

Title: Non-invasive brain stimulation and non-invasive peripheral stimulation for neglect syndrome following Acquired Brain injury

Running Title: Non-invasive brain and peripheral stimulation for the treatment of neglect

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Abstract

Background: Hemispatial neglect is a frequent condition usually following non-dominant hemispheric brain injury. It strongly affects rehabilitation strategies and everyday life activities. It is associated with behavioural and cognitive disability with a strong impact on patient's life.

Methods: We reviewed the published literature on the use of non-invasive brain stimulation, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), and of non-invasive peripheral muscle stimulation, as therapeutic strategies for rehabilitation of neglect after acquired brain injury (ABI), such as in stroke or in traumatic injuries. The studies were grouped as controlled or uncontrolled studies in each stimulation technics.

Results: Thirty-four studies were identified and 16 on rTMS, 10 on tDCS and 8 on vibration. All studies were conducted in adult patients who suffered a stroke, except for one that was conducted in a patient suffering traumatic ABI and another that was conducted in a patient with brain tumour. In spite of significant variability in treatment protocols, patients' features and assessment of neglect, improvement was reported in almost all studies with no side effects.

Conclusion: Non-invasive brain stimulation and neuromuscular vibration are promising therapeutic neuromodulatory approaches for ~~treatment of~~ neglect. Further randomized-controlled studies are needed to corroborate their effectiveness as separate and combined techniques.

Keywords: Non-invasive-brain-stimulation; Neglect; Neuromuscular Vibration; Rehabilitation; Stroke; Acquired brain injury;

Introduction

Visuospatial neglect is a common and disabling condition following unilateral brain damage, especially right hemispheric stroke.¹ Its clinical presentation is characterized by unawareness of the side contralateral to the hemispheric lesion, with a strong attention shift to the ipsilateral side.

The clinical picture of neglect is variable, ranging from mild to profound degree of impairment. In severe cases, patients may be unaware of the entire hemispace and show inability to use their contralesional limbs even though they have little or no weakness (motor neglect).^{2,3} Importantly, neglect may be associated with anosognosia, denying the existence of the impairment.³⁻⁵

The pathophysiological bases of neglect are probably heterogeneous, as different lesion sites have been associated with the clinical picture.^{4,6-10} The syndrome is much more likely to occur with involvement of the right than of the left hemispheres.^{1,11} Classical studies from Vallar and Husain^{5,12} identified the right inferior parietal lobe (IPL) and temporoparietal junction (TPJ) as the most likely anatomical substrates of neglect. More recently, other cortical areas such as the inferior frontal lobe¹³ and the superior temporal gyrus (STG),¹⁴ have been also related to specific manifestations of neglect. Severity of neglect seems to depend on the extension of the lesion.^{5,15-18}

Different theories on the neural mechanism underlying neglect have been proposed: Various investigators postulated that there is a central deficit in the ability to direct the focus of attention to the left side in right hemisphere patients with neglect.¹⁹⁻²¹ The classical rivalry theory from Mesulam¹⁹ proposes that the right hemisphere directs attention to both visual hemifields, whereas the left hemisphere directs attention to the right visual field only.^{19,22} Hence, the left hemisphere is unable to compensate for the contralateral damage in the case of a right hemisphere lesion, thereby resulting in visual neglect of the left hemispace. Kinsbourne²⁰ proposed an interhemispheric competition theory, developed on the basis that each hemisphere directs attention to the contralateral visual field and is counterbalanced through reciprocal intercallosal inhibition. After a unilateral lesion, the lack of contralateral inhibition provokes the inability of disengaging from the ipsilateral hemispace leading to the neglect syndrome.^{21,23,24}

Nearly half of all stroke patients are affected by some degree of neglect during acute and subacute phases,²⁵ and chronic neglect will be diagnosed in up to 45% of those patients at 1 year.²⁶ Most data on neglect have been gathered from stroke patients and substantially less is known about the incidence of neglect following traumatic brain injury (TBI). Apart from a few case studies,^{27,28} two retrospective series of patients identified signs of neglect in up to 45% of TBI patients.^{29,30} The mechanisms of neglect in TBI patients are less well known than in stroke survivors. Only the presence of mass-effect of the lesions has been associated to the presence of neglect.³⁰ Interestingly, McKenna and colleagues,²⁹ found that the presence of neglect correlated better with worsened motor function than with cognitive impairment. The authors stated that, as in stroke patients, neglect from TBI primarily worsens motor function, even though its primary manifestation is in the perceptual sphere.

