Research Paper

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Right secondary somatosensory cortex—a promising novel target for the treatment of drug-resistant neuropathic orofacial pain with repetitive transcranial magnetic stimulation

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Abstract

High-frequency repetitive transcranial magnetic stimulation (rTMS) of the motor cortex has analgesic effect; however, the efficacy of other cortical targets and the mode of action remain unclear. We examined the effects of rTMS in neuropathic orofacial pain, and compared 2 cortical targets against placebo. Furthermore, as dopaminergic mechanisms modulate pain responses, we assessed the influence of the functional DRD2 gene polymorphism (957C>T) and the catechol-*O*-methyltransferase (COMT) Val158Met polymorphism on the analgesic effect of rTMS. Sixteen patients with chronic drug-resistant neuropathic orofacial pain participated in this randomized, placebo-controlled, crossover study. Navigated high-frequency rTMS was given to the sensorimotor (S1/M1) and the right secondary somatosensory (S2) cortices. All subjects were genotyped for the DRD2 957C>T and COMT Val158Met polymorphisms. Pain, mood, and quality of life were monitored throughout the study. The numerical rating scale pain scores were significantly lower after the S2 stimulation than after the S1/M1 ($P = 0.0071$) or the sham ($P = 0.0187$) stimulations. The Brief Pain Inventory scores were also lower 3 to 5 days after the S2 stimulation than those at pretreatment baseline ($P = 0.0127$ for the intensity of pain and $P = 0.0074$ for the interference of pain) or after the S1/M1 ($P = 0.001$ and $P = 0.0001$) and sham ($P = 0.0491$ and $P = 0.0359$) stimulations. No correlations were found between the genetic polymorphisms and the analgesic effect in the present small clinical sample. The right S2 cortex is a promising new target for the treatment of neuropathic orofacial pain with high-frequency rTMS.

Keywords: Transcranial magnetic stimulation, Neuropathic pain, Motor cortex, Sensorimotor cortex, Secondary somatosensory cortex, Dopamine system genetics

1. Introduction

Neuropathic pain is challenging to treat. According to the guidelines of the European Federation of Neurological Societies (EFNS), less than half of the patients with chronic neuropathic pain achieve a significant pain relief with pharmacotherapy.[7,19] Consequently, there has been a growing interest in different neurostimulation techniques. Invasive electrical motor cortex stimulation for treatment of central pain was first described by Tsubokawa et al. in 1991.[57,58] The first noninvasive transcranial magnetic stimulation (TMS) study was performed in 1995[44] and the first placebo-controlled repetitive transcranial magnetic stimulation (rTMS) study in 2001.[38] Since then, rTMS of the primary motor cortex (M1) has been shown to have analgesic effects on neuropathic pain,[2,3,16,29,39–42,45] but further controlled trials to define the best parameters and targets for stimulation are still needed.

There is a wide interindividual variation in the treatment response to rTMS, possibly partly due to genetic factors.[13,31,32] This leads to ambiguous results in group-level analyses, especially when the groups are small. The striatal dopamine D2 receptors (DRD2) mediate analgesic effects in experimental animal models of pain.[5,14,43] Also in humans, studies using functional brain imaging show striatal DRD2 to be involved in the modulation of pain.[25–27,33] Moreover, rTMS given to the motor cortex induces striatal dopamine release in humans.[53] The regulation of DRD2 gene expression is at least partly modulated by synonymous single-nucleotide polymorphism 957C>T, which alters the mRNA folding and stability leading to decreased translation of the gene.[18] In our earlier work, rTMS given to the primary sensory (S1) cortex induced heat hypoalgesia, but only in subjects with DRD2 957C>T T/T genotype.[32] In another previous work with healthy subjects,[60] we discovered the most significant decrease in thermal pain sensitivity of the face after high-frequency rTMS

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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given to the right S2. Based on these findings, we wanted to compare the analgesic effects of rTMS given to the sensorimotor (S1/M1) and S2 cortical targets in chronic neuropathic orofacial pain. In addition to defining optimal cortical targets for rTMS, we wished to discover which aspects of pain this treatment influences the most. Therefore, we used several questionnaires evaluating pain, mood, and quality of life before and after the treatments. Furthermore, we wanted to find out whether the genetically determined differences in the brain dopamine system would influence the analgesic effects of rTMS.

