinot et al., 2019), 6 over left DLPFC (Atlas et al., 2019; Avery et al., 2015; Bilir et al., 2021; Cheng et al., 2018; Fitgibbon et al., 2018; Short et al. 2011) and 3 over right DLPFC (Carretero et al., 2009; Lee et al., 2012; Tanwar et al., 2020).

rTMS frequencies used were primarily 10 Hz with few exceptions: Carretero, Lee, Tanwar and Yağci and colleagues used 1 Hz rTMS. Intervention protocol varies from 8 (Pareja et al., 2020) to 20 sessions (Carretero et al., 2009; Fitzgibbon et al., 2018; Tanwar et al., 2020) in a period that varies from 2 weeks (Cheng et al., 2018; Izquierdo-Alventosa et al., 2021; Lee et al., 2012; Passard et al., 2007; Short et al., 2011; Yağci et al., 2014) to 21 weeks (Mhalla et al., 2011).

Among tDCS articles 5 were cross-over studies and 18 RCTs with Jadad score 3 or over for all studies except 3 (Bin Yoo et al., 2018; Foerster et al., 2015; Plazier et al. 2015). tDCS selected papers involved 965 subjects. Subjects' number varied from 9 (Plazier et al., 2015) to 127 (Samartin-Veiga et al., 2022, b). High percentages of female have been enrolled, frequently over 90% but never under 78,95% (De Ridder et al., 2017).

Included studies were conducted in Brazil (Brietzke et al., 2020; Jales Junior et al., 2015; Matias et al., 2022; Mendonca et al., 2011; Mendonca et al., 2016; Riberto et al., 2011; Valle et al., 2009), in the United States of America (Bin Yoo et al., 2018; Borckardt et al., 2018; Foerster et al.,2015; Fregni et al., 2006; Villamar, 2013), in Spain (Arroyo-Fernandez, 2021; Arroyo-Fernandez, 2022; De Melo et al., 2020; Gomez-Alvaro et al., 2022; Samartin-Veiga et al., 2022 (b); Samartin-Veiga et al., 2022 (a);), in Belgium (De Ridder et al, 2017; Plazier et al. 2015; To et al., 2017), in Norway (Fagerlund et al., 2015), and in Egypt (Khedr et al., 2017). All selected studies were written in English.

RCTs control groups were most frequently sham tDCS, except for few studies: Arroyo-Fernandez and colleagues (2022), Matias and colleagues and Mendonca and colleagues (2016) added physical exercise to tDCS and sham groups, while Borckardt and colleagues added CBT to both tDCS and sham groups.

Among the 22 studies 15 investigated the effect of tDCS over left M1 (Arroyo-Fernandez, 2021; Arroyo-Fernandez, 2022; De Melo et al., 2020; Fagerlund et al., 2015; Foerster et al., 2015; Jales Junior et al. 2015; Khedr et al., 2017; Matias et al., 2022; Mendonca et al., 2011; Mendonca et al., 2016; Samartin-Veiga et al., 2022 (a) and (b); Valle et al., 2009; Villamar, 2013), none over right M1, 7 over left DLPFC (Borckardt et al., 2018; Gomez-Alvaro et al., 2022; Fregni et al., 2006; Samartin-Veiga et al., 2022 (a) and (b); To et al., 2017; Valle et al., 2009), 3 over right DLPFC (Bin Yoo et al., 2018; Brietzke et al., 2020; To et al., 2017), 2 over left C2 (Bin Yoo et al., 2018; Plazier et al. 2015) and 2 over right C2 (Bin Yoo et al., 2018; De Ridder et al, 2017).

tDCS intensity used were primarily 2 mA with few exceptions: Bin Yoo and colleagues and De Ridder and colleagues used 1.5 mA over right C2, Plazier and colleagues used 1.5 mA over left C2, while Gomez-Alvaro and colleagues applied 1 mA over left DLPFC.

Intervention protocol varies from 1 single session (Mendonca et al., 2011; Borckardt et al., 2018) to 60 sessions (Brietzke et al., 2020) in a period that varies from 1 day (Mendonca et al., 2011; Borckardt et al., 2018) to 12 weeks (Brietzke et al., 2020).

2 RCT studies compared a rTMS protocol with a tDCS protocol. Forough and colleagues (2021, Iran) used a 3 sessions 10 Hz rTMS protocol over left DLPFC and a 3 sessions 2 mA anodal tDCS over left DLPFC. El-Badawy and colleagues (2021, Egypt) used the same parameters, but the cortical target was left M1.

In addition, 3 RCTs investigated tRNS (Curatolo et al., 2017, Italy), RINCE (Hargrove et al., 2012, United States) and multifocal transcranial current stimulation (MtCS) (Gardoki-Souto et al., 2021, Spain) and 1 cross-over study compared the application of tACS and tRNS, both associated to physician rehabilitation (Bernardi et al., 2021, Italy). Gardoki-Souto and colleagues compared a MtCS intervention with a sham control, but also an Eye Movement Desensitization and Reprocessing protocol was adjuncted to both, Curatolo and colleagues used 10 sessions of 1.5 mA tRNS over M1 and a sham control group. Lastly Hargrove and colleagues applied a RINCE procedure over the parietal region through 22 sessions.

3.3 Quantitative Data Synthesis

3.3.1 Pain Outcome

For rTMS studies, 19 measures of the treatment effect were extracted from the included rTMS studies, with a total amount of 553 subjects. A wide range of single effect values, varying from absent to very large effect (Hedges' *g* range: - 0.57 – 1.83) was obtained. Only 6 extracted measures demonstrate a positive effect (Hedges' g > 0.20). The relative statistics are reported in Table 7.

#	Study name - Stimulation site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Altas, 2019 - LEFT M1	-0,40	-1,32	0,50	5,00%
2	Altas, 2019 - LEFT DLPFC	0,38	-0,52	1,30	5,00%
3	Avery, 2015 - LEFT DLPFC	-0,57	-1,60	0,40	4,69%
4	Bilir, 2021 - LEFT DLPFC	0,42	-0,47	1,35	4,99%
5	Boyer, 2014 - LEFT M1	0,12	-0,52	0,77	6,01%
6	Cheng, 2019 - LEFT DELPFC	0,23	-0,66	1,15	5,00%
7	Fitzgibbon, 2018 - LEFT DLPFC	-0,08	-0,87	0,71	5,44%
8	Guinot, 2019 - RIGHT M1	-0,13	-0,79	0,53	5,93%
9	Izquierdo-Alventosa, 2021 - LEFT M1	1,83	1,04	2,70	5,21%
10	Lee, 2012 - LEFT M1	-0,26	-1,62	1,03	3,91%
11	Lee, 2012 - RIGHT DLPFC	0,60	-0,69	2,01	3,82%
12	Mhalla, 2011 - LEFT M1	1,79	0,97	2,71	5,07%
13	Passard, 2007 - LEFT M1	0,32	-0,40	1,07	5,65%
14	Short, 2011 - LEFT DLPFC	0,55	-0,35	1,49	4,96%
15	Tanward, 2020 - RIGHT DLPFC	0,99	0,54	1,45	6,80%
16	Tekin, 2014 - LEFT M1	1,76	1,13	2,44	5,93%
17	Yagci, 2013 - LEFT M1	0,45	-0,35	1,28	5,34%
18	El-Badawy, 2021 - LEFT M1	0,55	-0,18	1,30	5,61%
19	Forogh, 2021 - LEFT DLPFC	0,47	-0,25	1,23	5,63%

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; [a] CI, 95% confidence interval

Table 7 - Statistics for the included rTMS studies

Figure 3 shows the weights of the treatment effect estimations included in the analysis, as well as the forest plot. A 0.50 combined effect size was calculated using the Hedges' g value, with a standard error 0.16 (95% CI = 0.16 – 0.83). This suggests that **rTMS has a medium effect in ameliorating pain intensity in FM subjects**. There was medium to high heterogeneity noted (I_2 = 69,14%).

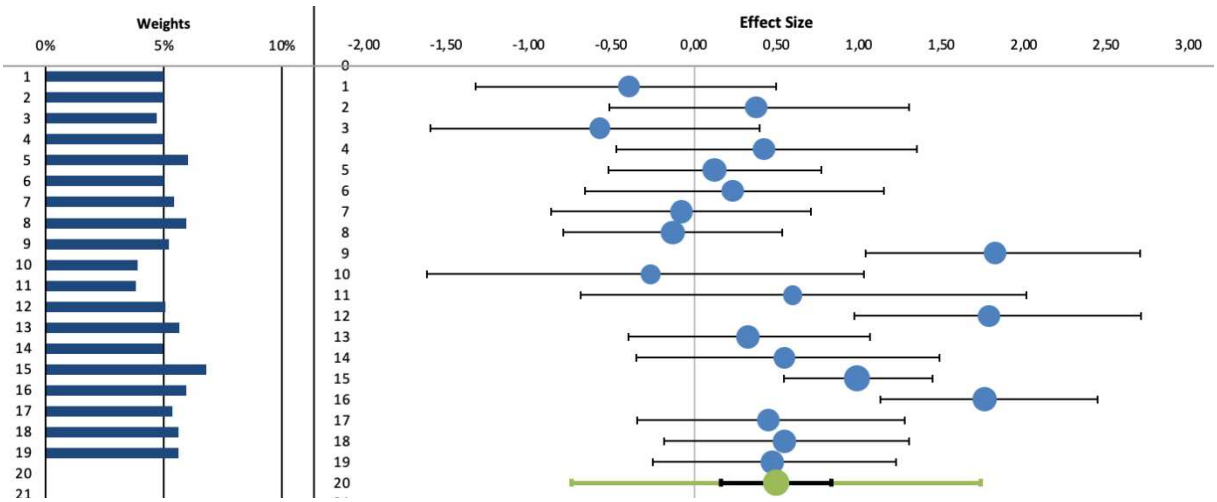

Figure 3 – Results of the meta-analysis for the rTMS studies. The bar plot on the left shows the weights of the included studies and the forest plot on the right shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The green horizontal bar indicates the Prediction Interval.

Subgroup analysis was performed to study the relationship between stimulation site (left M1 versus left DLPFC) and its effect of pain intensity. Measures from 3 studies were excluded because investigated the use on rTMS on right M1 (Guinot et al., 2019) or right DLPFC (Lee et al., 2012; Tanward et al., 2020). The studies' relative statistics and the forest plot are reported in Table 8 and Figure 4 respectively.

9 studies were pooled taking into consideration left M1 as focus on the stimulation. Although only 4 studies obtained a Hedges' g greater than 0.50, a **medium to large effect size was calculated** (Hedges' g = 0.71; 95% CI = 0.13 – 1.28).

Examining LEFT DLPFC subgroup, 7 studies were pooled. **No effect** was computed (Hedges' g = 0.22; 95% CI = -0.06 – 0.50).

Moreover, a subgroups' combined effect size was generated, indicating absence of statistical significance (Hedges' g = 0.40; 95% CI = -1.74 – 2.53). This new result reports a wide variability range and suggests an inconsistent effect.

