The analgesic effect of therapeutic rTMS is not mediated or predicted by comorbid psychiatric or sleep disorders

Pauliina Lindholm, MD[a,b,*], Salla Lamusuo, MD, PhD[a], Tero Taiminen, MD, PhD[c], Arja Virtanen, PhD[b], Antti Pertovaara, MD, PhD[d], Heli Forssell, DMD, PhD[e], Nora Hagelberg, MD, PhD[f], Satu Jääskeläinen, MD, PhD[b]

Abstract

Background: Mechanisms underlying alleviation of neuropathic pain by repetitive transcranial magnetic stimulation (rTMS) of primary motor cortex (M1) and right secondary somatosensory cortex (S2) are only partly known. Patients with chronic neuropathic pain often have comorbidities like depression and sleep problems. Through functional connectivity, rTMS of M1 and S2 may activate dorsolateral prefrontal cortex, the target for treating depression with rTMS. Thus, the analgesic effect of rTMS could be mediated indirectly via improvement of psychiatric comorbidities or sleep. We examined whether rTMS has an independent analgesic effect or whether its clinical benefits depend on effects on mood or sleep. We also evaluated if comorbid psychiatric or sleep disorders predict the treatment outcome.

Methods: Sixteen patients with chronic drug-resistant neuropathic orofacial pain participated in this randomized controlled crossover rTMS study. Patients' psychiatric history was evaluated by a specialist in psychiatry. Intensity and interference of pain, mood, and the quality of sleep and life were evaluated at baseline and after 2 active (primary somatosensory cortex [S1]/M1 and S2) and placebo rTMS treatments. A logistic regression analysis was done to investigate predictors of treatment outcome.

Results: The analgesic effect of the right S2 stimulation was not associated with improvement of psychiatric conditions or sleep, whereas S1/M1 stimulation improved sleep without significant analgesic effect ($P = 0.013$–0.046 in sleep scores). Psychiatric and sleep disorders were more common in patients than in the general population ($P = 0.000$–0.001 in sleep scores), but these comorbidities did not predict the rTMS treatment outcome.

Conclusion: We conclude that rTMS to the right S2 does not exert its beneficial analgesic effects in chronic neuropathic orofacial pain via indirect improvement of comorbid psychiatric or sleep disorders.

Abbreviations: BMI = body mass index, BMS = burning mouth syndrome, BNSQ = Basic Nordic Sleep Questionnaire, BPI = Brief Pain Inventory, DLPFC = dorsolateral prefrontal cortex, M1 = primary motor cortex, NRS = numerical rating scale, rTMS = repetitive transcranial magnetic stimulation, S1 = primary somatosensory cortex, S2 = secondary somatosensory cortex, SCID-I = structured clinical interview for axis I disorders. The MOS Sleep Scale scores: BDI = Beck Depression Inventory, NePIQoL = Neuropathic Pain Impact on Quality-of-Life, QS = quantity of sleep, SA = sleep adequacy, SLD = sleep disturbance, SNR = snoring, SOB = awakening with short of breath or a headache, SS = daytime somnolence.

Keywords: neuropathic orofacial pain, psychiatric disorders, repetitive transcranial magnetic stimulation, secondary somatosensory cortex, sleep disorders

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) targeting either the primary motor cortex (M1) or the dorsolateral prefrontal cortex (DLPFC) has been shown to have an analgesic effect on neuropathic pain.[1–7] When targeted to the DLPFC, rTMS has also been shown effective in treating depression.[7,8] In the first part of this study, we discovered that rTMS given to the right secondary somatosensory cortex (S2) at the posterior edge of the operculoinsular cortex

alleviated otherwise intractable neuropathic orofacial pain and proposed it to be a new potential treatment target.[9] In line, S2 stimulation has previously been shown to have analgesic properties also in healthy subjects.[10] Knowing that there are tight functional connections between the M1 and prefrontal cortex,[11–16] as well as between the insular cortex and prefrontal cortex,[17,18] it could be presumed that similar connections exist between the S2 and DLPFC. In line with this proposal, studies in nonhuman primates have revealed reciprocal anatomical connections between the S2 cortex and DLPFC.[19] Considering these connections, the previously reported analgesic effect of the right S2 stimulation[9] may be an indirect effect through improvement of patients' comorbid psychiatric conditions, which are frequent in neuropathic pain patients.

Pain is a common cause of sleep disruption,[20–22] and disrupted sleep increases pain sensitivity.[23–28] The relationship between pain and depression is also bidirectional.[21,29–32] Patients with treatment-resistant neuropathic pain are particularly susceptible to concomitant disorders such as sleep problems and depression.[33–36] These may share some common pathophysiological etiological factors such as low dopaminergic tone.[37–39]

Based on earlier observations of the multidirectional relationship between pain, depression, and sleep, we wanted to study whether analgesia induced with rTMS depends on the possible simultaneous improvement of patients' psychiatric conditions or sleep disorders. We examined the correlation of the comorbid psychiatric and sleep disorders with pain symptoms at baseline and evaluated if the existence of these comorbidities or use of certain medications could predict the rTMS treatment outcome. Furthermore, we compared the quality of life (QoL) and sleep disorders between neuropathic orofacial pain patients and the general population.

