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ASSOCIATION BETWEEN NEUROPATHIC PAIN AND DEPRESSION: FOCUSING ON THE TRANSCRANIAL MAGNETIC STIMULATION AS A PROMISING TREATMENT APPROACH

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SUMMARY

Background: *Neuropathic pain (NP) affects approximately 7% of the general population and is often accompanied by depressive symptoms with up to 85% of NP patients* are suffering from comorbid depression (CD). *The noninvasive neuromodulation technique of transcranial magnetic stimulation (TMS) is an established proven clinically effective nonpharmacological treatment for depression, and considered a highly promising option also for reducing the burden of NP by relieving pain perception and increasing patients' quality of life. In this article, we systematically review the various clinical protocols used in TMS treatments in patients suffering from NP and comorbid depression.*

Subjects and methods: *Using Scopus, Elsevier, and PubMed databases, our keyword search identified 639 articles, of which 22 were selected for detailed analysis based on the inclusion criteria and in consideration of the heterogeneous study design of the majority of small trials. We evaluated the clinical efficacy in NP and comorbid depression, in relation to various TMS protocol parameters including coil type, target brain area, locus of increased evoked motor potential, amplitude of stimulation, duration of session, number of sessions per day/month, as well as inter-session-intervals, number and frequency of trains, and number and frequency of pulses.*

Results: *The most effective TMS protocols for treating comorbid NP and depression, as marked by decreased pain and depression scores proved to entail figure-of-8 coils targeting the primary motor area (M1), and applying at least ten daily rTMS sessions using high frequency stimulation (10-20 Hz) with a sub threshold intensity of 80-90% RMT and a total number of pulses of at least 1500 per session. Performing an additional maintenance phase after the acute treatment phase may strengthen and prolong the therapeutic effects of rTMS.*

Conclusions: *Our database analysis suggests that a specific combination of TMS parameters is most effective for treating NP and comorbid depression. Although results are promising, the heterogeneity within the literature is such that many underpowered studies contribute rather little to the outcome, as evident by our inclusion / exclusion analysis. Moreover, we see a need for consensus on clinical protocols and inclusion of much larger clinical samples. Furthermore, we conclude that future research should entail advanced TMS procedures with multiple brain region stimulation (sequential or concurrent), and address issues of TMS maintenance and improved coil engineering for targeting deeper structures.*

Key words: *review - neuropathic pain - neuropsychiatry - comorbid depression - transcranial magnetic stimulation*

Abbreviations: *CD – comorbid depression; DLPFC – dorsolateral prefrontal cortex; F-8-C – figure-of-eight coil; IP – intertrain pause; MeP – motor evoked potentials; NP – neuropathic pain; RMT – resting motor threshold; rTMS – repeated transcranial magnetic stimulation*

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INTRODUCTION

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience, associated with actual or potential tissue injury or described in terms suggestive of such injury", pointing out at pain as one of the most common reasons for contacting a medical facility (Cherif et al. 2020). IASP defines neuropathic pain (NP) as a "pain associated with an injury or disease affecting the somatosensory system". NP affects approximately 7% of the general population (Cherif et al. 2020), and is often resistant

to analgesic treatments (Koutsomitros et al. 2021, Llorca-Torralba et al. 2022), causing many additional and secondary problems with 18-85% of NP patients suffering from comorbid depression (CD). Furthermore, up to one-third of patients with NP and depression comorbidity have severe CD, leading to even more complications and a high risk of suicide (Akram & Malik 2019). CD further reduces the already low efficacy of NP therapy and significantly decreases the quality of patient's lives (Llorca-Torralba et al. 2022), thus calling for new treatment approaches.

Repetitive transcranial magnetic stimulation (rTMS) is a procedure for noninvasive magnetic brain stimulation with repetitive rhythmic patterns causing small focal electrical currents in the cerebral cortex (Leung et al. 2020). In the European Union (EU), TMS is approved for depression and chronic pain treatment (MedGadget 2012). Ongoing research is aiming to optimize TMS protocols for the treatment of NP and CD with new studies appearing every year. In this article, we systematically reviewed the existing literature on TMS protocols for treating NP and depression comorbidity and aimed to identify the TMS parameters that currently seem most promising for managing NP and CD.