#	Study name - Subgroup name	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Altas, 2019 - LEFT DLPFC	0,38	-0,53	1,28	13,25%
2	Avery, 2015 - LEFT DLPFC	-0,57	-1,57	0,43	11,21%
3	Bilir, 2021 - LEFT DLPFC	0,42	-0,49	1,33	13,18%
4	Cheng, 2019 - LEFT DELPFC	0,23	-0,67	1,14	13,27%
5	Fitzgibbon, 2018 - LEFT DLPFC	-0,08	-0,86	0,71	17,05%
6	Short, 2011 - LEFT DLPFC	0,55	-0,37	1,46	12,98%
7	Forogh, 2021 - LEFT DLPFC	0,47	-0,26	1,21	19,06%
8	**LEFT DLPFC**	**0,22**	**-0,06**	**0,50**	**63,87%**
9	Altas, 2019 - LEFT M1	-0,40	-1,30	0,51	10,71%
10	Boyer, 2014 - LEFT M1	0,12	-0,52	0,77	12,08%
11	Izquierdo-Alventosa, 2021 - LEFT M1	1,83	1,00	2,66	11,02%
12	Lee, 2012 - LEFT M1	-0,26	-1,59	1,06	9,02%
13	Mhalla, 2011 - LEFT M1	1,79	0,92	2,66	10,81%
14	Passard, 2007 - LEFT M1	0,32	-0,41	1,06	11,62%
15	Tekin, 2014 - LEFT M1	1,76	1,10	2,42	11,98%
16	Yagci, 2013 - LEFT M1	0,45	-0,36	1,26	11,20%
17	El-Badawy, 2021 - LEFT M1	0,55	-0,20	1,29	11,56%
18	**LEFT M1**	**0,71**	**0,13**	**1,28**	**36,13%**
19	**Combined Effect Size**	**0,40**	**-1,74**	**2,53**	

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; [a] CI, 95% confidence interval

Table 8 - Statistics for the included rTMS studies and subgroups

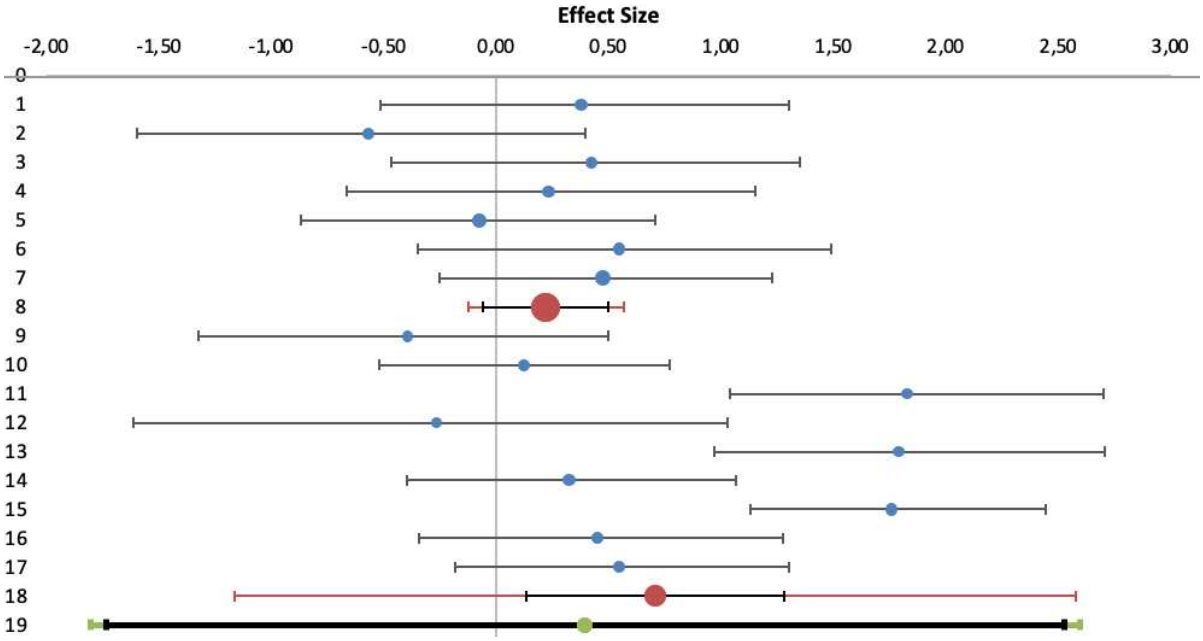

Figure 4 – Results of the meta-analysis for the rTMS studies and subgroups. The forest plot shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The red and green horizontal bars indicate the Prediction Interval.

In term of publication bias, considering all 19 rTMS studies, asymmetry was found and adjusted by imputing 2 potentially missing studies, accordingly to Trim-and-Fill method (Figure 5). After adjusting for publication bias, Hedges' g results 0.27 (Standard Error = 0.18; 95% CI = -0.10 – 0.65) indicating **absence of therapeutic effect**.

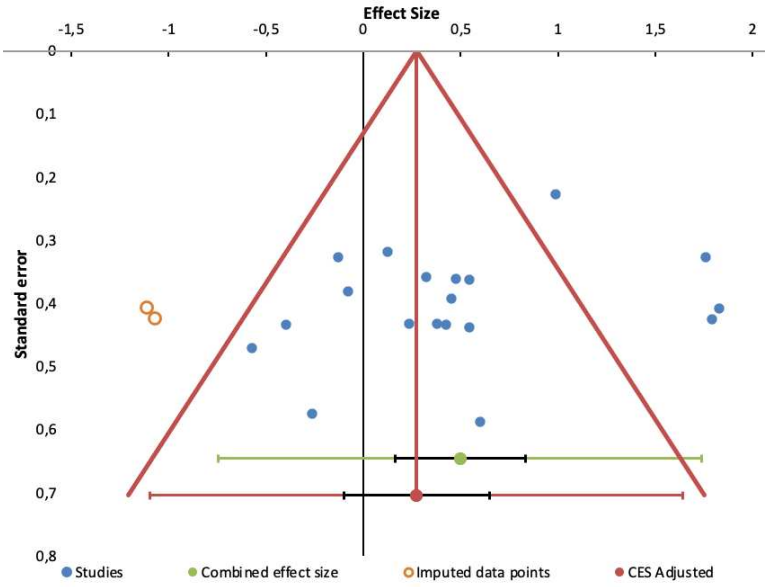

Figure 5 – Publication bias for rTMS included studies

For what concerns tDCS studies, 22 measures of the treatment effect were extracted from the included studies, with a total amount of 728 subjects. As for rTMS studies analysis, a wide range of effect size values, covering from absent to very large effect (Hedges' *g* range: -0.55 – 1.81) were calculated. Only 12 out of the 22 measures analyzed show a positive effect (Hedges' g > 0.20). Studies' relative statistics are reported in Table 9.

#	Study name - Stimulation site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Arroyo-Fernandez, 2022 - LEFT M1 + E	0,35	-0,09	0,80	6,39%
2	Bin Yoo, 2018- RIGHT ON	0,27	-0,38	0,94	5,02%
3	Bin Yoo, 2018- RIGHT DLPFC + RIGHT ON	0,24	-0,42	0,90	5,03%
4	Brietzke, 2020 - LEFT DELPFC	-0,48	-1,41	0,42	3,82%
5	De Melo, 2020 - LEFT M1 5 sessions	-0,08	-0,93	0,78	4,07%
6	De Melo, 2020 - LEFT M1 10 sessions	-0,11	-1,02	0,79	3,86%
7	Fagerlund, 2015 - LEFT M1	0,55	-0,02	1,14	5,49%
8	Foerster, 2015 - LEFT M1	0,30	-0,87	1,52	2,98%
9	Fregni, 2006 - LEFT M1	0,49	-0,40	1,42	3,82%
10	Fregni, 2006 - LEFT DLPFC	0,93	0,04	1,90	3,74%
11	Jales Lunior, 2015 - LEFT M1	0,87	-0,03	1,86	3,68%
12	Khedr, 2017 - LEFT M1	1,81	1,06	2,64	4,28%
13	Matias, 2022 - LEFT M1 + FE	0,07	-0,64	0,79	4,71%
14	Mendonca, 2016 - LEFT M1 + AE	0,30	-0,42	1,04	4,64%
15	Samartin-Veiga, 2022 (a) - LEFT M1	0,14	-0,40	0,68	5,76%
16	Samartin-Veiga, 2022 (a) - LEFT DELPFC	0,02	-0,54	0,57	5,67%
17	Samartin-Veiga, 2022 (a) - LEFT OIC	0,09	-0,46	0,63	5,73%
18	To, 2017 - LEFT DLPFC	1,24	0,42	2,14	4,01%
19	To, 2017 - LEFT ON	1,15	0,40	1,96	4,40%
20	Villamar, 2013 - LEFT M1	-0,11	-1,07	0,84	3,69%
21	El-Badawy, 2021 - LEFT M1	-0,55	-1,30	0,18	4,59%
22	Forogh, 2021 - LEFT DLPFC	-0,47	-1,23	0,25	4,61%

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; ON: occipital nerve; OIC: operculo-insular cortex; E: exercise; AE: aerobic exercise; FE: functional exercise; [a] CI, 95% confidence interval

Table 9 - Statistics for the included tDCS studies

Figure 6 displays the derived forest plot along with the weights of the treatment effect estimations included in the analysis. A combined Hedges' g of 0.31 was calculated (Standard Error = 0.12; 95% CI = 0.05 – 0.56). This suggests that **tDCS has a small effect in ameliorating pain intensity** in FM subjects. A medium heterogeneity was noted (I_2 = 56,36%).

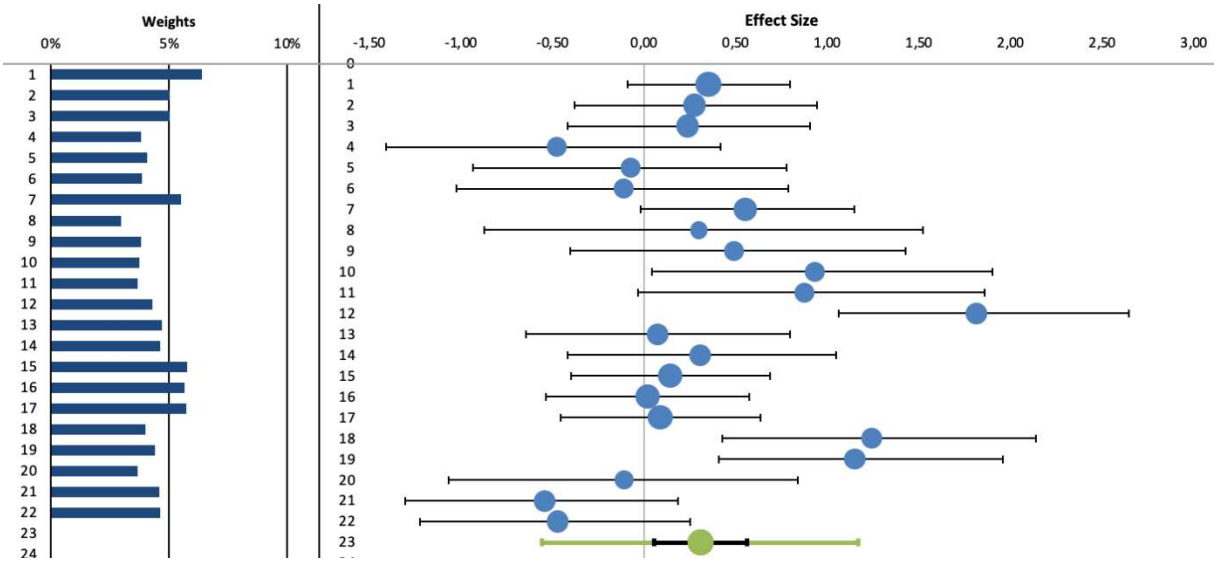

Figure 6 – Results of the meta-analysis for the tDCS studies. The bar plot on the left shows the weights of the included studies and the forest plot on the right shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The green horizontal bar indicates the Prediction Interval.

As it was done for rTMS studies, subgroup analysis was performed to study the relationship between stimulation site (left M1 versus left DLPFC) and its effect on pain intensity. Measure from 3 studies were not considered because researchers investigated the use of tDCS on right DLPFC or right occipital nerve (Bin Yoo et al., 2018), left occipital nerve (To et al., 2017), or operculo-insular cortex (Samartian-Veiga et al., 2022). The studies' relative statistics and the forest plot are reported in Table 10 and Figure 7 respectively.

Taking into consideration left M1 as the focus of stimulation, 11 studies were pooled. Less than half of the studies obtained a Hedges' g greater than 0.20, that is considered an index for positive small effect. A **combined small effect size** was derived (Hedges' g = 0.31; 95% CI = 0.00 – 0.62).

To what concerns LEFT DLPFC subgroup, 5 studies were selected. A combined **no effect** was computed (Hedges' g = 0.23; 95% CI = -0.47 – 0.92).

In addition, the subgroups' combined effect size demonstrates no statistical significance (Hedges' g = 0.30; 95% CI = -1.81 – 2.40).