2. Material and methods

2.1. Participants

Twenty patients (mean age 59 years, range 37–74 years, 2 men), who were previously diagnosed with drug-resistant neuropathic orofacial pain in Turku University Hospital, participated in this randomized placebo-controlled study examining the effects of rTMS on pain.[9] Two patients were later excluded; 1 because of significant brain pathology in magnetic resonance imaging and one for not fulfilling the inclusion criteria of pain intensity at baseline. Two patients dropped out during the study; 1 because of major depression and 1 for starting a new treatment during the study. Finally, 16 patients (mean age 59 years, range 39–74 years, 2 men) accomplished the whole study. Patients' mean body mass index (BMI) that may influence sleep was 27.4 (range 22.1–36.2, SD 4.1). Seven patients had trigeminal neuropathic pain, 4 atypical facial pain, and 5 burning mouth syndrome (BMS). The diagnoses were based on clinical examinations performed by an orofacial pain specialist and a neurologist and on abnormal findings in neurophysiological and psychophysical tests (electroneuromyography, brainstem reflex recordings, contact heat evoked potentials, and thermal quantitative sensory testing), performed as described in detail elsewhere.[9,39–41] Despite normal clinical sensory examination, all patients had abnormal findings in thermal quantitative sensory testing and contact heat evoked potential recordings indicating deficits in the function of the trigeminal small fiber system, some along with large fiber involvement shown in brainstem reflexes. The diagnostic criteria applied in this study comply with the current international criteria, ICHD 2013 by International Headache Society.[42] The main inclusion criterion was chronic daily neuropathic orofacial pain ≥4 in numerical rating scale (NRS) from 0 to 10 (0 for no pain at all and 10 for the worst imaginable pain). Patients' average daily pain intensity was 5.7 (SD 1.9) in NRS, and the mean duration of pain was 10.4 (range 2–30) years. Patients' demographic and clinical data are shown in detail in Table 1. None of the patients had contraindications for TMS, such as the use of a pacemaker or a history of seizures.[43]

3. Methods

The study was performed from 2009 to 2011 according to the Declaration of Helsinki. The present results of rTMS effects on sleep and QoL measures and predictors of treatment efficacy

---

Table 1

Patients' demographic and clinical data.

Gender/age in years	DG	Pain side	Duration in years	Lifetime psychiatric disorders	Current psychiatric disorders	Daily treatment
Female/60	AFP	Left	10	MDD, GAD[*]	–	ZOL
Female/64	AFP	Right	10	–	–	–
Female/55	AFP	Right	20	GAD[*], SpP	GAD[*], SpP	–
Female/55	AFP	Left	30	MDD	–	AMI + CHL, FLU TRA, ETO
Female/57	BMS	Bilateral	5	MDD, PaD	–	NOR
Female/67	BMS	Bilateral	20	MDD, SpP	MDD, SpP	–
Female/61	BMS	Bilateral	2	–	–	tCLO, ZOP
Female/74	BMS	Bilateral	7	–	–	tCLO, ZOP
Female/69	BMS	Bilateral	10	–	–	–
Female/65	TNP	Right	15	GAD[*], SoP	SoP	LTG
Female/57	TNP	Bilateral	5	MDD[*]	MDD[*]	PGB, NOR, ESC
Female/47	TNP	Left	6	MDD, SpP	SpP	PGB, CIT
Female/70	TNP	Right	10	SpP, PaD	SpP	PAR + COD, LOR
Female/69	TNP	Right	5	–	–	–
Male/39	TNP	Bilateral	7	GAD[*], SoP	–	DUL, NOR
Male/50	TNP	Right	5	–	–	–

AFP = atypical facial pain, AMI = amitriptyline, BMS = burning mouth syndrome, CHL = chlorediazepoxide, CIT = citalopram, COD = codeine phosphate hemihydrate, DG = diagnosis, DUL = duloxetine, ESC = escitalopram, ETO = etoricoxib, FLU = fluvoxamine, GAD = general anxiety disorder, LOR = lorazepam, LTG = lamotrigin, MDD = major depressive disorder, NOR = nortriptyline, PaD = panic disorder, PAR = paracetamol, PGB = pregabalin, SoP = social phobia, SpP = special phobia, tCLO = topical clonazepam, TNP = trigeminal neuropathic pain, TRA = tramadol, ZOL = zolpidem, ZOP = zopiclone.

[*] Onset after neuropathic pain.

form a part of a larger research project on the mechanisms and optimal targets for therapeutic, analgesic rTMS. The primary outcome measure was the change in pain intensity after rTMS compared to baseline, which has been previously reported.[9] Here, we describe the secondary outcomes of the effects of rTMS on psychiatric and sleep disorders, as well as the effects of these comorbidities on treatment outcome. The study protocol was approved by the Ethics Committee of the Hospital District of the Southwest Finland. All participants gave written informed consent.