SUBJECTS AND METHODS

In our study we conducted a search in the Scopus, Elsevier, and PubMed databases using the search term combinations "transcranial magnetic stimulation AND pain AND depression", and "transcranial magnetic stimulation AND neuropathic pain" over the last decade. We identified 639 articles, of which 22 we included in our analysis. Inclusion criteria were: use of rTMS in therapy of NP and CD; NP as a primary condition; assessment of changes in NP and CD with validated scales; sham-controlled study. Exclusion criteria were: non-neuropathic origins of pain; less than two assessments of NP and CD; absence of rTMS parameters data and NP and CD score changes after treatment. During the analysis we evaluated the efficacy in NP and CD treatment depending on various TMS protocol parameters including coil type, targeted brain area, locus of gained motor evoked potentials (MeP), amplitude of stimulation, duration of session, number of sessions per day/month and inter-session-intervals, number and frequency of trains, and number and frequency of pulses.

RESULTS

Lefaucheur et al. (2020) published recommendations regarding the clinical efficacy of rTMS for a large number of different neurological and psychiatric conditions, including NP and depression. They concluded that HF rTMS targeted at the contralateral primary motor cortex (M1) using a figure-of-8 coil (F-8-C) is definitely efficient in the treatment of NP in the context of postherpetic neuralgia (PHN). They also reported positive correlations between the general number of pulses and frequency and duration of the treatment effects (Nurmikko et al. 2016, Attal et al. 2016, Ma et al. 2015). This result was confirmed by Pei et al. (2019). Pei et al. (2019) also studied the efficacy difference between 5 and 10 Hz rTMS of contralateral M1 in patients with NP caused by PHN. The decrease in pain scores for the 10-Hz group was significantly stronger as compared to the 5-Hz group ($p<0.01$). Leung et al. (2020) confirmed the efficacy of this protocol for NP of cerebral origin with mild CD, and Khedr et al. (2015) reported positive results for malignant NP. The study of Hodaj et al. (2020) proved efficacy of the same HF rTMS protocol on patients with chronic orofacial, pudendal and limb NP. Lin et al. (2018), Zhao et al. (2021) and Ojala et al. (2021) found the rTMS protocol recommended by Lefaucheur et al. (2020) to be effective in relieving NP caused by stroke. Li et al. (2022) found this protocol promising in the treatment of NP arising from spinal cord injury. However, only five (Ma et al. 2015, Lin et al. 2018, Hodaj et al. 2020, Leung et al. 2020, Zhao et al. 2021) of these nine studies found the recommended rTMS protocol to be efficient for the treatment of both NP and CD. The recommended rTMS protocol was modified in three of five studies with positive results in both NP and CD. Ma et al. (2015) performed rTMS with 300 trains lasting 5 s and an intertrain pause (IP) of 3 s, for a total of 15,000 pulses per 40-minute session. Hodaj et al. (2020) conducted 12 daily inductive rTMS sessions for three weeks and ten maintenance sessions for the next five months, whereas Zhao et al. (2021) performed 18 daily sessions over three weeks, instead of ten over two weeks as generally recommended. Moreover, the studies that used shorter protocols and lower rTMS parameters showed lower efficacy and lower persistence of therapeutic effects equally for relief of NP and CD (Nurmikko et al. 2016, Attal et al. 2016, Hosomi et al. 2020). Therefore we conclude that the generally recommended rTMS protocol for NP is apparently insufficient for managing CD in NP, but needs to be extended.

Several works studied the effects of rTMS protocols with other coil types and targeted brain areas other than M1. Thus, Cervigni et al. (2018) invetsigated the effects of HF rTMS on patients with NP due to bladder disorders, utilizing the so-called H-coil for bilateral stimulation of the M1 regions, with a results of significantly decreased pain scores decrease, but no improvement in CD scores. Hodaj et al. (2020) used F-8-C coils for contralateral M1 HF rTMS in patients with orofacial pain, upper limb, or hemibody pain, and targeted the cranial vertex for patients with pudendal neuralgia or lower limb pain; they found reductions in pain and CD scores at the end of the maintenance phase (Hodaj et al. 2020). Leung et al. (2020) recommend performing of HF rTMS using F-8-C over the left DLPFC in patients with NP of cerebral origin and severe CD, in a study also including a maintenance phase.