The subgroups' combined effect size denotes inconsistency of the estimated effect (Hedges' g = 0.30; 95% CI = -1.81 – 2.40).

#	Study name - Subgroup name	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Brietzke, 2020 - LEFT DELPFC	-0,48	-1,39	0,44	18,63%
2	Fregni, 2006 - LEFT DLPFC	0,93	0,00	1,86	18,40%
3	Samartin-Veiga, 2022 (a) - LEFT DLPFC	0,02	-0,54	0,57	23,08%
4	To, 2017 - LEFT DLPFC	1,24	0,39	2,10	19,17%
5	Forogh, 2021 - LEFT DLPFC	-0,47	-1,21	0,26	20,72%
6	**LEFT DLPFC**	**0,23**	**-0,47**	**0,92**	**16,55%**
7	Arroyo-Fernandez, 2022 - LEFT M1 + E	0,35	-0,09	0,79	11,11%
8	De Melo, 2020 - LEFT M1 5 sessions	-0,08	-0,93	0,78	7,00%
9	De Melo, 2020 - LEFT M1 10 sessions	-0,11	-1,02	0,79	6,64%
10	Fagerlund, 2015 - LEFT M1	0,55	-0,03	1,13	9,51%
11	Foerster, 2015 - LEFT M1	0,30	-0,90	1,49	5,10%
12	Fregni, 2006 - LEFT M1	0,49	-0,43	1,40	6,56%
13	Jales Lunior, 2015 - LEFT M1	0,87	-0,07	1,82	6,32%
14	Khedr, 2017 - LEFT M1	1,81	1,02	2,60	7,38%
15	Matias, 2022 - LEFT M1 + FE	0,07	-0,65	0,79	8,13%
16	Mendonca, 2016 - LEFT M1 + AE	0,30	-0,43	1,04	8,01%
17	Samartin-Veiga, 2022 (a) - LEFT M1	0,14	-0,40	0,68	9,99%
18	Villamar, 2013 - LEFT M1	-0,11	-1,06	0,84	6,33%
19	El-Badawy, 2021 - LEFT M1	-0,55	-1,29	0,20	7,92%
20	**LEFT M1**	**0,31**	**0,00**	**0,62**	**83,45%**
21	**Combined Effect Size**	**0,30**	**-1,81**	**2,40**	

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; E: exercise; AE: aerobic exercise; FE: functional exercise; [a] CI, 95% confidence interval

Table 10 - Statistics for the included tDCS studies and subgroups

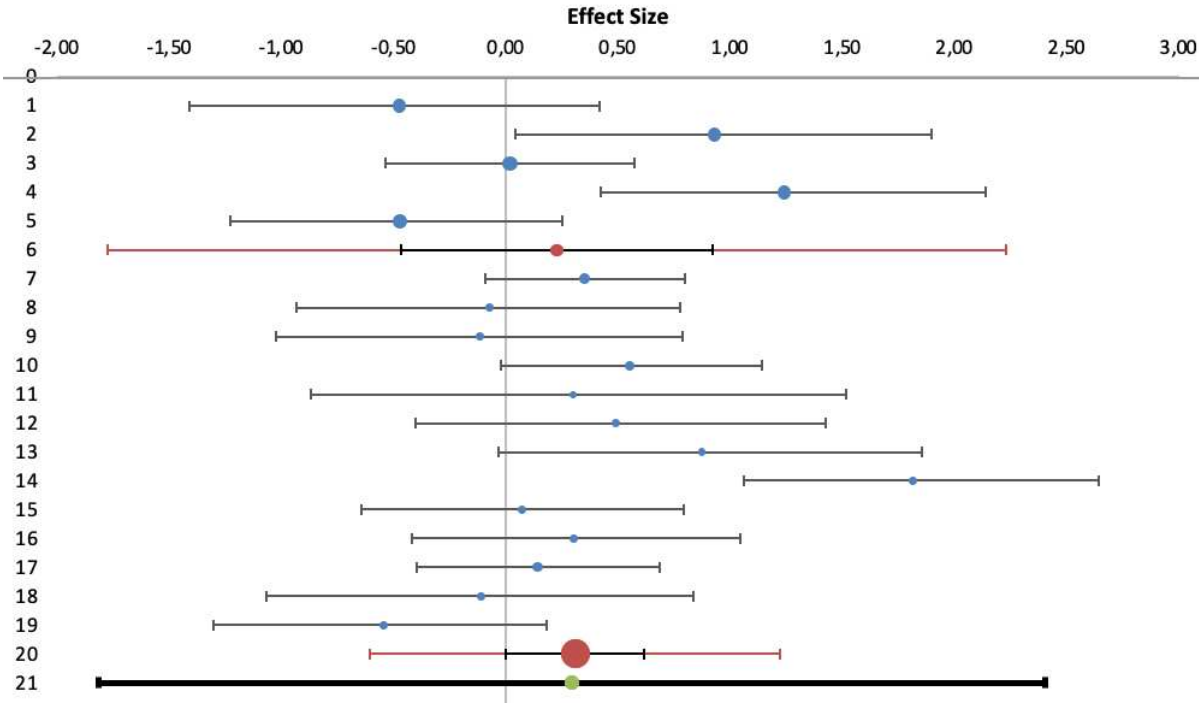

Figure 7 – Results of the meta-analysis for the tDCS studies and subgroups. The forest plot shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The red and green horizontal bars indicate the Prediction Interval.

In term of publication bias, considering tDCS studies, asymmetry was found and corrected in the funnel plot (Figure 8) through the automatic addition of 2 studies, bringing Hedges' g down to 0.10 (Standard Error = 0.15; 95% CI = -0.21 – 0.41). After adjustment, **no effect can be attributed to tDCS on pain**.

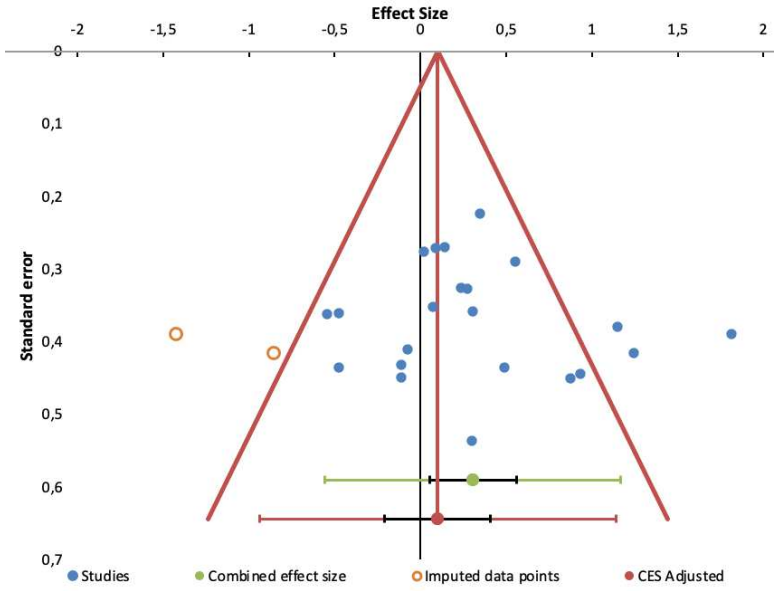

Figure 8 – Publication bias for tDCS included studies

Because of the absent to little effect after adjustment for publication bias, it was decided to unite all studies in a single analysis, including other stimulation sites, to assess the combined effect of both rTMS and tDCS in reducing pain intensity in FM subjects (Table 11, Figure 9). Considering all 41 measures a **small to medium effect was derived** (Hedges' g = 0.40; Standard Error = 0.10; 95% CI = 0.20 – 0.59). Results for tDCS subgroup was **a low effect size** (Hedges' g = 0.31; 95% CI = 0.07 – 0.54); while rTMS measures reports **a medium effect** (Hedges' g = 0.50; 95% CI = 0.18 – 0.81).

The subgroups' combined effect size demonstrates no statistical significance and inconsistence of the effect (Hedges' g = 0.38; 95% CI = -1.65 – 2.40).

#	Study name - Stimulation Site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Arroyo-Fernandez, 2022 - LEFT M1 + E	0,35	-0,09	0,79	6,39%
2	Bin Yoo, 2018- RIGHT ON	0,27	-0,39	0,94	5,02%
3	Bin Yoo, 2018- RIGHT DLPFC + RIGHT ON	0,24	-0,43	0,90	5,03%
4	Brietzke, 2020 - LEFT DELPFC	-0,48	-1,39	0,44	3,82%
5	De Melo, 2020 - LEFT M1 5 sessions	-0,08	-0,93	0,78	4,07%
6	De Melo, 2020 - LEFT M1 10 sessions	-0,11	-1,02	0,79	3,86%
7	Fagerlund, 2015 - LEFT M1	0,55	-0,03	1,13	5,49%
8	Foerster, 2015 - LEFT M1	0,30	-0,90	1,49	2,98%
9	Fregni, 2006 - LEFT M1	0,49	-0,43	1,40	3,82%
10	Fregni, 2006 - LEFT DLPFC	0,93	0,00	1,86	3,74%
11	Jales Lunior, 2015 - LEFT M1	0,87	-0,07	1,82	3,68%
12	Khedr, 2017 - LEFT M1	1,81	1,02	2,60	4,28%
13	Matias, 2022 - LEFT M1 + FE	0,07	-0,65	0,79	4,71%
14	Mendonca, 2016 - LEFT M1 + AE	0,30	-0,43	1,04	4,64%
15	Samartin-Veiga, 2022 (b) - LEFT M1	0,14	-0,40	0,68	5,76%
16	Samartin-Veiga, 2022 (b) - LEFT DLPFC	0,02	-0,54	0,57	5,67%
17	Samartin-Veiga, 2022 (b) - OIC	0,09	-0,46	0,63	5,73%
18	To, 2017 - LEFT DLPFC	1,24	0,39	2,10	4,01%
19	To, 2017 - LEFT ON	1,15	0,37	1,92	4,40%
20	Villamar, 2013 - LEFT M1	-0,11	-1,06	0,84	3,69%
21	El-Badawy, 2021 - LEFT M1	-0,55	-1,29	0,20	4,59%
22	Forogh, 2021 - LEFT DLPFC	-0,47	-1,21	0,26	4,61%
23	**tDCS**	**0,31**	**0,07**	**0,54**	**63,35%**

24	Altas, 2019 - LEFT M1	-0,40	-1,30	0,51	5,00%
25	Altas, 2019 - LEFT DLPFC	0,38	-0,53	1,28	5,00%
26	Avery, 2015 - LEFT DLPFC	-0,57	-1,57	0,43	4,69%
27	Bilir, 2021 - LEFT DLPFC	0,42	-0,49	1,33	4,99%
28	Boyer, 2014 - LEFT M1	0,12	-0,52	0,77	6,01%
29	Cheng, 2019 - LEFT DELPFC	0,23	-0,67	1,14	5,00%
30	Fitzgibbon, 2018 - LEFT DLPFC	-0,08	-0,86	0,71	5,44%
31	Guinot, 2019 - RIGHT M1	-0,13	-0,79	0,54	5,93%
32	Izquierdo-Alventosa, 2021 - LEFT M1	1,83	1,00	2,66	5,21%
33	Lee, 2012 - LEFT M1	-0,26	-1,59	1,06	3,91%
34	Lee, 2012 - RIGHT DLPFC	0,60	-0,75	1,95	3,82%
35	Mhalla, 2011 - LEFT M1	1,79	0,92	2,66	5,07%
36	Passard, 2007 - LEFT M1	0,32	-0,41	1,06	5,65%
37	Short, 2011 - LEFT DLPFC	0,55	-0,37	1,46	4,96%
38	Tanward, 2020 - RIGHT DLPFC	0,99	0,53	1,44	6,80%
39	Tekin, 2014 - LEFT M1	1,76	1,10	2,42	5,93%
40	Yagci, 2013 - LEFT M1	0,45	-0,36	1,26	5,34%
41	El-Badawy, 2021 - LEFT M1	0,55	-0,20	1,29	5,61%
42	Forogh, 2021 - LEFT DLPFC	0,47	-0,26	1,21	5,63%
43	**rTMS**	**0,50**	**0,18**	**0,81**	**36,65%**
44	**Combined Effect Size**	**0,38**	**-1,65**	**2,40**	