The rTMS treatments were given in a single-blind, within-subject crossover design with 4-week intervals. Each patient underwent 3 rTMS sessions (2 active and 1 placebo session). Active rTMS stimulations were given to the facial representation area of the primary sensorimotor cortex (S1/M1) and the right secondary somatosensory cortex (S2) in randomized order. Stimulation targets are shown in Fig. 1. The placebo treatment was targeted to the same area with same settings as S1/M1 stimulation, but there was a 75-mm plastic block attached to the coil, which minimized the electric field reaching the cortex negligible. The patients could not see the coil during the treatment sessions. Stimulation sessions consisted of 1000 (500 + 500) pulses with 10 Hz frequency. The stimulation was given with an E-field navigated TMS device and a biphasic figure-8 coil (eXimia NBS Navigation System and eXimia TMS stimulator, Nextim Ltd., Helsinki, Finland) in trains of 50 pulses at 10-second intervals and a 15-minute break after the first 500 pulses in order to cool the coil. The intensity of the stimulation was 90% of the resting motor threshold determined by single pulse stimulation of the motor cortex and surface ENMG recording from thenar

Figure 1. Repetitive transcranial magnetic stimulation targets. Yellow dot with arrows marks the secondary somatosensory cortex stimulation target, the red arrow showing the direction of the main induced electrical field vector. The orange dots mark the S1/M1 stimulation area, that is, the representation area of the face on the primary somatosensory cortex and primary motor cortex (M1). Uppermost green dot shows the left hand representation area on the M1 cortex where the resting motor threshold was measured.

muscles, as described earlier.[10] The complete rTMS protocol has been described in detail previously.[9]

Genetic analyses of the functional dopamine receptor *DRD2* gene polymorphism (957C > T) and the catechol-O-methyltrans-ferase Val158Met polymorphism were determined using standard procedures as described earlier.[39,44]

The psychiatric diagnoses were made by a specialist in psychiatry with the aid of the structured clinical interview for axis I disorders (SCID-I).[45] Patients' current and lifetime psychiatric diagnoses are shown in Table 1.

Patients' pain, sleep, mood, and the QoL were evaluated with diaries and multiple questionnaires at baseline and after the treatments. Patients kept pain and sleep symptom diaries from 4 weeks before the first treatment to 4 weeks after the last treatment. In the diary, pain and sleep were assessed by using NRS from 0 to 10. In the case of sleep, 0 indicated the poorest imaginable quality of sleep and 10 the best possible quality of sleep. The total amount of sleep was also recorded in hours per night. The intensity and the interference of pain were measured with Brief Pain Inventory (BPI)[46] at baseline, 3 to 5 days, and 1 month after the treatments. In the BPI, higher scores are associated with higher intensity and more interference. Patients' sleep characteristics during the 3 months preceding the study were evaluated with the Basic Nordic Sleep Questionnaire (BNSQ).[47] Sleep was more precisely assessed with Medical Outcomes Study (MOS) Sleep Measure[48] at baseline and 1 month after each treatment. The MOS Sleep Scale is a 12-item measure assessing 6 dimensions of sleep: sleep disturbance (SLD), snoring (SNR), awakening with short of breath or a headache (SOB), sleep adequacy (SA), daytime somnolence (SS), and quantity of sleep (QS).[49] The SLD subscore measures the ability to fall asleep and maintain restful sleep (4 items), the SA subscore measures the sufficiency of sleep (2 items), and the SS subscore measures daytime drowsiness (3 items).[50] The SNR, SOB, and QS (in hours) are 1-item subscores. Two sleep problem indices can be calculated from the subscores. The S6-index contains 6 questions concerning SLD, SA, respiratory impairment, and somnolence. The S9-index uses 3 more questions to summarize overall sleep problems. Neither of the indices includes the MOS Sleep Scale QS question, which is scored as the average hours slept per night. Other questions and the indices are scored on a 0 to 100 range, where a higher score indicates more sleep-related disorders. The MOS Sleep Scale has been shown to be useful in exploring SLDs in patients with neuropathic pain.[51] The health-related QoL was measured with a validated Finnish version of RAND-36[52,53] questionnaire at baseline and 1 month after the treatments. RAND-36 assesses 8 health concepts: physical functioning, role limitations caused by physical problems, role limitations caused by emotional problems, social functioning, emotional wellbeing, energy/fatigue, pain, and general health perceptions. The RAND scores range from 0 (worst possible health state) to 100 (best possible health state). The QoL was also measured with the Neuropathic Pain Impact on Quality-of-Life (NePIQoL) questionnaire, which is a specifically designed QoL measure for neuropathic pain patients.[54] The NePIQoL contains 42 items in 6 domains: psychological, physical, symptoms, personal care, relationships, and social/work activity. All domains have 5-point (1–5) scales with higher scores representing greater pain-related interference in QoL. Patients' mood was evaluated with the widely used and valid Beck Depression Inventory (BDI),[55] at baseline and weekly during the months following the treatments. In BDI, higher score implies more severe symptoms.
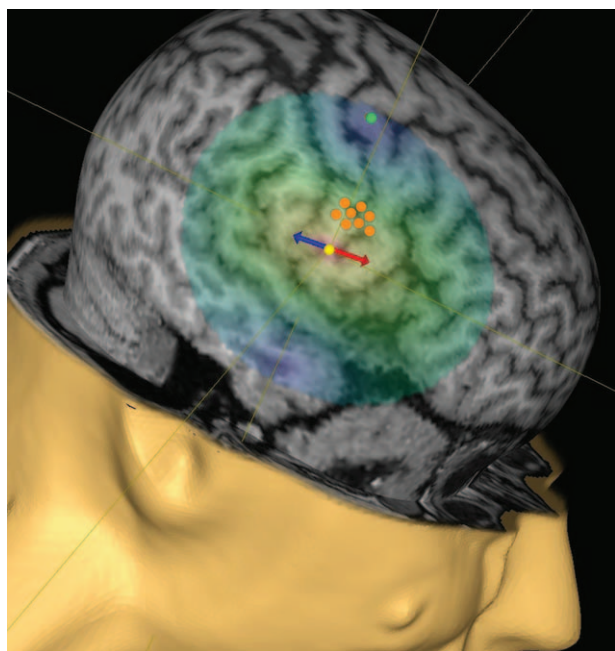
3.1. Statistical analyses