2. Methods

2.1. Study design

The study was performed in 2009 to 2011 according to the Declaration of Helsinki and approved by the Ethics Committee of The Intermunicipal Hospital District of Southwest Finland. All participants gave written informed consent.

The study was conducted in a randomized, single-blind, placebo-controlled, within-subject crossover design. All participants received 2 active rTMS treatments and 1 sham (placebo) treatment. The 3 treatments were separated from each other by 4 weeks, the sham treatment being in between the 2 active treatments, S1/M1 and S2, given in a randomized order. The S1/M1 target covered the anterior parts of the postcentral gyrus (S1) in addition to M1 on the precentral gyrus and is thus not exactly equal to the M1 target of many previous rTMS studies on pain. Patients kept pain diaries throughout the study period beginning 4 weeks before the first treatment and completing 4 weeks after the last treatment. The primary outcome measure was pain intensity at baseline before the treatments and after each rTMS treatment assessed using a numeric rating scale (NRS) of 0 (no pain) to 10 (worst imaginable pain). Pain and its effects on quality of life were also measured with the Brief Pain Inventory (BPI)[15] and the Neuropathic Pain Impact on Quality-of-Life (NePIQoL) questionnaire.[50] In addition, patients' health-related quality of life was measured with a validated Finnish version of the RAND-36 (SF-36) questionnaire,[1,28,61] and their mood was followed with Beck Depression Inventory (BDI).[10] The BPI was monitored at baseline, 3 to 5 days after the treatments and 1 month after the treatments, the NePIQoL and the RAND-36 at baseline and 1 month after the treatments, and the BDI at baseline and weekly for a month after the treatments. Moreover, patients were asked to mark with color pencils the area and the intensity of pain, paresthesia, or numbness on a schematic symptom chart immediately before and after each treatment, as well as 1 and 2 weeks after the treatments. The extent of the symptomatic area was estimated using transparent square millimeter sheets.

2.2. Subjects

Initially, 74 patients, who were previously diagnosed and treated for neuropathic orofacial pain in Turku University Hospital, were contacted and interviewed by telephone. Twenty patients, who still had clinically intractable pain, met the inclusion criteria, and were willing and able to participate, were recruited to the study. Patients, 2 of them male, all right-handed with a mean age of 59 (range, 37-74), were suffering from severe chronic drug-resistant pain. Nine patients had trigeminal neuropathic pain, 6 atypical facial pain and 5 burning mouth syndrome. Diagnoses of the neuropathic orofacial pain were performed according to the current International Criteria for Headache Disorders (ICHD 2013 by International Headache Society) after thorough clinical examinations performed by an experienced orofacial pain specialist and a neurologist. The neuropathic involvement of the trigeminal system was confirmed with neurophysiological and psychophysical tests: electroneuromyography, brainstem reflex recordings (blink reflexes), contact heat–evoked potential recording, and thermal quantitative sensory testing, performed as previously described in detail.[21,22,32] Neurophysiological findings according to diagnoses are listed in **Table 1**.

The main inclusion criterion was chronic daily neuropathic pain ≥4 in severity using NRS of 0 to 10. Patients had no history of seizure, pacemaker implantation, major stroke, or other contraindication for TMS.[51] Patients were randomized to 2 groups, group 1 receiving the S1/M1 stimulation first (11 patients) and group 2 receiving the S2 stimulation first (9 patients). One patient was excluded after the brain magnetic resonance imaging (MRI) scan because of multiple ischemic lesions and another after the pain diary follow-up because of average pain less than 4 on the NRS. Two patients dropped out during the study; one because of major depression and the other because of starting a new local anesthesia treatment during the study. Finally, 16 patients were analyzed, 10 of them from group 1 and 6 from group 2. Ten of the remaining 16 patients had a previous and 6 a present psychiatric disorder, which were diagnosed by a specialist in psychiatry on clinical basis with the aid of the structured clinical interview for axis I disorders, SCID-I.[20] The comorbid psychiatric disorders were mainly affective disorders (no bipolar or psychotic disorder) and are listed in **Table 2**. The lifetime rates of depressive and anxiety disorders were higher than in the general population, but did not differ from those reported earlier for a larger sample of Finnish patients with orofacial pain.[54] Study patients' regular pharmacological treatment remained stable during the study, and they were allowed to take their on-demand medication as before. Clinical and demographic data of the patients are summarized in **Table 2**.