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; ON: occipital nerve; OIC: operculo-insular cortex; E: exercise; AE: aerobic exercise; FE: functional exercise; [a] CI, 95% confidence interval

Table 11 - Statistics for the included rTMS and tDCS studies and subgroups

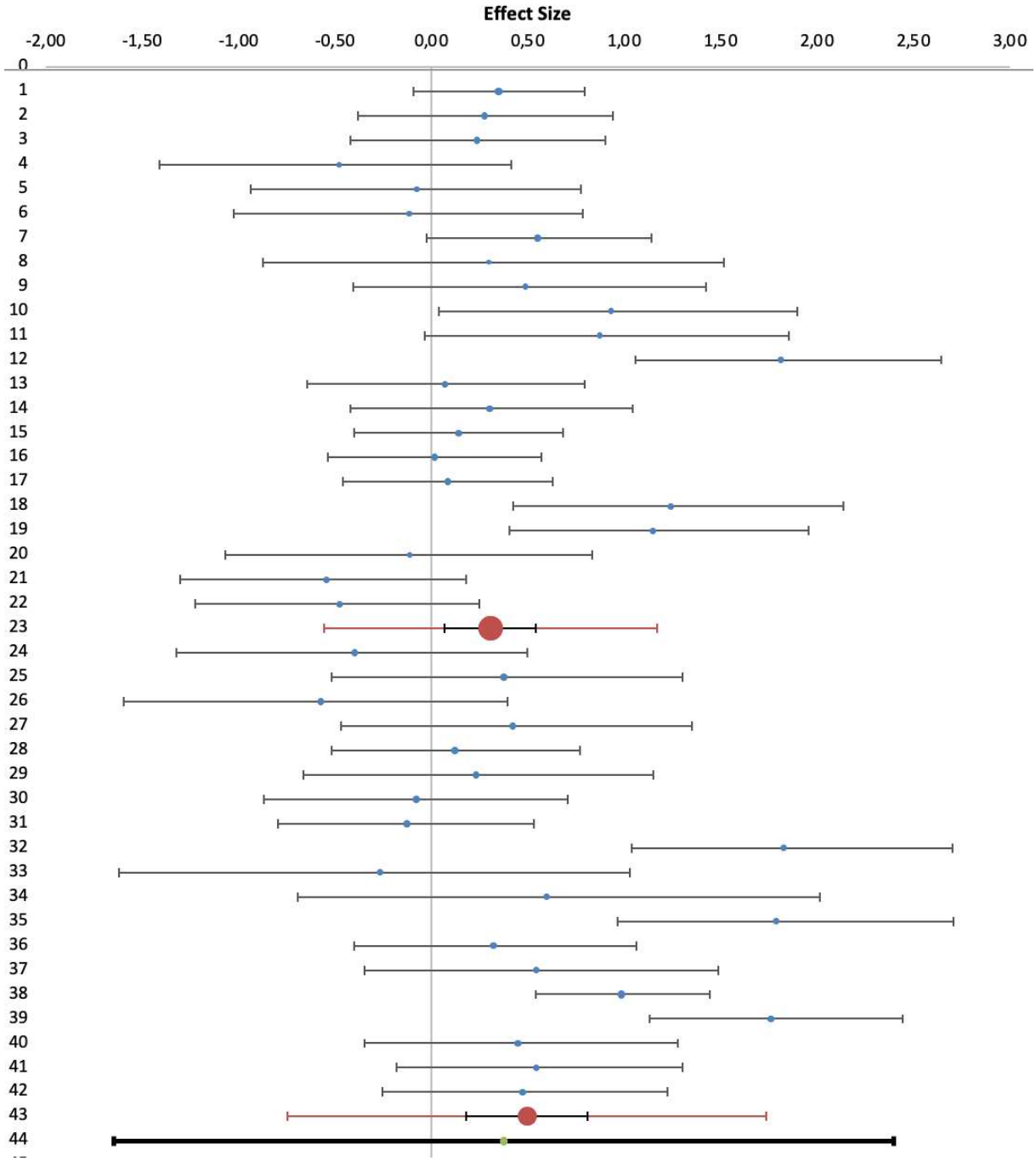

Figure 9 – Results of the meta-analysis for the rTMS and tDCS studies and subgroups. The forest plot shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The red and green horizontal bars indicate the Prediction Interval.

Publication bias funnel plot demonstrates asymmetry. For this reason, according to the Trim-and-Fill method, 5 studies were imputed, and Hedges' g reached 0.03 (Standard Error = 0.12; 95% CI = -0.22 – 0.27), indicating **no effect of these stimulation techniques on pain** (Figure 10).

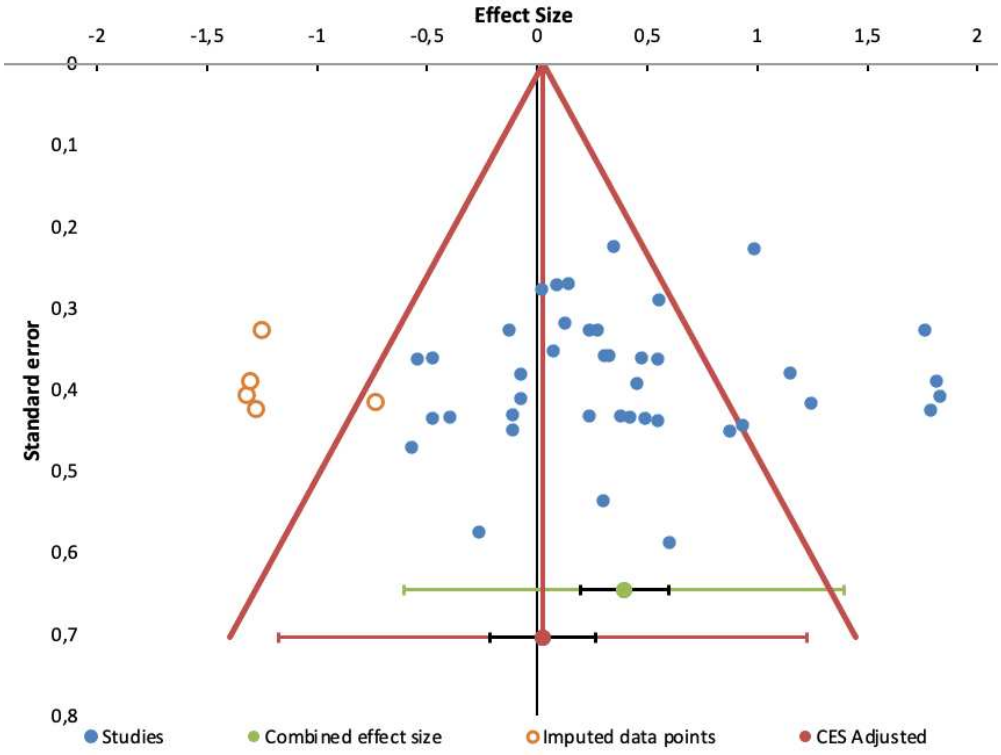

Figure 10 – Publication bias for rTMS and tDCS included studies.

3.3.2 Fibromyalgia Impact Questionnaire Outcome

FIQ total score was used to evaluate quality of life. Included measures from rTMS studies were 15, with 908 patients involved. Similar to the previous analyses, treatment effect magnitude included an extensive range of effect size values, which vary from negative to higher than 1.00 (Hedges' g range: -0.67 – 1.83). 9 out of the 15 outcome measures demonstrated a positive effect (Hedges' s > 0.20). Studies' relative statistics are reported in Table 12.

#	Study name - Stimulation Site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Altas, 2019 - LEFT M1	-0,67	-1,63	0,23	6,20%
2	Altas, 2019 - LEFT DLPFC	0,06	-0,84	0,96	6,33%
3	Bilir, 2021 - LEFT DLPFC	0,18	-0,71	1,09	6,32%
4	Boyer, 2014 - LEFT M1	0,65	0,01	1,33	7,45%
5	Fitzgibbon, 2018 - LEFT DLPFC	0,16	-0,62	0,96	6,84%
6	Guinot, 2019 - RIGHT M1	-0,09	-0,76	0,57	7,46%
7	Izquierdo-Alventosa, 2021 - LEFT M1	1,83	1,04	2,70	6,56%
8	Lee, 2012 - LEFT M1	-0,19	-1,53	1,11	4,94%
9	Lee, 2012 - RIGHT DLPFC	0,28	-1,02	1,63	4,93%
10	Mhalla, 2011 - LEFT M1	0,99	0,24	1,79	6,87%
11	Pareja, 2022	1,23	1,05	1,41	9,61%
12	Passard, 2007 - LEFT M1	1,35	0,58	2,20	6,68%
13	Short, 2011 - LEFT DLPFC	0,51	-0,38	1,45	6,26%
14	Yagci, 2013 - LEFT M1	0,85	0,04	1,72	6,58%
15	El-Badawy, 2021 - LEFT M1	0,82	0,09	1,60	6,96%

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; [a] CI, 95% confidence interval

Table 12 - Statistics for the included rTMS studies

Figure 11 displays the weights of the treatment effect estimations included in the analysis, beside the forest plot. A 0.57 combined effect size was calculated using the Hedges' g value, with a standard error of 0.17 (95% CI = 0.21 – 0.94). This suggests that **rTMS has a medium effect in ameliorating quality of life, and FIQ scores, in FM subjects**. There was a high heterogeneity noted (I_2 = 75,74%).

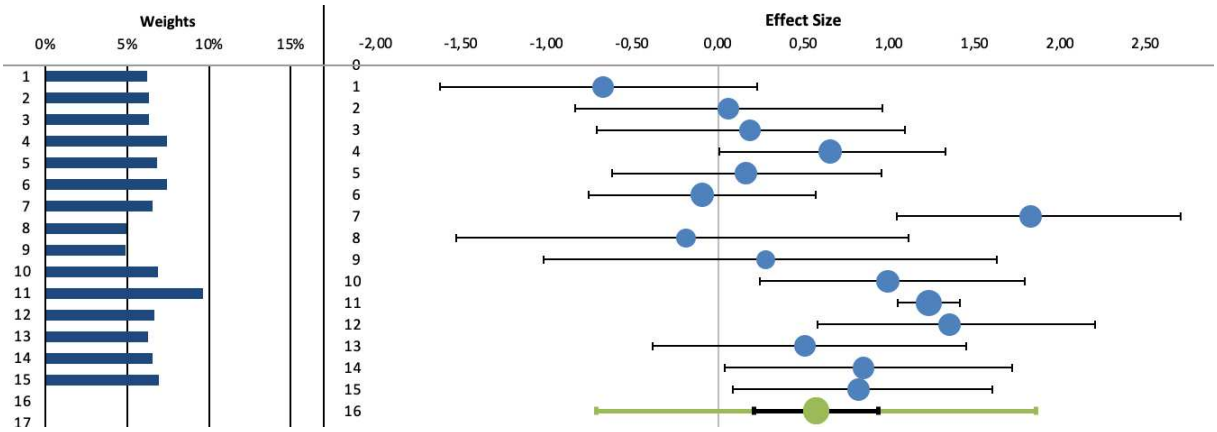

Figure 11 – Results of the meta-analysis for the rTMS studies. The bar plot on the left shows the weights of the included studies and the forest plot on the right shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The green horizontal bar indicates the Prediction Interval.

LEFT M1 and LEFT DLPFC subgroups analysis was performed. Table 13 shows statics relative to included studies, while Figure 12 displays the relative fortes plot.

To what concerns LEFT M1 subgroup, 8 measures were pooled. A **combined large effect size** was derived (Hedges' g = 0.74; 95% CI = 0.20 – 1.28).

In relation to LEFT DLPFC subgroup, 4 studies were selected. A combined **small effect** was computed (Hedges' g = 0.22; 95% CI = 0.04 – 0.41).