The effects of rTMS on pain, QoL, and mood were determined by repeated measures analysis of variance with time as the within-subject factor, and diagnosis and genotype as between-subject factors. P values less than 0.05 were considered statistically significant. In post hoc pairwise comparisons, a correction for multiple comparisons was done with Bonferroni, and adjusted P values are reported. Correlations between RAND, NePIQoL, MOS, BPI, and pain/sleep diary scores were tested using Pearson correlation coefficients. In addition, the patients' MOS and RAND scores at baseline were compared with published population reference values.[49,52] A logistic regression analysis was run to find out the possible predictive factors influencing the treatment effect. Variables used were the baseline pain intensity and quality of sleep, the existence of social phobia, special phobia, general anxiety disorder, depression or restless legs, and use of opioidergic or gabaergic medication that may influence the efficacy of rTMS. The dichotomous outcome variable was pain relief either more or less than 30% from baseline. Power analysis was done to estimate the minimum sample size required to detect clinically significant 30% decrease in pain intensity. Under the assumption of 20% dropout rate, with 80% statistical power and 2-sided alpha risk of 0.05, 20 patients had to be enrolled in the trial. All statistical analyses were carried out by SAS statistical software package for Windows (SAS Institute Inc., Cary, NC).

4. Results

Baseline sleep disorders (poor quality of sleep and restless legs), psychiatric disorders (depression, general anxiety disorder, social phobia, and specific phobia), or notable medications (opioids and gabaergic drugs) had no predictive value for the treatment outcome in any of the stimulation conditions. In the logistic regression analysis, only the baseline intensity of pain over 5 in NRS showed a tendency toward some predictive value ($P = 0.057$) for a positive treatment response following stimulation of the right S2 cortex.

There were no differences in the BDI scores measuring mood[9] or in the sleep diary measurements concerning the amount and the quality of sleep before and after the rTMS treatments.

There was a reduction in the neuropathic pain-specific NePIQoL total score after the S2 treatment ($P = 0.0031$) but no differences in the more general RAND-36 scores after any of the rTMS treatment sessions, as previously reported.[9] In the pairwise post hoc comparisons, the MOS Sleep Scale SOB subscore describing shortness of breath or headache was lower ($P = 0.027$) after the S2 stimulation than at baseline. The SLD subscore ($P = 0.046$), and both S6 ($P = 0.040$) and S9 ($P = 0.013$) index scores describing overall sleep problems, were lower after the S1/M1 stimulation than at the baseline. However, after correction for multiple comparisons, only the difference in S9 sleep index score remained significant. There were no significant changes in the MOS scores after the placebo treatment. The specific diagnoses, genotypes, or medications were not associated with the treatment responses.

According to the BNSQ questionnaire at baseline, 73% (11/15) of the patients experienced their sleep being usually poor. More than half (9/15; 56%) of the patients suffered from SS and early awakenings more than 3 times a week. A total of 11/16 (69%) experienced troubles falling asleep more than 3 times a week, and 6/16 (38%) suffered from awakenings more than 3 times per night. Almost half of the patients (7/16; 43%) used sleep medicine more than 3 times a week. A total of 14/16 (88%) had sometimes

snored, but none of them snored more than 3 times per week. Only 2/16 (13%) had experienced sleep apnea, which in these cases occurred less than once a week.

Neuropathic orofacial pain patients reported worse scores on 3 of 5 MOS Sleep Scale scores (SLD $P = 0.000$, SOB $P = 0.000$, and SS $P = 0.001$) compared to the US general population (original data of the US general population is available at http://gim.med.ucla.edu/FacultyPages/Hays/surveys/). The 9-item sleep problem index total score was also poorer in patients than in general population ($P = 0.000$). Comparison of the score profiles between the patients and healthy population is shown in Fig. 2.