Visuospatial neglect has been associated with lower performance in sensory and motor abilities³¹⁻³⁴ in both, stroke patients and TBI survivors.^{30,35,36}

Apart from the impairment itself, neglect complicates treatment, as the syndrome is associated with behavioural and cognitive disabilities that affect the rehabilitation strategies.^{37,38} Since 1970, various approaches to the rehabilitation of visuospatial neglect have been investigated. Initially, rehabilitation used empirical techniques, such as visual or auditory cues in the left hemispace to facilitate gaze shifting towards the left, although those approaches required an effort that many subjects were not able to make.³⁹⁻⁴¹ More recently, authors proposed an approach based on bottom up stimulation, which used sensory stimulation maneuvers to modulate the spatial reference system by acting on various sensory afferents such as vestibular and galvanic stimulation⁴² but, even though the effects are evident, they only last for a short period of time.⁴² Prism adaptation is a simple technique which uses the adaptation of sensorimotor inputs to influence high level spatial representation^{43,44} and it has been proved to be effective.⁴⁵ Finally, various pharmacological therapies have been tried with inconsistent results.⁴⁶

More recently, various noninvasive brain stimulation (NIBS) approaches have been explored for the rehabilitation of neglect suffering patients. They are based on the stimulation effects on neuroplasticity and the modulation of neural functions, either facilitating or inhibiting neural networks, including

synaptogenesis and the generation of changes in the neurons affected, akin to those known as long term potentiation (LTP) and long term depression (LTD) observed in laboratory preparations.⁴⁷

Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) are the two most commonly used non-invasive stimulation strategies for visuospatial neglect treatment. tDCS delivers a continuous current (1–2 mA) over the scalp, through anodal and cathodal contacts.⁴⁸ tDCS does not produce action potentials in cortical neurons: it modifies the discharge rate of already active neurons. When the anode is placed over the primary motor cortex, tDCS is thought to increase firing by hyperpolarizing the dendrites and depolarizing the cell body of vertically oriented pyramidal neurons by <1mV. The opposite effect is observed when the cathode is over the motor cortex. It is postulated that long term effects on corticospinal excitability (after 10m or longer stimulation periods) are consequent to the up- or down-regulation of membrane receptors⁴⁸ that lead to LTP- or LTD-like changes in cortical synapses. In addition to the polarity of stimulation, effects are modulated by the duration, intensity and area of stimulation as well as the placement of the electrodes. rTMS is a non-invasive and painless procedure that modulates excitability of cortical motor areas, inducing long-lasting changes in the descending corticospinal tract and trans-synaptically at distant sites. High frequency rTMS (≥ 5 Hz) increases cortical excitability, whereas low frequency rTMS (≤ 1 Hz) decreases cortical excitability.⁴⁹ Theta burst stimulation (TBS) refers to a rTMS protocol where pulses are applied in bursts of three, delivered at a frequency of 50 Hz, with an inter-burst interval of 200 ms (5 Hz).⁵⁰ Intermittent TBS (iTBS) involves the delivery of TBS pulses for 2s followed by an 8-second rest for a total of about 3 minutes; this is hypothesized to induce LTP-like changes in neural networks,⁵⁰ whereas continuous TBS pulses for 40 seconds (cTBS) generates an effect similar to LTD.

The rationale of the use of rTMS or tDCS in neglect syndrome is the intention to re-establish the altered interhemispheric balance, as postulated by Kinsbourne^{20,51} and corroborated in more recent studies.⁵² The delivery of cathodal current⁴⁸ or low frequency rTMS^{49,53} (or cTBS) on the spared hemisphere is supposed to decrease activity in the targeted cortical region and,

therefore, diminish the enhanced inhibitory effect over the affected homologous contralateral region. On the other hand, the application of anodal tDCS,⁴⁸ high frequency rTMS or iTBS^{49,53} on the lesioned side is presumed to have a facilitatory effect on the underlying neurons, so that a functional remapping both online and offline of the perilesional areas is favoured.