In addition, a subgroups' combined effect size was generated, indicating absence of statistical significance (Hedges' g = 0.42; 95% CI = -1.78 – 2.62). This derived result suggests an inconsistent estimated effect.

#	Study name - Subgroup name	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Altas, 2019 - LEFT DLPFC	0,06	-0,84	0,96	23,68%
2	Bilir, 2021 - LEFT DLPFC	0,18	-0,72	1,09	23,59%
3	Fitzgibbon, 2018 - LEFT DLPFC	0,16	-0,62	0,95	29,84%
4	Short, 2011 - LEFT DLPFC	0,51	-0,41	1,43	22,89%
5	**LEFT DLPFC**	**0,22**	**0,04**	**0,41**	**62,28%**
6	Altas, 2019 - LEFT M1	-0,67	-1,60	0,26	11,91%
7	Boyer, 2014 - LEFT M1	0,65	-0,01	1,32	14,14%
8	Izquierdo-Alventosa, 2021 - LEFT M1	1,83	1,00	2,66	12,55%
9	Lee, 2012 - LEFT M1	-0,19	-1,51	1,13	9,62%
10	Mhalla, 2011 - LEFT M1	0,99	0,22	1,77	13,12%
11	Passard, 2007 - LEFT M1	1,35	0,54	2,16	12,78%
12	Yagci, 2013 - LEFT M1	0,85	0,01	1,69	12,60%
13	El-Badawy, 2021 - LEFT M1	0,82	0,06	1,58	13,27%
14	**LEFT M1**	**0,74**	**0,20**	**1,28**	**37,72%**
15	**Combined Effect Size**	**0,42**	**-1,78**	**2,62**	

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; [a] CI, 95% confidence interval

Table 13 - Statistics for the included tDCS rTMS ad subgroups

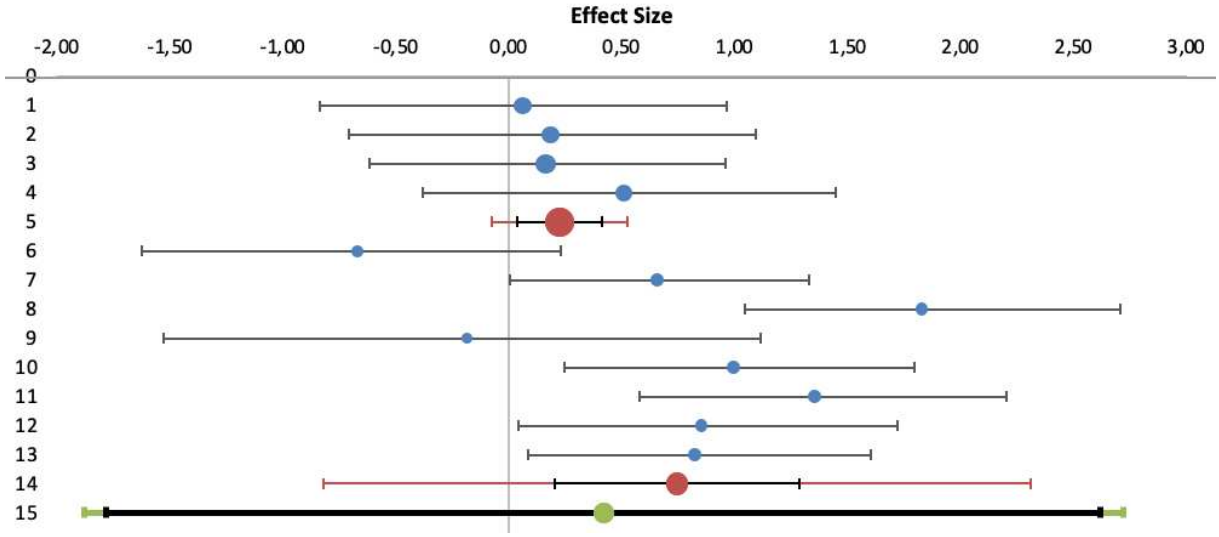

Figure 12 – Results of the meta-analysis for the rTMS studies and subgroups. The forest plot shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The red and green horizontal bars indicate the Prediction Interval.

Publication bias was also analyzed (Figure 13), and it was concluded for a symmetric funnel plot. Thus, results remained the same as mentioned above.

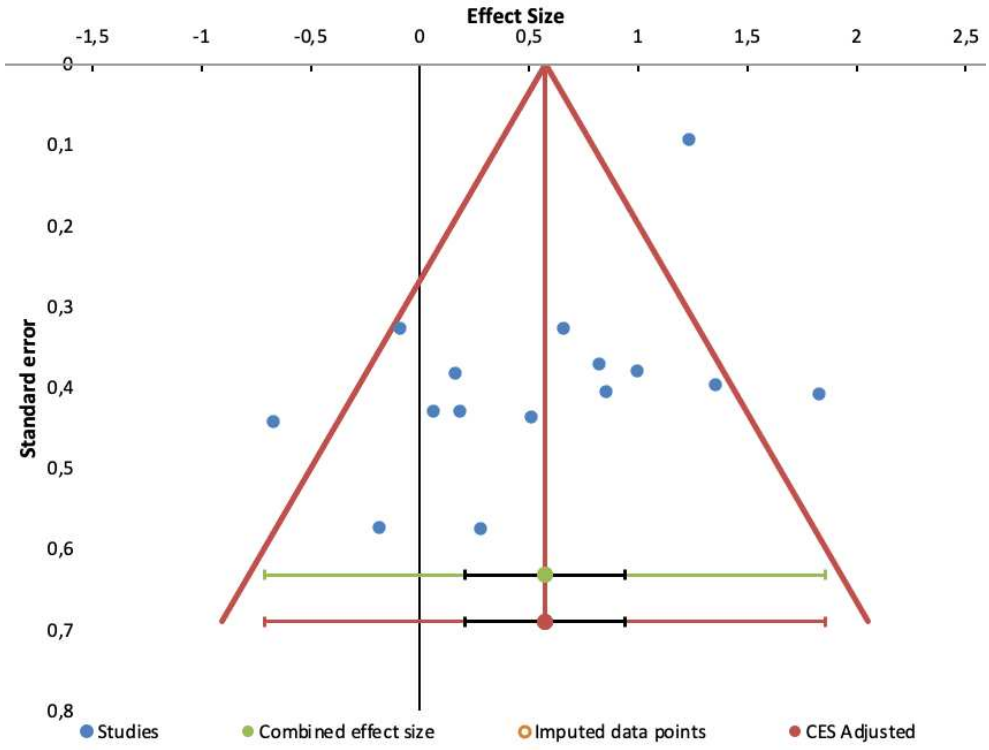

Figure 13 – Publication bias for tDCS included studies

Relate to tDCS studies, 12 measures of the treatment effect were extracted from the included studies, with a total amount of 485 subjects. Effect size values range appeared to cover from no effect to medium effect (Hedges' *g* range: -0.82 – 0.63). Only 2 out of 12 measures analyzed show a medium positive effect (Hedges' g > 0.50), while 7 overcome Hedges' g > 0.20. Studies' relative statistics are reported in Table 14.

#	Study name - Stimulation site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Arroyo-Fernandez, 2022 - LEFT M1 + E	-0,04	-0,48	0,40	15,47%
2	Bin Yoo, 2018- RIGHT ON	0,34	-0,32	1,01	7,70%
3	Bin Yoo, 2018- RIGHT DLPFC + RIGHT ON	0,26	-0,40	0,93	7,74%
4	Fagerlund, 2015 - LEFT M1	0,27	-0,30	0,84	9,90%
5	Fregni, 2006 - LEFT DLPFC	0,63	-0,24	1,56	4,58%
6	Jales Lunior, 2015 - LEFT M1	0,31	-0,59	1,22	4,58%
7	Matias, 2022 - LEFT M1 + FE	0,30	-0,42	1,03	6,66%
8	Riberto, 2011 - LEFT M1	0,63	-0,21	1,51	4,97%
9	Samartin-Veiga, 2022 (b) - LEFT M1	-0,11	-0,65	0,43	10,99%
10	Samartin-Veiga, 2022 (b) - LEFT DELPFC	0,13	-0,42	0,69	10,50%
11	Samartin-Veiga, 2022 (b) – LEFT OIC	0,15	-0,39	0,70	10,82%
12	El-Badawy, 2021 - LEFT M1	-0,82	-1,60	-0,09	6,09%

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; ON: occipital nerve; OIC: operculo-insular cortex; E: exercise; AE: aerobic exercise; FE: functional exercise; [a] CI, 95% confidence interval

Table 14 - Statistics for the included tDCS studies

Figure 14 displays the derived forest plot along with the weights of the treatment effect estimations included in the analysis. A Hedges' g of 0.13 was calculated relatively to the combined effect size, associated to a standard error of 0.10 (95% CI = -0.08 – 0.34). This brings to the conclusion that **tDCS has a no effect in ameliorating quality of life** in FM subjects. A low heterogeneity was derived (I_2 = 7,83%).

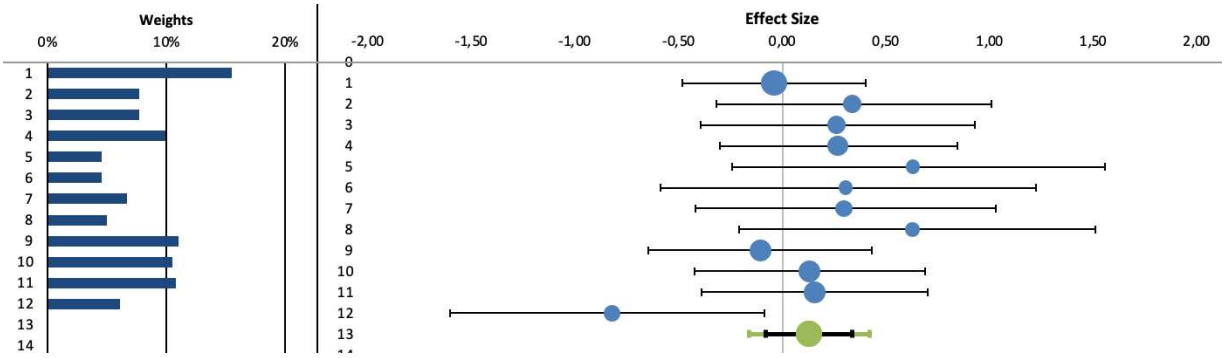

Figure 14 – Results of the meta-analysis for the rTMS studies. The bar plot on the left shows the weights of the included studies and the forest plot on the right shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The green horizontal bar indicates the Prediction Interval.

Subgroup analysis was performed to study the relationship between stimulation site (left M1 versus left DLPFC) and its effect on quality of life. Measure from 2 studies were not considered because researchers investigated the use of tDCS on right DLPFC or right occipital nerve (Bin Yoo et al., 2018), or operculo-insular cortex (Samartian-Veiga et al., 2022). The studies' relative statistics and the forest plot are reported in Table 15 and Figure 15 respectively.

Taking into consideration LEFT M1 subgroup, 7 studies were pooled. Only 4 studies obtained a Hedges' g greater than 0.20, and 1 was greater than 0.50. A combined **absent effect was derived** (Hedges' g = 0.05; 95% CI = -0.26 – 0.36).

LEFT DLPFC subgroup counted 2 studies only. The computed effect size was 0.28 (95% CI = -0.18 to 0.73), demonstrating **no effect of treatment on quality of life (FIQ scores)**.

As for the previous outcome measures analyzed, the subgroups' combined effect size demonstrates an extensive variability associated to no statistical significance (Hedges' g = 0.12; 95% CI = -2.18 – 2.43).