Based on SCID-I interviews, 6 (38%) of the patients had a present and 10 (63%) a lifetime psychiatric disorder, either depressive or anxiety disorder or both (Table 1). The lifetime rates of depressive and anxiety disorders were similar to those reported earlier for a larger sample of Finnish orofacial pain patients[37] and higher than in general population.[56] Clinical and demographic data of the patients are presented in Table 1. All but 1 of the depressive disorders preceded the neuropathic pain condition, and the only 1 following the onset of the neuropathic pain was not related to the pain state. On the contrary, all general anxiety disorders developed only after the onset of pain and were closely pain related. The remaining anxiety disorders were phobias and panic disorders that had begun before the pain. Especially, specific phobias were chronic.

The QoL of the patients at baseline was very variable according to the RAND scores. In older patients (≥65 years), scores did not differ from the general population. In the younger age group (18–64 years), patients were clearly more painful than the general population, but otherwise, scores differed so much between individual patients that the results of the statistical analyses remained nonsignificant, and no firm conclusions could be made.

At baseline, higher scores in the BDI (meaning more depressive symptoms) were associated with lower quality of sleep (R -0.51932, $P = 0.040$), more interference of pain according to BPI (R 0.70519, $P = 0.002$), and higher total score in the NePIOoL (meaning lower QoL, R 0.77825, $P = 0.000$). The only RAND score correlating with BDI was the social functioning, which was
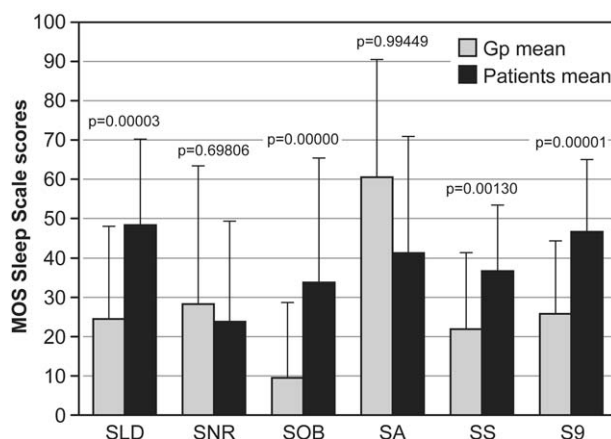

Figure 2. Comparison of the MOS Sleep Scale scores between the neuropathic orofacial pain patients and the US general population. Patients reported significantly worse scores on sleep disturbance, awakening with short of breath or headache, daytime somnolence, and 9-item sleep problem index total score compared to the US general population (P values for the comparisons are shown above the bars for each score). Scores measuring sleep adequacy and snoring did not differ between the groups.

lower with higher BDI scores (R −0.62404, $P = 0.010$). There was an association between QoL and quality of sleep when measuring the QoL with the NePIQoL questionnaire (better quality of sleep correlating with better QoL and lower NePIQoL total score, R −0.74518, $P = 0.001$). The RAND questionnaire could not reveal this association in this patient group. High NePIQoL total scores were associated with high BPI interference of pain scores (R 0.75736, $P = 0.001$), both measuring the disturbance caused by pain in daily life. High MOS index scores, indicating more sleep problems, had some association with the higher interference of pain in the BPI (S6 R 0.50969, $P = 0.044$). Simple sleep diary scores were well in line with both MOS index scores: better quality of sleep was associated with lower MOS index scores (S6 r/R −0.64590, $P = 0.007$ and S9 r/R −0.62431, $P = 0.010$).

5. Discussion

The present results show that the analgesic effect of rTMS given to the right S2 cortex as previously reported[9] is most likely due to a direct action on specific top–down pain modulation networks rather than a result of an indirect action via improvement of comorbid psychiatric or sleep disturbances. In line with this interpretation, the S2 stimulation had no effect on depressive symptoms, sleep diary measures, or the MOS sleep scale index scores. Furthermore, comorbidities such as depression, anxiety disorders, and sleep problems did not predict the rTMS treatment outcome. The analgesic effect of the S2 stimulation in these neuropathic orofacial pain patients comply with earlier findings in healthy subject suggesting that S2 stimulation both impairs the subjective appraisal of painful stimuli and reduces the perceived pain intensity.[10,57,58]

Although we have not been able to show a significant analgesic effect with S1/M1 stimulation,[9] this target seemed to have a positive effect on the MOS sleep scale index scores (S6 and S9) describing overall sleep problems, and to the sleep disturbance subscore describing ability to fall asleep and maintain restful sleep. This discrepancy highlights the importance of precise anatomical navigation in rTMS treatment, because rather closely located cortical targets (Fig. 1) may mediate very specific and distinct effects, and the benefits reported in pain patients may be mediated via different brain mechanisms. This is in line with the current understanding of the neurophysiological mechanisms behind rTMS effects.[59] Of special interest is that the placebo rTMS had no significant effects on any of the many mood, sleep, and QoL variables analyzed in this study, although placebo effect is usually considered to be approximately 30% in pain trials. The positive effect of the S2 stimulation on the MOS sleep scale SOB subscore measuring SOB while awakening could be explained by the stimulation's analgesic effect on orofacial pain, ergo, pain in the head. Patients did not report sleep apnea in the baseline sleep questionnaire, and the mean BMI was normal, so changes in this MOS subscore were unlikely due to obstructive sleep apnea syndrome.