Apart from cortical stimulation, peripheral stimulation has been used to treat visuospatial neglect. One such form of peripheral stimulation is neuromuscular vibration (NMV). NMV is a non-invasive stimulation method of the neuromuscular system. Under the definition of vibration therapies, different approaches have been developed: whole body vibration or non-invasive segmental (or focal) muscle vibration. NMV mainly focus on the ability of segmental vibration to modulate neuromuscular system in various neurological conditions. The rationale for using NMV in rehabilitation of neglect is that vibration on neck muscles could modulate sensory inputs from the peripheral sensory organs into body-centered reference allowing for improvement in spatial attention.⁵⁴ Preliminary studies on NMV showed promising results, reorienting the patient's attention when applied on the contralesional side.⁵⁵ Once activated by vibration, muscle spindles generate afferent inputs that can create an illusion of movement, as they are interpreted as a change in muscle length at the corresponding areas of the central nervous system.⁵⁶ When applied to the posterior neck muscles, such NMV-generated illusion can affect the entire egocentric coordinated system, shifting the center of attention towards the side where the NMV is applied.^{57,58} Interestingly, these effects can skip subjective awareness.⁵⁹⁻⁶¹

NMV may induce persistent excitability changes in the implicated central nervous system neuronal circuits⁶² that may be beneficial in various neurological diseases, such as stroke, spinal cord injury multiple sclerosis, Parkinson's' disease and dystonia.⁵⁷ Vibration is well tolerated, effective and easy to use. It could be used to reduce spasticity, to promote motor activity and motor learning, even in gait training, independent from aetiology of the neurological condition.⁵⁷ It is known from previous works that proprioceptive input from the muscle spindles provides information not only for the creation of a subjective map of the body, but also for the orientation of this map in the external world.⁶³ Moreover, it is known that segmental muscle vibration induce

changes in the sensorimotor cortex.^{64–66}

The use of NIBS to modulate cortical activity in a target area in patients with neglect was the topic of three recent meta-analysis.^{67–69} However, the authors found no clear positive effect of NIBS for the treatment of neglect following stroke. Some limitations in the scope of these meta-analysis must be pointed out: first, only cerebrovascular disease patients were included; secondly, the authors did not evaluate the type of sham used in the experiments and the blinding of evaluators, and third, the results suffered from bias due to small number of patients and strong heterogeneity of the protocol of NIBS applied with only few randomized controlled studies retrieved. Therefore, we considered that a wider scope of the review may be worth exploring. We decided to add patients with traumatic brain injury (TBI) to those with stroke, as NMV has seen to be effective in patients with TBI. Also, we added NMV to NIBS. Even though NIBS and NMV are two conceptually different treatment strategies for visuospatial neglect, a review of the effects of both may provide more solid ground for an eventual study of the combined effects of the two of them for a more effective therapy of visuospatial neglect, as already pointed out in a very recently published study.⁷⁰

Methods

We included articles published in English in PubMed, Cochrane Library and MEDLINE databases that explored neglect rehabilitation after acquired brain injuries in adults or pediatric patients up to March 2019. For the literature search, we used the terms “Non-invasive brain stimulation”, “non-invasive stimulation”, “repetitive transcranial magnetic stimulation (rTMS)”, “transcranial direct current stimulation (tDCS)”, “vibration”, “muscle vibration (NMV)”, “neck muscle vibration (NMV)”, “segmental vibration”, “Neglect”, “hemispatial neglect”, “visuomotor neglect”, “stroke”, “traumatic brain injury” and “rehabilitation”. We included only studies in which visuospatial neglect was quantified by using cancellation tasks (Albert’s task,⁷¹ Bells test⁷² or other cancellation tests^{107,109}), the line bisection test (LBT)⁷⁴ or more complex tests such as the behavioural inattention test (BIT)⁷⁵ or the Vienna test.⁷⁶ Articles exploring physiological mechanisms without clinical translation were excluded from the study.

We included uncontrolled and controlled studies. We defined a study as controlled if the study designed involved a control condition, either in the form of healthy subjects or placebo groups. Controlled studies were divided between randomized and non-randomized, according to whether or not a randomization process was described in the manuscript. We further separated reports of single cases or a small group of patients (less than 3) from studies including a larger group of patients and, lastly, blinded from unblinded studies, including them in the blinding group when at least the patients were blinded to treatment (Figure 1).