#	Study name / Subgroup name	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Fregni, 2006 - LEFT DLPFC	0,63	-0,27	1,53	29,14%
2	Samartin-Veiga, 2022 (b) - LEFT DELPFC	0,13	-0,42	0,69	70,86%
3	**LEFT DLPFC**	**0,28**	**-0,18**	**0,73**	**32,85%**
4	Arroyo-Fernandez, 2022 - LEFT M1 + E	-0,04	-0,48	0,40	21,69%
5	Fagerlund, 2015 - LEFT M1	0,27	-0,31	0,84	16,61%
6	Jales Lunior, 2015 - LEFT M1	0,31	-0,60	1,21	9,45%
7	Matias, 2022 - LEFT M1 + FE	0,30	-0,43	1,02	12,61%
8	Riberto, 2011 - LEFT M1	0,63	-0,23	1,49	10,09%
9	Samartin-Veiga, 2022 (b) - LEFT M1	-0,11	-0,65	0,43	17,76%
10	El-Badawy, 2021 - LEFT M1	-0,82	-1,58	-0,06	11,80%
11	**LEFT M1**	**0,05**	**-0,26**	**0,36**	**67,15%**
12	**Combined Effect Size**	**0,12**	**-2,18**	**2,43**	

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; E: exercise; FE: functional exercise; [a] CI, 95% confidence interval

Table 15 - Statistics for the included tDCS studies and subgroups

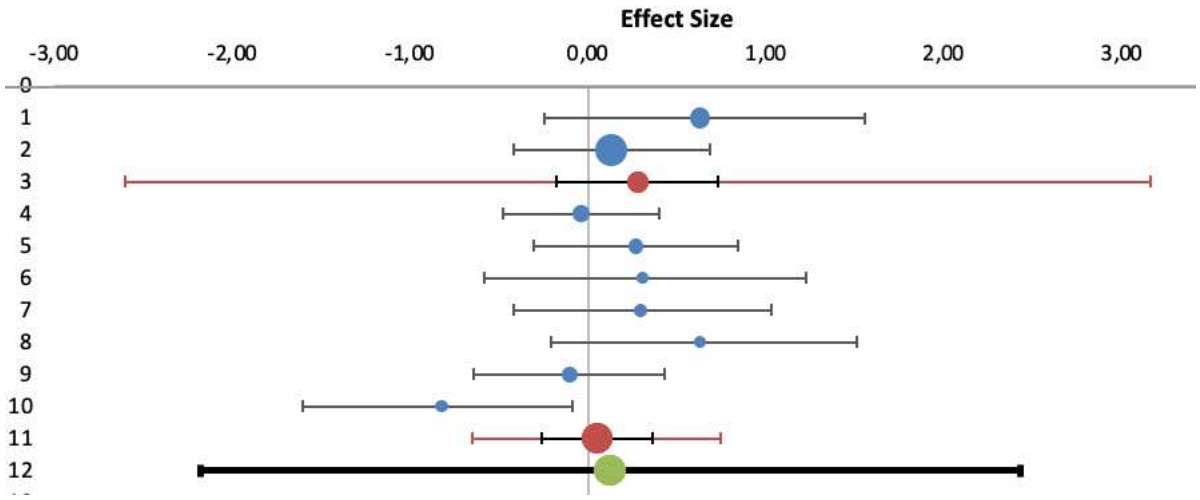

Figure 15 – Results of the meta-analysis for the tDCS studies and subgroups. The forest plot shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The red and green horizontal bars indicate the Prediction Interval.

Publication bias was assessed by examining the funnel plot symmetry (Figure 16). **No effect can be attributed to tDCS on quality of life**, measured through the FIQ outcome. Hedges' g was confirmed to be 0.13. No adjustment was performed because of the symmetry of the graph.

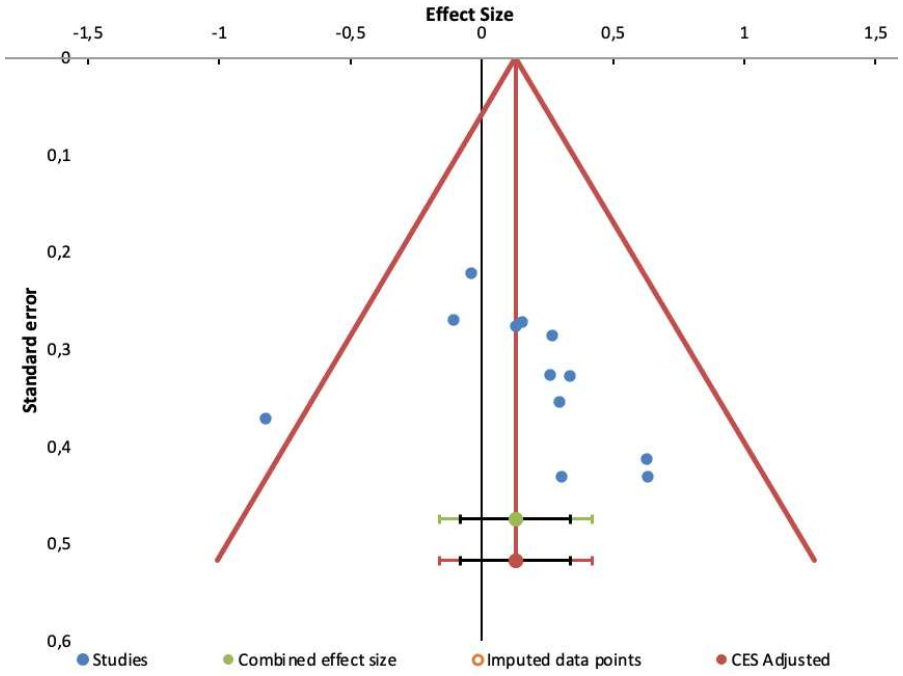

Figure 16 – Publication bias for tDCS included studies

A global analysis, including all studies and stimulation sites was conducted. Results of this data merging was **a medium effect size** (Hedges' g = 0.38; Standard Error = 0.11; 95% CI = 0.11 – 0.61) and a high heterogeneity (I^2 = 78.32%). Subgroups for type of techniques were analyzed (Table 16, Figure 17). **tDCS studies seems to have no effect** (Hedges' g = 0.13; 95% CI = -0.06 – 0.32), while **rTMS appears to have a medium effect** (Hedges' g = 0.57; 95% CI = 0.24 – 0.91) on quality of life (FIQ score).

Combined effect size indicates inconsistency of the result (Hedges' g = 0.33; 95% CI = -1.73 – 2.38).

#	Study name / Subgroup name	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Arroyo-Fernandez, 2022 - LEFT M1 + E	-0,04	-0,48	0,40	15,47%
2	Bin Yoo, 2018- RIGHT ON	0,34	-0,33	1,00	7,70%
3	Bin Yoo, 2018- RIGHT DLPFC + RIGHT ON	0,26	-0,40	0,92	7,74%
4	Fagerlund, 2015 - LEFT M1	0,27	-0,31	0,84	9,90%
5	Fregni, 2006 - LEFT DLPFC	0,63	-0,27	1,53	4,58%
6	Jales Lunior, 2015 - LEFT M1	0,31	-0,60	1,21	4,58%
7	Matias, 2022 - LEFT M1 + FE	0,30	-0,43	1,02	6,66%
8	Riberto, 2011 - LEFT M1	0,63	-0,23	1,49	4,97%
9	Samartin-Veiga, 2022 (b) - LEFT M1	-0,11	-0,65	0,43	10,99%
10	Samartin-Veiga, 2022 (b) - LEFT DELPFC	0,13	-0,42	0,69	10,50%
11	Samartin-Veiga, 2022 - OIC	0,15	-0,39	0,70	10,82%
12	El-Badawy, 2021 - LEFT M1	-0,82	-1,58	-0,06	6,09%
13	**tCDS**	**0,13**	**-0,06**	**0,32**	**55,07%**
14	Altas, 2019 - LEFT M1	-0,67	-1,60	0,26	6,20%
15	Altas, 2019 - LEFT DLPFC	0,06	-0,84	0,96	6,33%
16	Bilir, 2021 - LEFT DLPFC	0,18	-0,72	1,09	6,32%
17	Boyer, 2014 - LEFT M1	0,65	-0,01	1,32	7,45%
18	Fitzgibbon, 2018 - LEFT DLPFC	0,16	-0,62	0,95	6,84%
19	Guinot, 2019 - RIGHT M1	-0,09	-0,75	0,57	7,46%
20	Izquierdo-Alventosa, 2021 - LEFT M1	1,83	1,00	2,66	6,56%
21	Lee, 2012 - LEFT M1	-0,19	-1,51	1,13	4,94%
22	Lee, 2012 - RIGHT DLPFC	0,28	-1,05	1,60	4,93%
23	Mhalla, 2011 - LEFT M1	0,99	0,22	1,77	6,87%
24	Pareja, 2022	1,23	1,05	1,41	9,61%
25	Passard, 2007 - LEFT M1	1,35	0,54	2,16	6,68%
26	Short, 2011 - LEFT DLPFC	0,51	-0,41	1,43	6,26%

27	Yagci, 2013 - LEFT M1	0,85	0,01	1,69	6,58%
28	El-Badawy, 2021 - LEFT M1	0,82	0,06	1,58	6,96%
29	**rTMS**	**0,57**	**0,24**	**0,91**	**44,93%**
30	**Combined Effect Size**	**0,33**	**-1,73**	**2,38**	

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; E: exercise; FE: functional exercise; [a] CI, 95% confidence interval

Table 16 - Statistics for the included rTMS and tDCS studies and subgroups

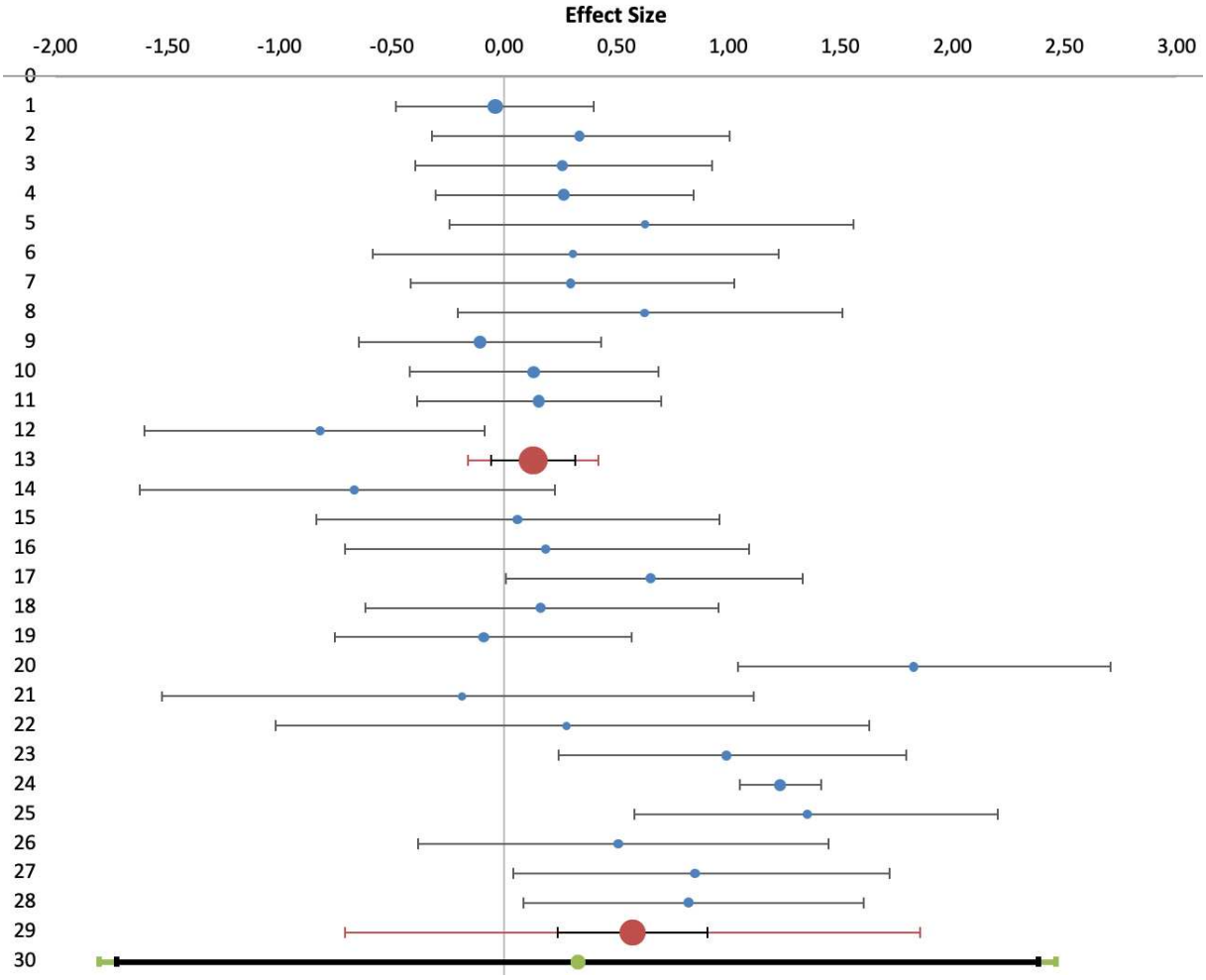

Figure 17 – Results of the meta-analysis for the rTMS and tDCS studies and subgroups. The forest plot shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The red and green horizontal bars indicate the Prediction Interval.