2.3. Repetitive transcranial magnetic stimulation

Magnetic stimulation was applied 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). The stimulation was given to the contralateral S1/M1

Table 1

Neurophysiological findings according to diagnoses.

Sex/age in years	Dg	BLINK	BRHAB	QST	CHEP
F/65	TNP	LoF	GoF	LoF	LoF
F/57	TNP	N	N	LoF	LoF
F/47	TNP	N	N	LoF	LoF
F/70	TNP	LoF	N	LoF	LoF
F/69	TNP	LoF	N	LoF	LoF
M/39	TNP	N	GoF	LoF	LoF
M/50	TNP	LoF	N	LoF	LoF
F/60	AFP	N	GoF	LoF	LoF
F/64	AFP	N	GoF	LoF and GoF	LoF
F/55	AFP	LoF	N	LoF	N
F/55	AFP	LoF	N	LoF	N
F/57	BMS	N	N	LoF	LoF
F/67	BMS	N	GoF	LoF	LoF
F/61	BMS	N	N	LoF	LoF
F/74	BMS	LoF	N	LoF	LoF
F/69	BMS	N	N	LoF	LoF

AFP, atypical facial pain; BLINK, blink reflex; BMS, burning mouth syndrome; BRHAB, blink reflex habituation; CHEP, contact heat–evoked potential; F, female; GoF, gain of function (deficient habituation of the blink reflex or thermal allodynia); LoF, loss of function (absent response, prolonged latency, hypoesthesia, anesthesia, hypoalgesia, analgesia); M, male; N, normal; QST, thermal quantitative sensory test; TNP, trigeminal neuropathic pain.

Table 2

Patients' clinical data.

No.	Age	Sex	957C>T	COMT	Diagnoses	Pain side	Duration, years	SCID-I: lifetime	SCID-I: current	Daily treatment
1	60	f	T/T	M/M	AFP	Left	10	F33.4, F41.8	—	ZOL
2	64	f	T/T	V/V	AFP	Right	10	—	—	—
3	65	f	C/T	V/M	TNP	Right	15	F41.8, F40.1	F40.1	LAM
4	55	f	C/C	V/M	AFP	Right	20	F41.8, F40.2	F41.8, F40.2	—
5	57	f	C/C	V/V	BMS	Bilateral	5	F33.9, F41.0	—	NOR
6	55	f	T/T	V/M	AFP	Left	30	F33.1	—	AMI + CHL, FLU TRA, ETO
7	57	f	C/C	M/M	TNP	Bilateral	5	F33.2	F33.2	PGB, NOR, ESC
8	67	f	C/T	M/M	BMS	Bilateral	20	F33.1, F40.2	F33.10, F40.2	—
9	47	f	C/C	V/V	TNP	Left	6	F32.2, F40.2	F40.2	PGB, CIT
10	70	f	C/T	M/M	TNP	Right	10	F41.0, F40.2	F40.2	PAR + COD, LOR
11	69	f	T/T	V/M	TNP	Right	5	—	—	—
12	61	f	T/T	V/M	BMS	Bilateral	2	—	—	tCLO, ZOP
13	74	f	T/T	M/M	BMS	Bilateral	7	—	—	tCLO, ZOP
14	39	m	T/T	M/M	TNP	Bilateral	7	F40.1, F41.8	—	DUL, NOR
15	69	f	T/T	V/M	BMS	Bilateral	10	—	—	—
16	50	m	C/C	V/M	TNP	Right	5	—	—	—

957C>T, dopamine D2 receptor 957C>T genotype; COMT, COMT Val158Met genotype.
Diagnoses: AFP, atypical facial pain; BMS, burning mouth syndrome; TNP, trigeminus neuropathy.
SCID-I: psychiatric diagnoses *ICD-10*: F32-33, depressive disorders; F40-41, anxiety disorders.
Treatments: AMI, amitriptyline; BUB, buprenorphine patch; CHL, chlordiazepoxide; CIT, citalopram; COD, codeine phosphate hemihydrate; DUL, duloxetine; ESC, escitalopram; ETO, etoricoxib; FLU, fluvoxamine; LAM, lamotrigine; LOR, lorazepam; NOR, nortriptyline; PAR, paracetamol; PGB, pregabalin; tCLO, topical clonazepam; TRA, tramadol; ZOL, zolpidem; ZOP, zopiclone.