We examined demographic and clinical features of the patients (age, time since injury onset, number of subjects), stimulation characteristics (study design, NIBS or NMV protocol, site of stimulation, neglect assessment, outcome and follow up) and concomitant treatments including conventional rehabilitation (Table 1 and 2).

Results

Thirty-four studies were finally included that matched our search criteria.^{10,55,84–93,58,94–103,77,104–107,78–83} Figure 1 shows a schematic distribution of the studies according to the groups defined above. Tables 1 and 2 summarize the main points evaluated in each study. The number of participants in the studies varied widely from 1 to 32 patients. Patients' age ranged from 20 to 84 years. In 14 studies,^{55,79,102,104,105,107,82,83,85,91,97–99,101} the authors reported concomitant treatments such as occupational therapy, prism adaptation or other rehabilitation approaches. Most studies were performed during the chronic phase of the acquired brain injury (ABI).^{10,58,95,97,99,102,106,107,78,79,81,82,84,87,90,93} All studies were conducted in adult stroke patients, except for one in a patient with TBI⁸⁴ and another in a patient with brain tumor.⁵⁸ . No side effects were reported in any of the studies.

Clinical impairment, measured with acute stroke scales, was usually severe,^{58,91} although scarce clinical data other than neglect were usually supplied. The affected hemisphere was the right in all the studies retrieved. The severity of the neglect was clearly reported in only 7 studies (20.6%)^{55,58,81,89,91,101,106} and was classified as severe in all of them (table 1).

Transcranial Magnetic stimulation (TMS):

The effects of rTMS on neglect were reported in 16 articles.^{77,78,88,102–105,108,79–84,86,87} In all of them, rTMS was applied over the parietal cortex of the unaffected hemisphere. In the majority of the studies, the authors applied inhibitory stimulation, such as LFrTMS (7 studies; 43.5%)^{77–80,82,85,87,103} or cTBS (7 studies; 43.5%).^{81,83,84,86,102,104,105} HFrTMS was used as a stand-alone treatment method in only one open label study (6.5%)⁹³ and iTBS was applied over the dorsolateral prefrontal cortex (DLPFC) in another study.⁷⁷

In most studies^{55,79,100–102,104,105,107,108,82,83,86,91,93,96–98}, patients continued other forms of therapy, while rTMS was added-on. In these instances, significantly more improvement is reported with the addition of rTMS than with conventional therapy alone, although no information is given on whether the effect was maintained or not. The number of therapy sessions used ranged between 1 and 20 in a two weeks period. The usual session duration was 30 minutes (table 2), except for TBS sessions, which duration was less than 1 minute. The number of pulses per session varied between 600 and 1200 (table 2). A true sham coil was used in only 4 studies (25%),^{81,83,87,104} while other sham strategies included a reversed coil¹⁰² (scalp facing the “inactive” side of the coil) or holding the coil perpendicular to the scalp.^{77,85,86,103,105}

Some degree of improvement in the tests used to assess neglect was reported in all studies. In some of them, neuroimaging methods were also used to examine a possible surrogate of the clinical changes: Shindo et al.⁷⁹ failed to show a significant change in brain activity by single photon emission tomography performed just after the last session. Bonni et al.⁸⁴ showed a bilateral increase of functional connectivity in the frontoparietal network in 1 patient suffering neglect after TBI who underwent 7 sessions of cTBS over the left parietal cortex (P3). Cao et al.⁸⁸ found a large-scale reduction in the resting state fMRI connectivity extent in the right attention network in patients receiving iTBS over the left DLPFC. In a prospective, double-blind, sham-controlled trial, Kim et al.⁸⁵ compared LFrTMS over the unaffected parietal cortex versus HFrTMS over the affected parietal cortex and found no differences between the two forms of real stimulation, which were significantly more effective than sham stimulation in several neglect-assessment tests, although patients reported no clear improvement in daily life activity.