Publication bias was assessed to be low, and the funnel plot demonstrates symmetry (Figure 18). Thus, no adjustment was performed.

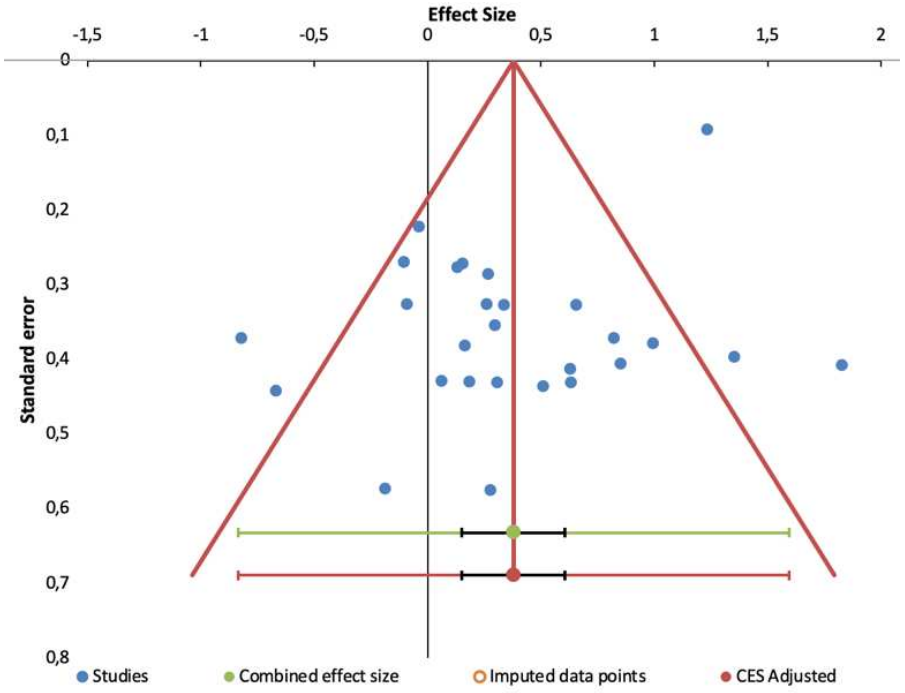

Figure 18 – Publication bias for rTMS and tDCS included studies

3.3.3 36-Item Short-Form Survey

SF-36 analysis was addresses to the specific study of the item Physical Functioning and Mental Health, which are recognized as better representing the 2 components of the survey: Physical Component and Mental Component. Because of the limited number of measures available, subgroup analysis was not worth running.

For the Physical Function item analysis, 3 measures withing 2 studies have been identified in relation to rTMS. Subjects included in this analysis have been 58. **No effect of rTMS on Physical Function, assessed through the SF-36**, outcome was derived (Hedges' g = 0.09; Standard Error = 0.15, CI 95% = -0.57 – 0.75). Table 17 and Figure 19 show statistics of the included studies and the relative forest plot.

#	Study name - Stimulation Site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Altas, 2019 - LEFT M1 (Physical Functioning)	0,37	-0,52	1,30	34,51%
2	Altas, 2019 - LEFT DLPFC (Physical Functioning)	0,03	-0,87	0,93	35,16%
3	Avery, 2015 - LEFT DLPFC (Physical Functioning)	-0,16	-1,14	0,81	30,33%

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; [a] CI, 95% confidence interval

Table 17 - Statistics for the included rTMS studies

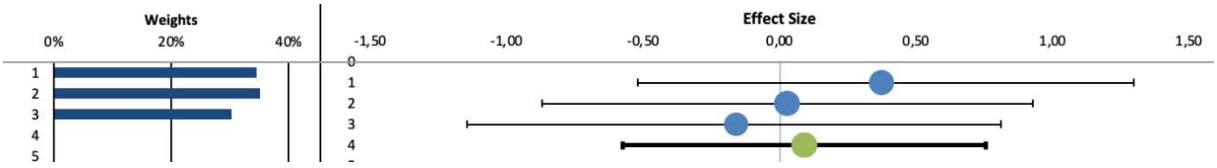

Figure 19 – Results of the meta-analysis for rTMS included studies. The bar plot on the left shows the weights of the included studies and the forest plot on the right shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The green horizontal bar indicates the Prediction Interval.

The same studies reporting the Physical Function Item results, display the Mental Health values also (Table 18 and Figure 20). A negative effect size has been calculated (Hedges' g = -0.34; Standard Error = 0.27; CI 95% = -1.49 – 0.82). Thus, **no effect can be associated to rTMS on Mental Health in people with FM**.

#	Study name - Stimulation Site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Altas, 2019 - LEFT M1 (Mental Health)	-0,19	-1,10	0,70	35,72%
2	Altas, 2019 - LEFT DLPFC (Mental Health)	-0,86	-1,84	0,04	32,86%
3	Avery, 2015 - LEFT DLPFC (Mental Helath)	0,05	-0,92	1,03	31,42%

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; [a] CI, 95% confidence interval

Table 18 - Statistics for the included rTMS studies

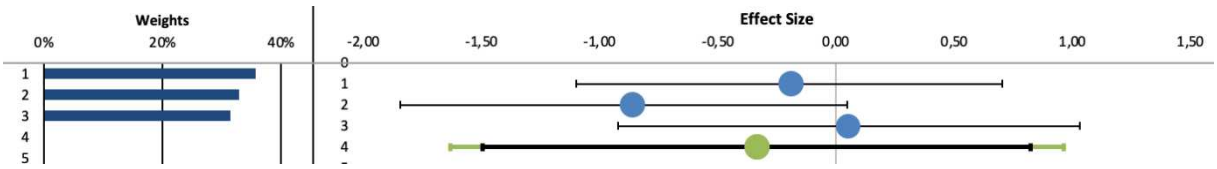

Figure 20 – Results of the meta-analysis for rTMS included studies. The bar plot on the left shows the weights of the included studies and the forest plot on the right shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The green horizontal bar indicates the Prediction Interval.

5 measures from 3 studies were extracted, in order to analyze tDCS effect on Physical Functioning, with a total of 205 subjects included. **No effect of treatment was calculated** (Hedges' g = -0.11; Standard Error = 0.26; CI 95% = -0.83 – 0.60). In Table 19 and Figure 21 statistics from included studies and the resulting forest plot are shown.

#	Study name - Stimulation Site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Jales Lunior, 2015 - LEFT M1 (Physical Functioning)	-1,42	-2,50	-0,47	12,98%
2	Mendonca, 2016 - LEFT M1 + AE (Physical Functioning)	0,22	-0,50	0,96	18,33%
3	Samartin-Veiga, 2022 (b) - LEFT M1 (Physical Functioning)	0,11	-0,43	0,65	23,22%
4	Samartin-Veiga, 2022 (b) - LEFT DLPFC (Physical Functioning)	-0,08	-0,64	0,47	22,81%
5	Samartin-Veiga, 2022 (b) - OIC (Physical Functioning)	0,11	-0,45	0,67	22,65%

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; OIC: operculo-insular cortex; AE: aerobic exercise; [a] CI, 95% confidence interval

Table 19 - Statistics for the included rTMS studies

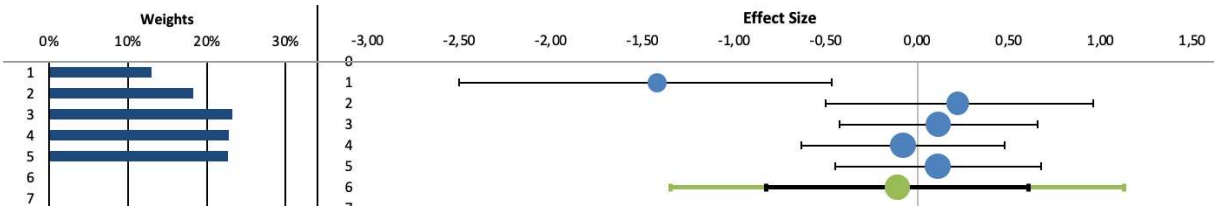

Figure 21 – Results of the meta-analysis for tDCS included studies. The bar plot on the left shows the weights of the included studies and the forest plot on the right shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The green horizontal bar indicates the Prediction Interval.

As far as Mental Health is concerned 208 subjects were included. **Adverse effect could be attributed to tDCS on Mental Health** (Hedges' g = -0.23; Standard Error = 0.04; CI 95% = -0.35 – -0.11) (Table 20 and Figure 22).

#	Study name - Stimulation Site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Jales Lunior, 2015 - LEFT M1 (Mental Health)	-0,36	-1,29	0,53	10,01%
2	Mendonca, 2016 - LEFT M1 + AE (Mental Health)	-0,17	-0,90	0,56	14,74%
3	Samartin-Veiga, 2022 (b) - LEFT M1 (Mental Health)	-0,12	-0,66	0,42	25,78%
4	Samartin-Veiga, 2022 (b) - LEFT DLPFC (Mental Health)	-0,31	-0,87	0,24	24,26%
5	Samartin-Veiga, 2022 (b) - OIC (Mental Health)	-0,25	-0,80	0,29	25,22%

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; OIC: operculo-insular cortex; AE: aerobic exercise; [a] CI, 95% confidence interval

Table 20 - Statistics for the included rTMS studies

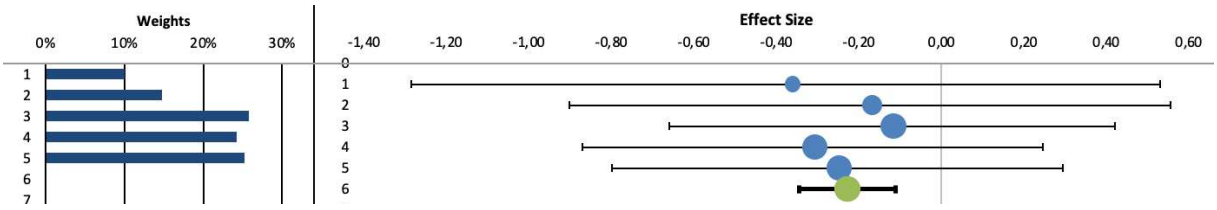

Figure 22 – Results of the meta-analysis for tDCS included studies. The bar plot on the left shows the weights of the included studies and the forest plot on the right shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The green horizontal bar indicates the Prediction Interval.

We decided to merge all studies in a single analysis, including other stimulation sites, to assess the combined effect of both rTMS and tDCS in ameliorating Physical Function or Mental Health in FM subjects. **The conclusion for Physical Functioning data is the absence of effect** (Hedges' g = -0.04; Standard Error = 0.16; CI 95% = -0.42 - 0.35) (Table 21 and Figure 22).