Galhardoni et al. (2019) studied rTMS using double-cone and H-6 coils on patients with NP caused by stroke or spinal cord lesions, founding no difference in pain and CD scores as compared to a control group. Ojala et al. (2021) utilized F-8-C coils to compare the effects of HF rTMS targeting the contralateral M1 and at the secondary somatosensory cortex (S2). For NP, they considered 41% of patients in each group to be short-term responders, versus 18% long-term responders for S2-stimulated patients and only 6% long-term responders for M1-stimulation; there were no concomitant decreases in CD scores in either groups. That study also reported that the stimulation of M1 was more efficient in patients with the homozygous dopamine D2 receptor T/T genotype, and that there were no differences between rTMS effects in groups of patients with various SNVs of the *COMT* and *BDNF* genes (p=0.039) (Ojala et al. 2021). The meta-analysis performed by Yu et al. (2020) showed that HF rTMS using F-8-C targeted at the DLPFC, M1, or cervical segments was without effect on pain perception in patients with spinal cord injury. Lefaucheur et al. (2020) stated that stimulation of other than M1 brain areas did not affect the changes in NP perception (Onesti et al. 2013, Shimizu et al. 2017, Yilmaz et al. 2014, Defrin et al. 2007, Kang et al. 2009).

There is also a variability of the choice of F-8-C orientation among studies. Khedr et al. 2015 used F-8-C oriented parallel to the interhemispheric midsagittal line, and Lin et al. (2018) used F-8-C oriented 45° at posterior to the midline. Both studies reported some efficacy of HF rTMS in NP and CD. Other works did not report the applied F-8-C orientation.

Thus, we find that older studies applying HF rTMS using F-8-C targeted at areas other than M1 are not encouraging for the management of CD in NP patients (Onesti et al. 2013, Shimizu et al. 2017, Yilmaz et al. 2014, Defrin et al. 2007, Kang et al. 2009, Lefaucheur et al. 2020). Two more recent studies also reported that HF rTMS using F-8-C over M1 is without great efficacy (Ojala et al. 2021, Yu et al. 2020), although S2 stimulation may be promising in NP treatment (Ojala et al. 2021). Two other studies found HF rTMS using F-8-C targeted at the vertex or the DLPFC to be effective in managing both NP and CD (Leung et al. 2020, Hodaj et al. 2020). One study reported efficacy of HF rTMS using H-coils for bilateral stimulation of the M1 region (Cervigni et al. 2018), whereas another study reported that using a double-cone and H-6 coil was ineffective (Galhardoni et al. 2019). Thus, the data regarding alternative cortical targeting are inconsistent and incomplete, calling for further research targeting other areas and using different types of coils with different penetration strengths and orientation options.

Several studies also looked at the long-term efficacy of HF rTMS in NP and CD (Ma et al. 2015, Khedr et al. 2015, Cervigni et al. 2018, Hodaj et al. 2020, Ojala et al. 2021, Lin et al. 2018). The effects of HF rTMS lasted as long as three months in the study with a total of 15,000 pulses (Ma et al. 2015), although the most stable effects were achieved conducting an additional five-months maintenance phase (Ojala et al. 2021). The results of these two latter studies highlight the importance of modifications exceeding the usually recommended HF rTMS protocol and the importance of an a priori TMS maintenance strategy in clinical practice.

DISCUSSION

The generally recommended rTMS protocol for NP (Lefaucheur et al. 2020) is apparently insufficient for managing CD in NP patients, but needs to be extended by increasing the number of rTMS sessions and total pulses, and also by implementing a TMS maintenance therapy following the acute treatment with rTMS (Ma et al. 2015, Hodaj et al. 2020, Zhao et al. 2021). The use of other than the F-8-C coil types for targeting either DLPFC, S2, or cervical segments without rTMS protocol extension are apparently ineffective in NP with CD treatment (Onesti et al. 2013, Shimizu et al. 2017, Yilmaz et al. 2014, Defrin et al. 2007, Kang et al. 2009).