In several randomized sham-controlled LFrTMS studies^{80,87,102,103,108}, the authors reported improvement of neglect for up to 1 week after treatment. In those using cTBS^{83,86,102,104,105} the authors found improvement that lasted a variable time after treatment, ranging from 2 weeks after 2 daily sessions for 10 days¹⁰⁵, to 4 weeks after 2 daily sessions for 2 weeks⁸⁶. A modified cTBS protocol was investigated by Nyffeler and colleagues.⁸¹ The protocol consisted of 801 pulses delivered in 267 bursts of 3 pulses at 30 Hz, repeated every 100 ms. The authors reported a benefit that lasted up to 32 hours after a single session of 4 TBS trains. Using the same protocol but doubling the number of TBS trains (4 each day in two consecutive days), Cazzoli et al.⁸³ found a strong improvement in test performance that persisted 3 weeks after the treatment.

HFrTMS over the unaffected hemisphere was used as a stand-alone method for treatment by Oliveri et al.⁷⁷ in an uncontrolled, open-label, study. These authors intended to produce a transient virtual lesion to diminish the inhibitory effect over the homologous area in the affected hemisphere. The beneficial effects were short-lasting. More recently, Yang et al.¹⁰² compared three different rTMS modalities, delivered on the left hemisphere, LFrTMS, HFrTMS and cTBS, against sham, in 38 stroke patients. All treatments lasted for 2 weeks while patients were engaged in an intense rehabilitation therapy program. The authors found that cTBS, applied according to the protocol described above for Nyffeler et al.,⁸¹ produced the stronger effect, followed by LFrTMS and, then, HFrTMS, which all were significantly different from sham. The improvement was still present at 1 month follow-up.

tDCS

The effects of tDCS on neglect were reported in 10 articles.^{10,89-94,101,106,107} In 3 of them, the authors explored the effects of anodal current over the affected parietal cortex with the cathode over the contralateral supraorbital region.^{89,93,94,101,106} In the remaining studies, the anode was placed over the affected posterior parietal cortex and the cathode over the contralateral, unaffected, area.^{10,90,92,107} The number of therapy sessions ranged from 1 to 15 and the average duration of each session was 20 minutes. The intensity used was between 1 and 2 mA. All studies included a control group either as a

separate sham stimulation group or in a cross-over design. All but one study,¹⁰⁶ showed some degree of improvement in hemineglect syndrome.

Sparing et al.¹⁰ used a cross-over study design to investigate the effects of anodal vs cathodal stimulation. Ten patients with right hemispheric stroke received anodal or cathodal stimulation over the unaffected hemisphere, anodal stimulation over the affected hemisphere or placebo stimulation. All the stimulations were performed on different days in a randomized fashion. The authors found that both the cathodal tDCS applied over the unaffected hemisphere and anodal tDCS applied over the affected hemisphere ameliorated hemi-spatial neglect. Similar methods were used by Ladavas et al.,¹⁰⁷ who demonstrated that only anodal stimulation over the right parietal cortex led to a significantly more improvement in the prism adaptation task than sham, while no amelioration beyond sham was seen in the cathodal stimulation over the left parietal cortex.

Sunwoo et al.⁹⁰ compared the effects of dual stimulation (anode over the affected parietal cortex and cathode over the unaffected parietal cortex) with single anodal stimulation (anode over the affected parietal cortex and cathode over the contralateral supraorbital area) and concluded that both stimulation modalities led to improvement, but this was significantly larger with the dual stimulation method than with the single anodal stimulation method. Biparietal tDCS was also found to potentiate the beneficial effects of rehabilitation in a double blind, sham-controlled study of a single case,⁹¹ as well as of an optokinetic task in a group of 32 patients.¹⁰¹ In both studies, the effect was maintained for some time after treatment: up to 1 month in the single patient and up to 6 days as a mean in the group study. A similar benefit of combined therapies was reported by Bang et al.⁹³ using just anodal stimulation of the left parietal cortex (with cathode placed over the contralateral supraorbital area). The study was carried out in a group of patients submitted to feedback training, who exhibited a significant improvement in all measuring tests when real tDCS was added to the treatment.

Smit et al.¹⁰⁶ carried out a double-blind, placebo-controlled study of the effects of a biparietal stimulation montage (anode on P4 and cathode on P3) in 5 patients with severe chronic hemispatial neglect, after exclusion of a large number of patients because of contraindications for stimulation, presence of

other medical conditions or only mild neglect. In their study, these authors did not find differences between real tDCS or placebo, applied for 20 minutes with an intensity of 2 mA during 5 consecutive days.