cortex representing the face area (approximately 2 cm^2 covering part of the pre- and post-central gyri and the central sulcus) when symptoms were unilateral and to the right S1/M1 in case of bilateral symptoms. The S2 stimulation was always given to the right side. The S1 area was included in the S1/M1 stimulation target area because we had found in a previous study that it may be efficient in healthy subjects with a certain DRD2 genotype (TT[32,60]). The 2 cortical stimulation targets are shown in **Figure 1**. The sham stimulation was given with the same settings as the active stimulation at S1/M1, but there was a 75-mm plastic block between the coil and the head, which minimized the electric field reaching the cortex close to 0 V/m. The acoustic and sensory effects of the stimulations were similar, except for high stimulation intensities when the active S2 stimulation induced temporal muscle contraction (the location was slightly altered in these cases). The navigated device located the optimal coil position and direction using the individual head MRI and infrared tracking unit. Each stimulation session consisted of 1000 (500 + 500) pulses with 10-Hz frequency. The stimulation was given in trains of 50 pulses at 10-second intervals and a 15-minute break in the middle of session to cool the coil. The intensity of stimulation was 90% of resting motor threshold (RMT). The RMT was determined before the first session by single pulse stimulation of the right motor cortex as described earlier.[60] Motor-evoked potentials (MEP) were recorded with surface electrodes on the left thenar muscles using the Viking electroneuromyography device (Viking; Nicolet, Madison, WI). The area giving the largest MEP was mapped, and the RMT was determined with an automated computerized program.[8] The representation area of the facial muscles in the relevant motor cortex was determined with single TMS pulses at intensity 10% to 20% above the previously determined RMT. The elicited MEPs were recorded with surface electrodes on contralateral frontal, nasal, and mental muscles, and the area giving the best response to the nasal muscle was chosen to be the M1 stimulation area and the area just behind it on the postcentral gyrus was the S1 area; together S1/M1 target. The S2 area was assumed to be at the most lateral edge of the postcentral gyrus, near the operculum, and it was defined according to the individual MRI data similarly as described in our earlier study.[60]

2.4. Genetic analysis

Patients gave a venous blood sample from which the DNA was extracted using standard procedures. The 957C>T polymorphism (GenBank NM_000795.3:c.957C>T, rs6277) was determined similarly as described earlier.[18,30,32] The COMT enzyme Val158Met polymorphism (GenBank NM_000754.3:c.472G>A, rs4680) was determined using the PCR-RFLP method of Woo et al.[63] After the digestion, the fragments were separated by 2.5% BMA MetaPhor (Oriola, Espoo, Finland), agarose gel electrophoresis containing 0.5 μg/mL ethidium bromide, and documented with UV transillumination as described earlier.[30,32]

2.5. Statistical analysis

Power analysis was performed to estimate the minimum sample size required to detect a clinically meaningful 30% decrease in pain intensity. Under the assumption of 20% dropout rate, with 80% statistical power and a 2-sided alpha risk of 0.05, a total of 20 patients had to be enrolled in the trial.

Statistical analyses were performed with SAS Inc software Mixed Procedure (SAS Institute Inc, Cary, NC). All main effects and interaction effects were analyzed. Comparisons between the means were done by contrasts, and no adjustments were applied. The effects of rTMS on pain, quality of life, and mood evaluations were determined by repeated measures analysis of variance (rmANOVA) with time as the within-subject factor and diagnosis and genotype as between-subject factors. For the right S2 stimulation, a separate rmANOVA was conducted with the side of pain symptoms as the between-subject factor. As regard to rmANOVA analyses and results, estimates of mean (EM), ±SE are given. *P* values less than 0.05 were considered statistically significant.