#	Study name - Stimulation Site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Altas, 2019 - LEFT M1	0,37	-0,52	1,30	9,43%
2	Altas, 2019 - LEFT DLPFC	0,03	-0,87	0,93	9,56%
3	Avery, 2015 - LEFT DLPFC	-0,16	-1,14	0,81	8,53%
4	Jales Lunior, 2015 - LEFT M1	-1,42	-2,50	-0,47	7,91%
5	Mendonca, 2016 - LEFT M1 + AE	0,22	-0,50	0,96	12,49%
6	Samartin-Veiga, 2022 (b) - LEFT M1	0,11	-0,43	0,65	17,75%
7	Samartin-Veiga, 2022 (b) - LEFT DELPFC	-0,08	-0,64	0,47	17,26%
8	Samartin-Veiga, 2022 (b) - OIC	0,11	-0,45	0,67	17,07%

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; OIC: operculo-insular cortex; AE: aerobic exercise; [a] CI: 95% confidence interval

Table 21 - Statistics for Physical Functioning outcome

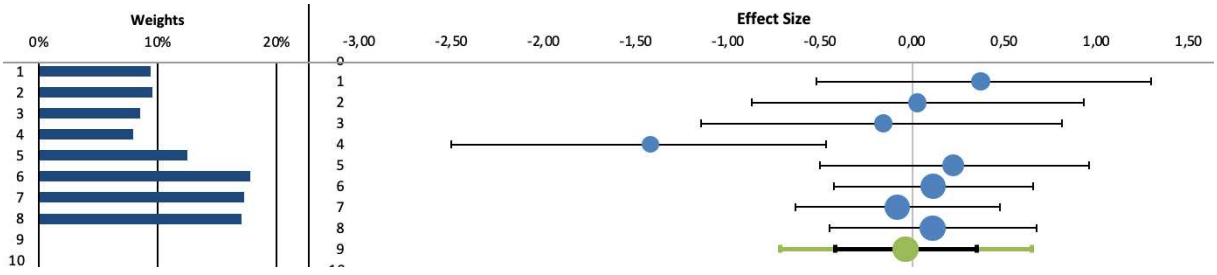

Figure 22 – Results of the meta-analysis for rTMS and tDCS included studies. The bar plot on the left shows the weights of the included studies and the forest plot on the right shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The green horizontal bar indicates the Prediction Interval.

An adverse effect was identified in relation to Mental Health (Hedges' g = -0.25; Standard Error = 0.07; CI 95% = -0.43 – -0.07) (Table 22 and Figure 23).

#	Study name - Stimulation Site	Hedges' g	CI[a] Lower limit	CI[a] Upper limit	Weight
1	Altas, 2019 - LEFT M1	-0,19	-1,10	0,70	7,90%
2	Altas, 2019 - LEFT DLPFC	-0,86	-1,84	0,04	7,21%
3	Avery, 2015 - LEFT DLPFC	0,05	-0,92	1,03	6,87%
4	Jales Lunior, 2015 - LEFT M1	-0,36	-1,29	0,53	7,81%
5	Mendonca, 2016 - LEFT M1 + AE	-0,17	-0,90	0,56	11,50%
6	Samartin-Veiga, 2022 (b) - LEFT M1	-0,12	-0,66	0,42	20,11%
7	Samartin-Veiga, 2022 (b) - LEFT DELPFC	-0,31	-0,87	0,24	18,92%
8	Samartin-Veiga, 2022 (b) - OIC	-0,25	-0,80	0,29	19,67%

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; OIC: operculo-insular cortex; AE: aerobic exercise; [a] CI: 95% confidence interval

Table 22 - Statistics for Mental Health outcome

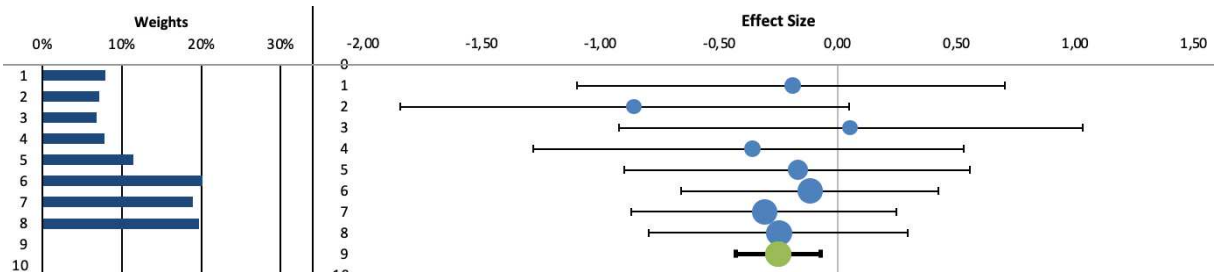

Figure 23 – Results of the meta-analysis for rTMS and tDCS included studies. The bar plot on the left shows the weights of the included studies and the forest plot on the right shows the corresponding effect size estimates. The size of the circles reflects the weight for each effect size and the horizontal error bars indicate their 95% confidence interval. The green horizontal bar indicates the Prediction Interval.

4. DISCUSSION AND CONCLUSION

FM is a complex chronic nervous system syndrome, in which pain represents the main symptom complained by patients. This condition is linked to a reduction in quality of life, involving multiple activities and domains, from the cognitive and psychological sphere to the physical function.

Scope of this study was to provide an updated analysis of the effect of different NIBS techniques for the treatment of FM, with specific focus on pain intensity and quality of life. The main transcranial stimulation means investigated are rTMS and tDCS, while only few are the studies addressed to tACS, tRNS and RINCE.

In 2018 a Cochrane Review on the application of NIBS for the treatment of chronic pain was published (O'Connell et al.). In addition, 1 meta-analysis concerning the effect of tDCS on pain in FM subjects (Lloyd et al., 2019) and 2 meta-analyses regarding the specific use of rTMS in FM (Toh et al., 2022, Sun et al., 2022) can be found in scientific literature. They all reported a positive effect of NIBS in ameliorating pain. Lloyd and colleagues cite the study by Khedr and his research team (2017) as their work among the other included articles, displayed the greatest effect of tDCS with a protocol comprised by 2 mA atDCS 10 consecutive sessions (20 minutes per session, on working days) over left M1 in 40 FM patients. Other studies applied the same protocol but with lower effect. Sun and colleagues (2022) concluded for strong evidence in favor of rTMS in relieving pain and enhancing quality of life in FM subjects. Their conclusion appears in contrast with previous meta-analyses, which reported only a positive trend (Knijnik et al., 2016) or no effect (Saltychev et al., 2017) in relieving pain. These more dated reviews counted 5 (Knijnik et al., 2016) and 7 screened articles (Saltychev et al., 2017). Sun and colleagues concluded for a predominancy effect of M1 rTMS stimulation in improving quality of life, while DLPFC stimulation did not. M1 target is reported to have also statistically significant effect in pain reduction, but only after sensitivity analysis. The authors report a short-term pain reduction after high-frequency rTMS, while low-frequency rTMS did not show any effect. In the same review low-frequency rTMS over right DLPFC is declared to be "the most suitable protocol for relieving pain".

As it was already stated in the above-mentioned previous reviews, difference in the stimulation site represents one of the main features to be discussed. Different cortical stimulation focus can determine a potential dissimilar effect, which need to be deeply investigated.

General effects of NIBS are linked to an induced plasticity mediated by LTP and LTD processes (Huang et al., 2017). The main 2 cortical targets for NIBS interventions are M1 and DLPFC, which are both recognized to be part of the so-called “neuromatrix”, together with other cerebral regions like primary and secondary sensory cortices, amygdala, thalamus, etc. (Melzack, 1999, 2001). Melzack proposed this new theory as an attempt to explain the distributed cerebral pain network, responsible for pain processing. Accordingly with its intricate information processing role, M1 seems to be involved in the sensory discriminative aspects of pain (Xiong et al., 2022). As a matter of fact, M1 has a somatotopic organization and receives connections from many regions: the periphery of the body, through the thalamus and the somatosensory cortices, the premotor cortex and the sensory association areas, the basal ganglia, and the cerebellum (Witney, 2018). tDCS applied over M1 appears to cause a reduction of glutamate concentration in the ACC and thalamus but also to lowering central sensitization, and pain levels, by increasing the activities of the descending pain inhibitory system (Lim et al., 2021). DLPFC displays connections with orbitofrontal cortex and other areas of the “neuromatrix”, including descending modulatory networks, through the periaqueductal gray. Its functional e anatomical organization confers DLPFC a key role in the affective-emotional and cognitive pain perception (Xiong et al., 2022) as well as sensorimotor processing, monitoring of motor performance, and integration of memory and stimulus features (Witney, 2018).

Since last meta-analyses, which were described above, more studies were published. Although rTMS previous meta-analyses investigated different outcomes (pain intensity, depression, anxiety, quality of life, etc.), the recent tDCS meta-analysis (Lloyd, 2020) examined only stimulation the stimulation effect on pain intensity.

The large majority of the studies included in this study obtained a Jadad score of 3 or higher with only one exception among rTMS papers, with a score of 2 (Pareja et al., 2022), and 3 exceptions through tDCS studies, gaining a score of 2 (Bin Yoo et al.,

2018; Plazier et al. 2015) and 1 (Foerster et al., 2015). In general, substantial heterogeneity was found.

In this research, possible publication bias was recognized in almost all analyses performed. After adjustment, effect size values decreased to a small effect for rTMS or no effect for tDCS on pain intensity (NPRS). Analysis of data referred to the outcome FIQ and SF-36 di non request publication bias correction. Only the application of rTMS seems associated to better FIQ scores, particularly when left M1 in stimulated (Hedges' g = 0.74), compared to left DLPFC (Hedges' g = 0.22). In particular, a positive medium effect was found on pain with the use of rTMS, especially if left M1 is stimulated (rTMS Hedges' g = 0.50; LEFT M1 subgroup Hedges' s = 0.71). Although this result, after adjustment, the effect size becomes small and 95% CI includes 0, indicating that the result is not statistically significant (Hedges' g = 0.27; 95% CI = -0.10 – 0.65). A positive small effect on pain intensity seems to be associated to the use of tDCS with higher effect after stimulation of left M1 (Hedges' g = 0.31). These findings are canceled when correction for bias is conducted, as the consequent effect size results 0.10 and 95% include 0 (95% CI = -0.21 – 0.41). Moreover, combined effect size after subgroup analyzes demonstrates wide variability range and no statistical significancy. This fact denotes inconsistency of the estimated effects.

As anticipated FIQ scores improve only after rTMS with better performance when left M1 is the stimulation focus (rTMS Hedges' g = 0.50; LEFT M1 subgroup Hedges' g = 0.74; LEFT DLPFC Hedges' g = 0.22). No publication bias correction was needed.

SF-36 Physical Function do not obtain a beneficial effect from the use of either rTMS or tDCS. Effect size results < 0.10 in all analyses, with mainly negative values. SF-36 Mental Health seems to undergo an adverse effect after the stimulation through tDCS (Hedges' g = -0.23; Standard Error = 0.04; CI 95% = -0.35 - -0.11), and when rTMS and tDCS are analyzed together Hedges' g = -0.25; Standard Error = 0.07; CI 95% = -0.43 – -0.07).

Follow-up were not analyzed because of the limited number of measures extracted from the studies and in view of the fact that limited to absent effect was found post-treatment.

Limitations to the current review can been found in studies major differences. Along with a large variety in the geographic locations, main dissimilarities interest the protocol of stimulation application in terms of signal intensity/frequency, sessions' number, and the protocol development in time. In addition, a wide range in sample sizes can be recognized through the different studies. 1 rTMS paper did not displayed enough results (Carretero et al., 2009), in addition to 7 tDCS studies (Arroyo-Fernandez, 2021; De Ridder, 2017; Gomez-Alvaro et al., 2022; Mendonca et al., 2011; Plazier et al. 2015; Valle et al., 2009; To, 2017). For this reason, they have been excluded for the meta-analysis. This last point becomes particularly relevant as concerns transparency and clarity in information and method displaying.

In conclusion, in contrast with previous works, no effect of rTMS or tDCS was found on pain, when publication bias adjustment is conducted. Quality of life, assessed through the condition specific FIQ, demonstrates an improvement only after rTMS intervention, considering stimulation of left M1 as better performative. Conversely, SF-36 Physical Functioning is not positively affected by rTMS or tDCS, while SF-36 Mental Health seems to undergo adverse effects after tDCS treatment. A general inconsistency of the estimated effects was demonstrated.

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