NMV

The effects of NMV on neglect were reported in 8 articles.^{58,61,84–89} They were all carried out in chronic stroke patients, with a study population varying from a single subject to 20 patients. The vibration utilized ranged from 80 to 600Hz and the most common used site of treatment delivery was the posterior neck muscles contralateral to the affected hemisphere. Only 3 studies (37.5%) repeated the NMV sessions more than once.^{55,98,100} In most studies, NMV was applied in addition to various forms of neglect therapy. In 5 studies,^{95–97,99,100} such therapy was used as a control condition and, in all of them, there was significantly more improvement with NMV. Duration of the improvement was up to 1.4 years in 6 patients studied by Johanssen et al.⁹⁸

Karnath et al.⁹⁵ examined the effects of neck muscle NMV on neglect symptoms in three patients with right hemisphere lesions. The authors used different conditions of trunk rotation while the patients were asked to identify visual stimuli in both hemi-visual fields. They found that NMV applied to the left side of the neck improved the detection of the stimuli presented, hypothesizing a shift of the body centre induced by the applied vibration. To further investigate their results, the same authors compared contralateral neck vibration with electrical stimulation and hand vibration⁹⁶. Only the neck vibration significantly improved the performance in cancellation and copying tasks, with no or little effect of the other modalities. The authors hypothesized that the Ia fibres are directly involved in representation of the egocentric space.

Discussion

Our systematic review explores the use of non-invasive stimulation technics which includes brain stimulation (NIBS) and muscle vibration stimulations (NMV) to improve neglect syndrome following acquired brain injury. Almost all non-invasive stimulation treatments (rTMS, tDCS or NMV) included in

this review reported a significant improvement of neglect in observational as well as in controlled studies. The single exception being the lack of tDCS effect reported by Smit et al.¹⁰⁶ in a group of 5 patients with severe chronic neglect after a right hemisphere stroke. On the other side, no-one reported improvement in control or sham group. Randomized studies including placebo group are important to validate the effectiveness of the neuromodulation therapies. Our study has shown more methodological variability in the approach to the design of the control condition in rTMS and NMV studies than in tDCS studies, but results were consistently similar in all therapies.

In overall, results were promising for improvement of neglect regardless of (i) whether the stimulation is applied to the brain or to the muscle, (ii) what stimulation technique is used; (iii) whether the study is controlled, blinded or randomized. Remarkably, however, only one study⁸³ explored the effects of treatment in daily life activities, while only two studies reported improvement in functional scales such as Catherine Bergego Scale.^{85,92}

In most instances, brain stimulation was applied in order to inhibit activity in the unaffected hemisphere: LFrTMS or cathodal tDCS over the unaffected parietal cortex (P3-P5, according to EEG nomenclature). Non-invasive brain stimulation for stroke is based on the interhemispheric competition model facilitating ipsilesional cortical excitability and suppressing contralesional cortical excitability for balancing cortical excitability and interhemispheric inhibition levels between hemispheres.^{109–111} In these studies, rTMS and tDCS were predominantly used to decrease the hyperactivity of the unaffected hemisphere, hence diminishing its excess inhibitory effect over the damaged hemisphere.⁴⁹ In fact, unilateral neglect is thought to be secondary to an imbalance in interhemispheric rivalry.¹¹² The decrease in interhemispheric inhibition from the affected to the unaffected hemisphere may lead to an exaggerated activity of the healthy hemisphere, which in turn force the deviation of the attention of the subject from the affected hemibody towards the contralateral one.²⁵ Brain stimulation therapies are intended to restore the disrupted interhemispheric balance by inhibiting the unaffected hemisphere,⁴⁹ activating the affected hemisphere or both. NMV is intended to increase the saliency of sensory inputs to the lesioned hemisphere⁵⁷ and potentiate in this way the patient's awareness of the contralateral hemi-space.