In this small sample of neuropathic orofacial pain patients, genotypes related to brain dopamine system did not influence any of the effects of the rTMS treatment. Nevertheless, higher reported pain intensity at baseline seemed to have a borderline predictive value for better treatment response, which is of interest as high subjective pain scores have previously been shown to associate with the pain-sensitive 957TT homozygote form of the DRD2 gene.[39] Small sample size was indeed a limitation of our study, but according to power analysis, the sample size was considered sufficient to detect clinically meaningful changes. Another clear

limitation was the absence of a placebo coil. When asked after the study was completed, 6 of the 16 patients recognized correctly the placebo stimulation, 2 because of the muscle contraction during active rTMS and 4 because of the beneficial effects of the active treatments. The effects of the previous active stimulation did not have an impact on the following placebo session.

Sleep disturbances were far more common among chronic neuropathic orofacial pain patients than in general population, which is in line with earlier reports on BMS patients[60,61] and neuropathic pain patients in general.[33,35,36] Sleep disturbances were associated with more interference caused by pain in daily life (NePIQoL and BPI), but not with the mere intensity of pain. The same trend was seen with depressive symptoms that were also more pronounced in patients reporting more interference of pain in daily life (NePIQoL and BPI) and poorer quality of sleep, whereas the intensity of pain was not associated with the occurrence of depressive symptoms. It has been shown earlier that a negative cognitive and affective response to pain, so-called pain catastrophizing, might contribute to sleep disturbance in chronic pain.[62,63] We did not have questionnaires to measure pain catastrophizing, but in the NePiQoL questionnaire there were many questions concerning coping with the pain and the NePiQoL total score correlated with the sleep disturbance, whereas pain intensity in the BPI and pain diary did not.

The neuropathic orofacial pain patients had more depressive and anxiety disorders than the general population. Depressive disorders mostly preceded the onset of pain, which is in line with other studies concerning orofacial pain.[37,64,65] In contrast, general anxiety disorders followed the pain and were closely pain related. The association between chronic pain and psychiatric disorders has been considered before,[37,66,67] and in the case of neuropathic orofacial pain, the shared vulnerability through hypofunctional brain dopamine activity could be a possible underlying predisposing factor both to depression and chronic pain.[39,68–72] This hypothesis is further supported by the fact that the pain vulnerable DRD2 gene genotype 957TT carriers with low striatal dopamine content were overrepresented (50% vs 27% in general population) in this study group of neuropathic orofacial pain patients, as reported earlier.[39] The occurrence of the anxiety disorder after the onset of pain could also be explained by the hypofunctional dopamine activity, as it has been suggested that the personality trait of harm avoidance is associated with low levels of dopamine in the striatum.[73] The personality trait of harm avoidance predisposes to worrying and catastrophizing about the pain and may lead to the onset of a general anxiety disorder, which in turn is shown to be associated with low striatal dopamine synthesis capacity.[74] The analgesic effect of S2 stimulation could therefore depend on the dopamine release induced change in attentional factors related to coping with pain, as it has been earlier shown that S2 stimulation induced an early decrease in discriminative capacity[10,57] and after a delay, an increase in response criterion.[10] This attitude change toward disregarding pain stimuli may underlie the clinical effects of S2 stimulation.

6. Conclusion

The rTMS applied to the right S2 cortex does not seem to exert its beneficial effects via indirect improvement of mood or sleep disturbances that the orofacial neuropathic pain patients had. Patients had more psychiatric and sleep disorders than the general population, but these comorbidities did not predict the rTMS treatment outcome either. There were associations between

baseline depressive symptoms, sleep, and the interference of pain supporting the known complex relationship between these disorders.

References

[1] Hirayama A, Saitoh Y, Kishima H, et al. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. Pain 2006;122: 22–7.

[2] Cruccu G, Sommer C, Anand P, et al. EFNS guidelines on neuropathic pain assessment: revised 2009. Eur J Neurol 2010;17:1010–8.

[3] Leo RJ, Latif T. Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: a review. J Pain 2007;8:453–9.

[4] André-Obadia N, Mertens P, Gueguen A, et al. Pain relief by rTMS: differential effect of current flow but no specific action on pain subtypes. Neurology 2008;71:833–40.

[5] Borckardt JJ, Smith AR, Reeves ST, et al. A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. Pain Med 2009;10:840–9.

[6] Leung A, Donohue M, Xu R, et al. rTMS for suppressing neuropathic pain: a meta-analysis. J Pain 2009;10:1205–16.

[7] Lefaucheur JP, André-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125:2150–206.

[8] Slotema CW, Blom JD, Hoek HW, et al. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 2010;71:873–84.

[9] Lindholm P, Lamusuo S, Taiminen T, et al. Right secondary somatosensory cortex—a promising novel target for the treatment of drug-resistant neuropathic orofacial pain with repetitive transcranial magnetic stimulation. Pain 2015;156:1276–83.