The present analysis of original research studies and associated review articles on the use of rTMS for treating NP and CD showed a noticeable variety and heterogeneity of TMS equipment, study designs, clinical TMS protocols and TMS procedures being used. This is a general problem and limitation for the field of TMS therapy, and it makes the formulation of clear recommendations for effective protocols challenging. Nonetheless, it becomes apparent that the most frequently used coil type was the F-8-C, albeit with variations in the orientation: with some researchers (Khedr et al. 2015) orienting the coil parallel to the interhemispheric midsagittal line, and others (Lin et al. 2018) placing the coil at 45° posterior to the midline. Unfortunately, many other studies do not report the F-8-C orientation, which should by now be a standard in methods sections of every TMS study. Two studies used a double-cone coil and H-coil instead of a standard F-8-C (Galhardoni et al. 2019, Hosomi et al. 2020). The most frequently stimulated brain area for treating NP and CD was M1 contralateral to the site of the pain. Nonetheless, several studies also assessed the effects of rTMS applied over the vertex (Hosomi et al. 2020), contralateral S2 (Ojala et al. 2021), bilateral M1 (Cervigni et al. 2018) and/or left DLPFC (Leung et al. 2020). The most commonly performed number of rTMS sessions applied in this patient population was ten over the course of two weeks. Interestingly, one of the studies used two phases of rTMS application: an induction phase with 12 sessions for three weeks and a maintenance phase with one biweekly session during the next five months (Hosomi et al. 2020), with some indication that the maintenance phase

Table 1. Summary of rTMS protocols parameters used across the original studies targeting the neuropathic pain and its comorbid depression

Authors	Primary condition	Type of the coil	Area of stimulation	Session	Train	Frequency and intensity	Area of RMT obtaining	Assessment instruments	Results
Ma et al. 2015, Lefaucheur et al. 2020	Postherpetic neuralgia	Figure-of-8	Contralateral M1	№10 over 2 weeks; 40-min durability	№300; 5s durability; 3s interval; 15000 pulses	10 Hz; 80% RMT	Abductor pollicis brevis muscle	VAS, QOL scale	50% were considered responders; average pain reduction 50%, lasting for 3 months ($p<0.01$)
Pei et al. 2019	NP caused by postherpetic neuralgia	Figure-of-8	Contralateral M1	№15 over 3 weeks; 17.5-min durability	№300; 1500 pulses 5 Hz: 1s durability; 2.5s interval; 10 Hz: 0.5s durability; 3s interval;	5 Hz; 80% RMT 10 Hz; 80% RMT	Abductor pollicis brevis muscle	VAS, SF-MPQ, SDS, PGIC, PCS and MCS of SF-36	The decrease in pain scores of the 10-Hz group was significantly stronger than that of the 5-Hz group ($p<0.01$). There was no difference in depression and QoL scores between these groups ($p<0.01$)
Khedr et al. 2015, Lefaucheur et al. 2020	Malignant NP	Figure-of-8 coil, oriented parallel to the interhemispheric midsagittal line	Contralateral M1	№10 over 2 weeks; 7-min durability	№10; 10s durability; 30s interval; 2000 pulses	20 Hz; 80% RMT	Abductor pollicis brevis muscle	VAS, VDS, LANSS, HAM-D	80% responders; average pain reduction 50%; duration of the effects was less than 1 month ($p<0.01$)
Cervigni et al. 2018	Bladder disorders	H-coil	Bilateral M1	№10 over 2 weeks; 20-min durability	№30; 2.5s durability; 30s interval; 1500 pulses	20 Hz; 110% RMT	Anterior tibial muscle	VAS, FPPS, NPSI, MPQ, OABq, BDI	Pain decrease at least 3 weeks after the last session ($p<0.01$); reduction in depression scores was not observed
Galhardoni et al. 2019	NP caused by stroke or spinal cord lesions	Double-cone; H-6	Bilateral anterior cingulate cortex	№15 over 3 weeks; 15-min durability	№15; 10s durability; 50s interval; 1500 pulses	10 Hz; 90% RMT	Anterior tibial muscle	VAS, HAM-D	The results stated no difference in pain and depression scores with control groups ($p<0.01$)
Hodaj et al. 2020	Chronic orofacial, pudendal and limb NP	Figure-of-8	Contralateral M1 for orofacial pain, upper limb or hemibody pain; Vertex for pudendal neuralgia or lower limb pain	№12 daily inductive rTMS sessions for 3 weeks, №10 maintenance sessions for next 5 month; 20-min durability	№40; 5s durability; 25s interval; 2000 pulses	10 Hz; 80% RMT	Anterior tibial muscle	NPSI, HADS, PCS, MCS of SF-36	Responders were more than two-third of patients, there was a reduction in pain and depression scores at the end of maintenance phase ($p<0.01$)