The following points determine the potential interest of the present review for future studies:

- A) There was a substantial variability of the size of study population, varying between single case studies and a study group of up to 32 patients.
- B) There is a scarcity of studies on efficacy and clinical relevance of the results for daily life activity, data being limited to experimental tests.
- C) The associated neurological deficits and comorbidities are not usually considered.
- D) The results obtained with rTMS and tDCS are consistent with the pathophysiological concepts derived from the theory of inter-hemispheric competition and, therefore, favor these pathophysiological mechanisms as those underlying neglect.
- E) There is need for refinement of stimulation methods for rTMS (type, intensity, duration and frequency of the sessions), tDCS (number of sessions, duration, exact location) and NMV (frequency, stimulation site and side, number of sessions) to define the optimal stimulation protocols.
- F) The safety and secondary effects of long-term effects of repeated sessions for rTMS, tDCS and NMV should be considered in relation to the benefit obtained. This mainly refers to long term follow-up, which has not been longer than 6 weeks in most of the studies reviewed.
- G) Optimal post-stroke delay (acute vs chronic state) has not been defined yet, in terms of effectiveness or harmlessness.
- H) The selection of patients that could benefit more from stimulation treatments must consider location and size of the lesion, clinical characteristics, severity of hemineglect.
- I) Combined care management within a neuromodulation approach should be explored.

Our results complement those published in previous metanalysis on the efficacy of NIBS for treatment of unilateral neglect.⁶⁷⁻⁶⁹ Although the authors found mild evidence of the efficacy of rTMS for the treatment of neglect, no

significant positive effect was found regarding tDCS. Furthermore, recently 1 systematic review on TBS and neglect¹¹³ found a positive effect on the symptoms although a strong heterogeneity of protocols and assessment was found. As stated, only cerebrovascular disease patients were included, the results were biased by the small number of patients and strong heterogeneity of the protocol of NIBS.

Consequently, we widened the scope of the previous reviews adding, patients suffering brain tumor and traumatic brain injury, and , more importantly we included studies exploring the use of NMV for neglect treatment.

Recently Perasso et al.⁷⁰ investigated the possibility to consolidate the cortical aftereffect of NMV by combining tendon vibration with a concomitant high-frequency 5-Hz rTMS protocol. The group found that this protocol induced a pattern of unbalanced M1 excitability between vibrated muscle and its antagonist with increased excitability of the agonist and decreased excitability of the antagonist muscle cortical areas, which persisted up to 30 min, demonstrating a synergic effect. Those neuromodulatory strategies have a different mechanism of action, although a synergic effect might hypothetically exist, given the mostly top down use of NIBS and the bottom up effect of NMV. Thus, the combination of different therapies, based on complementary and synergic effects might be a new and important field of investigation.

In conclusion, non-invasive stimulation, either of the brain (rTMS or tDCS) or the muscle (NMV) is a promising addition to the treatment of neglect. In addition, non-invasive stimulation tools combined with specific training methods could induce sustainable and functional improvement. There is a need for further investigations with randomized sham controlled trials that include large samples and evaluate the long term efficacy of repeated sessions of non-invasive stimulation procedures. The combination of rTMS or tDCS with NMV is of special interest, as it has demonstrated its feasibility in a recent study.⁷⁶ Future studies should include the evaluation of effects on activities of daily living and the potential transfer to daily life situations.

Clinical Message

- Non-invasive brain modulation and neuromuscular vibration are effective tools to improve neglect after stroke although the heterogeneity of studies is high.
- Combination of different treatments may improve the outcome
- Further randomized controlled large-sample trials are needed

Conflicting interests:

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Table 1 . Clinical and demographical features of patients included in the studies reviewed.