[10] Valmunen T, Pertovaara A, Taiminen T, et al. Modulation of facial sensitivity by navigated rTMS in healthy subjects. Pain 2009;142: 149–58.

[11] Bates JF, Goldman-Rakic PS. Prefrontal connections of medial motor areas in the rhesus monkey. J Comp Neurol 1993;336:211–28.

[12] Civardi C, Cantello R, Asselman P, et al. Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. Neuroimage 2001;14:1444–53.

[13] Rowe JB, Stephan KE, Friston K, et al. The prefrontal cortex shows context-specific changes in effective connectivity to motor or visual cortex during the selection of action or colour. Cereb Cortex 2005;15: 85–95.

[14] Rothwell JC. Using transcranial magnetic stimulation methods to probe connectivity between motor areas of the brain. Hum Mov Sci 2011;30:906–15.

[15] Duque J, Labruna L, Verset S, et al. Dissociating the role of prefrontal and premotor cortices in controlling inhibitory mechanisms during motor preparation. J Neurosci 2012;32:806–16.

[16] Hasan A, Galea JM, Casula EP, et al. Muscle and timing-specific functional connectivity between the dorsolateral prefrontal cortex and the primary motor cortex. J Cogn Neurosci 2013;25:558–70.

[17] Peltz E, Seifert F, DeCol R, et al. Functional connectivity of the human insular cortex during noxious and innocuous thermal stimulation. Neuroimage 2011;54:1324–35.

[18] Almashaikhi T, Rheims S, Jung J, et al. Functional connectivity of insular efferences. Hum Brain Mapp 2014;35:5279–94.

[19] Yeterian EH, Pandya DN, Tomaiuolo F, et al. The cortical connectivity of the prefrontal cortex in the monkey brain. Cortex 2012;48:58–81.

[20] Pilowsky I, Crettenden I, Townley M. Sleep disturbance in pain clinic patients. Pain 1985;23:27–33.

[21] Morin CM, Gibson D, Wade J. Self-reported sleep and mood disturbance in chronic pain patients. Clin J Pain 1998;14:311–4.

[22] Smith MT, Perlis ML, Smith MS, et al. Sleep quality and presleep arousal in chronic pain. J Behav Med 2000;23:1–3.

[23] Affleck G, Urrows S, Tennen H, et al. Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. Pain 1996;68:363–8.

[24] Moldofsky H. Sleep and pain. Sleep Med Rev 2001;5:385–96.

[25] Wilson KG, Eriksson MY, D'Eon JL, et al. Major depression and insomnia in chronic pain. Clin J Pain 2002;18:77–83.

[26] Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain 2013;14:1539–52.

[27] Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. Sleep Med Rev 2006;10:357–69.

[28] Bigatti SM, Hernandez AM, Cronan TA, et al. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. Arthritis Rheum 2008;59:961–7.

[29] Romano JM, Turner JA. Chronic pain and depression: does the evidence support a relationship? Psychol Bull 1985;97:18–34.

[30] Magni G, Moreschi C, Rigatti-Luchini S, et al. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. Pain 1994;56:289–97.

[31] Von Korff M, Simon G. The relationship between pain and depression. Br J Psychiatry Suppl 1996;30:101–8.

[32] Fishbain DA, Cutler R, Rosomoff HL, et al. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. Clin J Pain 1997;13:116–37.

[33] Gore M, Brandenburg NA, Dukes E, et al. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. J Pain Symptom Manage 2005;30:374–85.

[34] Argoff CE. The coexistence of neuropathic pain, sleep, and psychiatric disorders: a novel treatment approach. Clin J Pain 2007;23:15–22.

[35] Poliakov I, Toth C. The impact of pain in patients with polyneuropathy. Eur J Pain 2011;15:1015–22.

[36] Bouhassira D, Letanoux M, Hartemann A. Chronic pain with neuropathic characteristics in diabetic patients: a French cross-sectional study. PLoS One 2013;8:e74195.

[37] Taiminen T, Kuusalo L, Lehtinen L, et al. Psychiatric (axis I) and personality (axis II) disorders in patients with burning mouth syndrome or atypical facial pain. Scand J Pain 2011;2:155–60.

[38] Jääskeläinen SK. Pathophysiology of primary burning mouth syndrome. Clin Neurophysiol 2012;123:71–7.

[39] Jääskeläinen SK, Lindholm P, Valmunen T, et al. Variation in the dopamine D2 receptor gene plays a key role in human pain and its modulation by transcranial magnetic stimulation. Pain 2014;155: 2180–7.

[40] Forssell H, Jääskeläinen S, Tenovuo O, et al. Sensory dysfunction in burning mouth syndrome. Pain 2002;99:41–7.

[41] Forssell H, Tenovuo O, Silvoniemi P, et al. Differences and similarities between atypical facial pain and trigeminal neuropathic pain. Neurology 2007;69:1451–9.

[42] Headache Classification Committee of the International Headache Society (IHS)The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808.

[43] Rossi S, Hallett M, Rossini PM, et al. Safety of TMS Consensus GroupSafety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39.