Note: NP - neuropathic pain; RMT - resting motor threshold; scales used mentioned in the order of presenting in the Table: VAS - Visual Analog Scale; QOL - Quality of Life scale; SF-MPQ - short-form McGill Pain Questionnaire; SQ - Sleep quality scale; SDS - Self-Rating Depression Scale; PGIC - Patient Global Impression of Change; VDS - verbal descriptor scale; LANSS - Leeds assessment of neuropathic symptoms and signs; HAM-D - Hamilton rating scale for depression; FPPS - the Functional Pelvic Pain Syndrome scale; NPSI - the Neuropathic Pain Symptom Inventory; MPQ - the McGill Pain Questionnaire; OABq - Overactive Bladder Questionnaire: BDI - the O'Leary-Saint Questionnaire, and a bladder ultrasound for the study of bladder residue, Beck Depression Inventory; PCS, MCS - Physical and Mental Component Summaries of the Short Form Health Survey (SF-36); NRS - The Numeric Rating Scale; SF-MPQ-2 - Short-form McGill Pain Questionnaire-2 (Chinese version); PDI - Pain Disability Index

Table 1. Continues

Authors	Primary condition	Type of the coil	Area of stimulation	Session	Train	Frequency and intensity	Area of RMT obtaining	Assessment instruments	Results
Zhao et al. 2021	NP caused by stroke	Figure-of-8	Contralateral M1	№18 over 3 weeks; 7.5-min durability	№100; 1.5s durability; 3s interval; 1500 pulses	10 Hz; 80% RMT for affected hemisphere or 100% RMT for not affected hemisphere, when RMT wasn't defined Abductor pollicis brevis muscle for affected one	First dorsal interosseous muscle	NRS, SF-MPQ-2, HAM-D	All patients showed significant reduction of pain and depression scores (p=0.01)
Ojala et al. 2021	NP caused by stroke	Figure-of-8	Contralateral M1; Contralateral S2	№10 over 2 weeks; 50-min durability	№50; 10s durability; 50s interval; 5050 pulses	10 Hz; 90% RMT	Abductor pollicis brevis muscle	NRS, BDI, QoL	Short-term responders 41% patient of each group; long-term responders 18% for S2-stimulated patients and 6% for M1-stimulated ones (p = 0.001). Decrease in depression scores wasn't observed.
Lin et al. 2018	NP caused by poststroke thalamic lesions	Figure-of-8; oriented 45° at posterior to the midline	Contralateral M1	№10 over 2 weeks; 11-min durability	№10; 10s durability; 60s interval; 1000 pulses	10 Hz; 90% RMT	First dorsal interosseus muscle	VAS, HAM-D	The pain decrease was up to 66.7% at the maximum of 2 month after the last session, correlating with depression scores decrease (p<0.01)

Note: NP - neuropathic pain; RMT - resting motor threshold; scales used mentioned in the order of presenting in the Table: VAS - Visual Analog Scale; QOL - Quality of Life scale; SF-MPQ - short-form McGill Pain Questionnaire; SQ - Sleep quality scale; SDS - Self-Rating Depression Scale; PGIC - Patient Global Impression of Change; VDS - verbal descriptor scale; LANSS - Leeds assessment of neuropathic symptoms and signs; HAM-D - Hamilton rating scale for depression; FPPS - the Functional Pelvic Pain Syndrome scale; NPSI - the Neuropathic Pain Symptom Inventory; MPQ - the McGill Pain Questionnaire; OABq - Overactive Bladder Questionnaire: BDI - the O'Leary-Saint Questionnaire, and a bladder ultrasound for the study of bladder residue, Beck Depression Inventory; PCS, MCS - Physical and Mental Component Summaries of the Short Form Health Survey (SF-36); NRS - The Numeric Rating Scale; SF-MPQ-2 - Short-form McGill Pain Questionnaire-2 (Chinese version); PDI - Pain Disability Index