Author, year	NIBS	Stroke / TBI	N of patients	Severity of lesion	Age, y	Duration, d/w/m/y	Concomitant treatments
UNCONTROLLED STUDIES							
Olivieri, 2001 (31)	rTMS	Stroke	7	N/A	between 54-79	1-48 w	N/A
Brighina, 2003 (33)	rTMS	Stroke	3	N/A	between 46-67	4-6 m	N/A
Shindo, 2006 (22)	rTMS	Stroke	2	N/A	between: 59 -61	6 m	OT, PT 5 times/ week without special adaptations or treatment for USN.
Bonni, 2013 (19)	rTMS	TBI	1	N/A	20	2y	N/A
Cao, 2016 (37)	rTMS	Stroke	10	N/A	mean: 55 ± 12	32 ± 17 d	N/A
Johannsen, 2003 (27)	NMV	Stroke	6	N/A	between 54-77	19–159 d	CT: PT, OT, NPT.
Pitteri, 2013	NMV	<u>Stroke</u>	1	Severe	43	63 d	CT
Ceyte, 2018 (20)	NMV	Stroke	1	NIHSS. 17	53	18 m	N/A
CONTROLLED STUDIES							
Song, 2009 (32))	rTMS	Stroke	14	N/A	between 43 -80	15 -60 d	N/A
Nyffeler, 2009 (30)	rTMS	Stroke	11	moderate to severe	between 40-69	4-36 m	N/A
Lim, 2010 (23)	rTMS	Stroke	7	N/A	mean: 68±11.4	9 – 330 d	OT
Koch 2012	rTMS	Stroke	20	N/A	N/A	N/A	CT/OT
Cazzoli, 2012 (24)	rTMS	Stroke	24	N/A	mean: 58±2.2	26 ±4.4 d	OT, NPT, PT
Kim, 2013 (21)	rTMS	Stroke	27	N/A	mean 68 ± 14	14 d	CT, PT, OT,

							cognitive therapies
Agosta, 2014	rTMS	Stroke	6	N/A	between 51 -78	8 – 33 m	N/A
Hopfner, 2015	rTMS	Stroke	18	N/A	mean: 62±10.6	18 - 63 d	Smooth pursuit eye movement training
Yang, 2015	rTMS	Stroke	38	N/A	mean: 48±12	100 ±38 d	CT
Fu, 2015 (36)	rTMS	Stroke	22	N/A	between :37-78	17-114 d	CT
Cha, 2015 (34)	rTMS	Stroke	30	N/A	mean: 64 ± 12.1	4 ±1 m	N/A
Ko, 2008 (29)	tDCS	Stroke	15	Moderate to severe	between :44-74	31-83 d	N/A
Sparing, 2009 (39)	tDCS	Stroke	10	N/A	mean: 57.3±16.9	2.9±3.5 m	N/A
Sunwoo, 2013 (38)	tDCS	Stroke	10	N/A	mean:62.6±13.3	27.8±60.4 m	N/A
Brem, 2014 (25)	tDCS	Stroke	1	NIHSS 11	72	26 d	BT
You Gyoung Yi, 2015 (40)	tDCS	Stroke	32	N/A	between 39-82	N/A	N/A
Bang, 2015 (42)	tDCS	Stroke	6	N/A	mean:66.0 ± 4.2	6.5 ± 1.6	CT
Smit, 2015	tDCS	Stroke	5	Severe (BI 10-18)	between 52 - 76	1 – 12 y	N/A
Ladavas, 2015	tDCS	Stroke	30	N/A	between 46 - 80	2 – 8 m	Prism Adaptation
Turgut, 2016	tDCS	Stroke	32	Moderate (BI 23±10)	mean: 68.6 ±2.2	20 ± 15 d	Optokinetic drift
Bornheim, 2017 (41)	tDCS	Stroke	4	N/A	between 59-74	2 d	N/A
Karnath, 1993 (43)	NMV	Stroke	8	N/A	between 44-84	20 d-43 m	N/A
Karnath, 1995 (44)	NMV	Stroke	4	N/A	between 48-61	5-115 d	TENS
Schindler, 2002 (26)	NMV	Stroke	20	N/A	between 24-78	2-30 m	Visual exploration training
Saevarsson 2010	NMV	Stroke and brain	12	NA	between 47-83	3-57 m	Prism adaptation

(28)		tumor					
Kamada, 2011 (45)	NMV	<u>Stroke</u>	11	N/A	between 54–79	4–17 w	CT, OT

n: number of patients; N/A: not available; d:day;w:week; m:month; y:year; rTMS: repetitive transcranial stimulation; tDCS: transcranial direct current stimulation; NMV: neuromuscular vibration; USN: unilateral spatial neglect; TBI: traumatic brain injury; NIHSS: National Institute of Health Stroke Scale; TENS: transcutaneous electrical nerve stimulation; BT: Behavioural therapy; OT: occupational therapy; CT: conventional treatment ; PT: physiotherapy; NPT: neuropsychological training; BI: Barthel Index.