[44] Hirvonen MM, Lumme V, Hirvonen J, et al. C957T polymorphism of the human dopamine D2 receptor gene predicts extrastriatal dopamine receptor availability in vivo. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:630–6.

[45] First MB, Spritzer RL, Gibbon M, et al. Structured clinical interview for DSM-IV axis I disorders (SCID-I, 4/97 version). New York, NY:Biometrics Research Department, New York State Psychiatric Institute; 1997.

[46] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–38.

[47] Partinen M, Gislason T. Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. J Sleep Res 1995;4: 150–5.

[48] Spritzer KL, Hays RD. MOS sleep scale: a manual for use and scoring, Version 1.0. Los Angeles, CA:2003, November.

[49] Hays RD, Martin SA, Sesti AM, et al. Psychometric properties of the Medical Outcomes Study Sleep measure. Sleep Med 2005;6:41–4.

[50] Allen RP, Kosinski M, Hill-Zabala CE, et al. Psychometric evaluation and tests of validity of the Medical Outcomes Study 12-item Sleep Scale (MOS sleep). Sleep Med 2009;10:531–9.

[51] Rejas J, Ribera MV, Ruiz M, et al. Psychometric properties of the MOS (Medical Outcomes Study) Sleep Scale in patients with neuropathic pain. Eur J Pain 2007;11:329–40.

[52] Aalto AM, Aro AR, Teperi J. RAND-36 elämänlaadun mittarina. Tutkimuksia 101. 1999;Helsinki:STAKES, http://urn.fi/URN:NBN: fi-fe201211089642

[53] Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ 1993;2:217–27.

[54] Poole HM, Murphy P, Nurmikko TJ. Development and preliminary validation of the NePIQoL: a quality-of-life measure for neuropathic pain. J Pain Symptom Manage 2009;37:233–45.

[55] Beck AT, Rial WY, Rickels K. Short form of depression inventory: cross-validation. Psychol Rep 1974;34:1184–6.

[56] Pirkola SP, Isometsä E, Suvisaari J, et al. DSV-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population—results from the Health 2000 Study. Soc Psychiatry Psychiatr Epidemiol 2005;40:1–0.

[57] Lockwood PL, Iannetti GD, Haggard P. Transcranial magnetic stimulation over human secondary somatosensory cortex disrupts perception of pain intensity. Cortex 2013;49:2201–9.

[58] Uglem M, Omland PM, Engstrom M, et al. Non-invasive cortical modulation of experimental pain in migraine. Clin Neurophysiol 2016;127:2362–9.

[59] Moisset X, de Andrade DC, Bouhassira D. From pulses to pain relief: an update on the mechanisms of rTMS-induced analgesic effects. Eur J Pain 2016;20:689–700.

[60] Adamo D, Schiavone V, Aria M, et al. Sleep disturbance in patients with burning mouth syndrome: a case–control study. J Orofac Pain 2013;27:304–13.

[61] Chainani-Wu N, Madden E, Silverman SJr. A case–control study of burning mouth syndrome and sleep dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:203–8.

[62] Smith MT, Perlis ML, Carmody TP, et al. Presleep cognitions in patients with insomnia secondary to chronic pain. J Behav Med 2001;24:93–114.

[63] Buenaver LF, Quartana PJ, Grace EG, et al. Evidence for indirect effects of pain catastrophizing on clinical pain among myofascial temporomandibular disorder participants: the mediating role of sleep disturbance. Pain 2012;153:1159–66.

[64] Lascelles RG. Atypical facial pain and depression. Br J Psychiatry 1966;112:651–9.

[65] Lamey PJ, Lamb AB. Prospective study of aetiological factors in burning mouth syndrome. Br Med J (Clin Res Ed) 1988;296:1243–6.

[66] Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: research findings and theoretical considerations. Psychosom Med 2002;64:773–86.

[67] Diatchenko L, Nackley AG, Slade GD, et al. Idiopathic pain disorders—pathways of vulnerability. Pain 2006;123:226–30.

[68] Jääskeläinen SK, Forssell H, Tenovuo O. Abnormalities of the blink reflex in burning mouth syndrome. Pain 1997;73:455–60.

[69] Jääskeläinen SK, Rinne JO, Forssell H, et al. Role of the dopaminergic system in chronic pain—a fluorodopa-PET study. Pain 2001;90:257–60.

[70] Hagelberg N, Forssell H, Rinne JO, et al. Striatal dopamine D1 and D2 receptors in burning mouth syndrome. Pain 2003;101:149–54.

[71] Hagelberg N, Forssell H, Aalto S, et al. Altered dopamine D2 receptor binding in atypical facial pain. Pain 2003;106:43–8.

[72] Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 2003;299:1240–3.

[73] Kim JH, Son YD, Kim HK, et al. Association of harm avoidance with dopamine D2/3 receptor availability in striatal subdivisions: a high resolution PET study. Biol Psychol 2011;87:164–7.

[74] Laakso A, Wallius E, Kajander J, et al. Personality traits and striatal dopamine synthesis capacity in healthy subjects. Am J Psychiatry 2003;160:904–10.