prolonged the efficacy. The duration of stimulation per session ranged from seven to 50 minutes (Khedr et al. 2015, Ojala et al. 2021). The number of pulses per session was usually around 1500, although there was one report entailing 15,000 pulses per session (Ma et al. 2015); it remains to be established if there is a simple dose-response relationship. All studies used HF rTMS (5-20 Hz). The most frequently used intensity was 80% RMT, thus constituting a sub-threshold stimulation. The body area for receiving motor evoked potentials to determine the RMT depended on the painful zone and the respective cortical areas of M1 representations. The highest short-term efficacy (up to one month of rTMS in NP) was reported in a study that used ten trains of 10-s each with 30 s IP, 20 Hz frequency and 80% RMT intensity for 7-minutes of contralateral M1 rTMS stimulation (Khedr et al. 2015). The most remarkable long-term outcomes for monophasic studies (lasting up to three months) were reported after applying rTMS to the contralateral M1 with ten daily 40-minutes sessions of 300 5-s trains and3-s IP, at 10 Hz frequency and 80% of RMT intensity (Ma et al. 2015). At the same time, the work of Hodaj et al. (2020) showed increasing of rTMS efficacy during the phase of maintenance. The least effective protocols used stimulation targets other than M1 (Galhardoni et al. 2019), briefer sessions (Nurmikko et al. 2016, Attal et al. 2016, Hosomi et al. 2020), or lower (5 Hz) stimulation frequency (Hosomi et al. 2020, Pei et al. 2019). However, some studies did report effective application of rTMS in stimulation of S2 (Ojala et al. 2021) and the vertex (Hodaj et al. 2020). About half of the analyzed studies did not show any reduction in CD scores (Ma et al. 2015, Pei et al. 2019, Cervigni et al. 2018, Galhardoni et al. 2019, Ojala et al. 2021). The materials and methods of the analyzed studies testify to the heterogeneity of NP-caused nosologies, and also for the differing methods for assessing pain and CD.

CONCLUSIONS

We have reviewed and discussed the different TMS protocols that have been used in the treatment of patients suffering from NP and CD. Our compilation of the literature indicate that the most strongly recommended and effective protocols were performed using a F-8-C coils targeted over the contralateral M1 area, applying ten or more daily rTMS sessions with high frequency between 10-20 Hz, sub threshold intensity of 80-90% RMT, and at least 1500 pulses per session with the extensions in number of sessions and total pulses, and/or with performing the maintenance phase. The results of our analysis also show that there is a need for a consensus in TMS parameters being tested systematically across studies, as well as a need for consensus on how to report TMS protocols (e.g., with standard reporting of the F-8-C orientation variants). We found no data on the effects of combined stimulation of multiple brain regions such as S2 and DLPFC (Ojala et al. 2021, Leung et al. 2020), that may be even more promising than exclusively targeting M1. The results of several studies (Hodaj et al. 2020, Leung et al. 2020) indicated that performing an additional maintenance phase after the acute treatment phase may strengthen and prolong the therapeutic effects of rTMS. Comparing the results of multiple studies (Table 1), we also conclude that studies with a lower number of sessions and total number of pulses tended to also have lower clinical efficacy and persistence.

Limitations

Due to the heterogeneous study designs of the analyzed studies, we see a need for further clarification of the recommendations related to the precise parameters of rTMS protocols targeting the comorbid states of NP and depression.

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Contribution of individual authors:

Arseny J. Gayduk, Yan V. Vlasov & Daria Smirnova have composed the primary idea and specified the hypothesis.

Arseny J. Gayduk & Tatiana I. Shishkovskaia have been responsible for the literature data collection, its systematization and analysis, and wrote the first draft of the manuscript.

Paul Cumming, Theodoros Koutsomitros, Alexander T. Sack, Yan V. Vlasov & Daria Smirnova managed the research documents formalization, detailed manuscript editing and revision, and gave their final approval of the manuscript for submission.

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