Effect sizes (Cohen d) were calculated for the mean differences of the NRS scores on the third day after active treatments vs the sham treatment. In addition, effect sizes were calculated for the

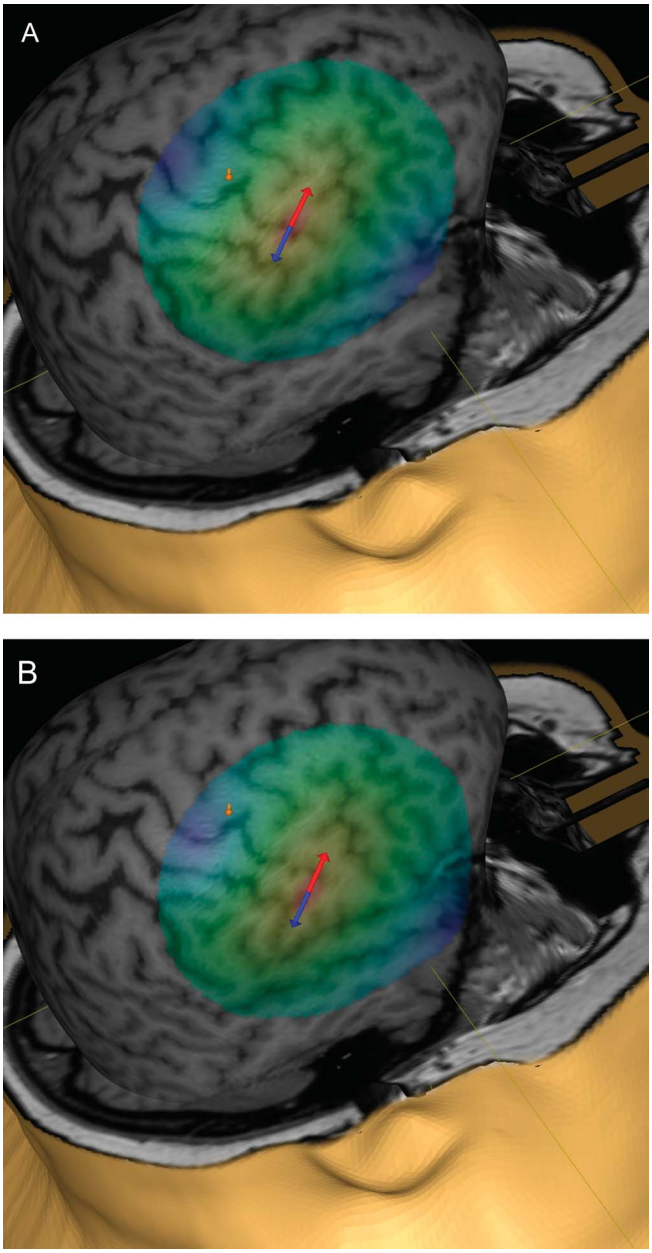

Figure 1. Cortical targets for the active repetitive transcranial magnetic stimulation treatments were the S1/M1 cortex representing the face area (A) and the right secondary somatosensory cortex (B). The induced electrical fields are shown; the red arrow head marks the position and direction of the main vector. The small yellow tag marks the hand representation area on the M1.

mean differences before the treatments and on the third day after each treatment. In calculating the effect size, mean, and SD values were used. The responder rate (rr) was calculated by dividing the number of responders, ie, patients who received at least 30% decrease in NRS, by the number of all the patients in the group.

3. Results

Pain intensity (NRS) was lowest on the third day after the S2 stimulation (EM: 3.8, SE: 0.6) being significantly lower than after the S1/M1 stimulation (EM: 5.4, SE: 0.6; $P = 0.0071$) or sham (EM: 5.3, SE: 0.6; $P = 0.0187$). The S2 treatment (mean: 3.8, SD: 2.0) was effective compared with the sham treatment (mean: 5.0, SD: 2.0) with an effect size (Cohen d) of 0.6. The S1/M1 treatment (mean: 5.4, SD: 2.0) had a slight negative effect, Cohen d = −0.2. When compared with the baseline pain before the treatments (mean: 5.7, SD: 1.9), the Cohen d for the S2 treatment was 1.0, for the S1/M1 treatment 0.1, and for the sham treatment 0.4. The average pain intensities at baseline and after the 3 rTMS treatments are shown in **Figure 2**. The treatment effects varied widely between the patients; individual variation is illustrated in **Figures 3 and 4**. The rr for the S1/M1 stimulation was 13%, for the S2 stimulation 38%, and for sham stimulation 25%.

The BPI pain intensity scores 3 to 5 days after the S2 session were significantly lower (estimate of mean: 4.5, SE: 0.4) than the scores before the sessions (EM: 5.4, SE: 0.4; $P = 0.0127$) or after the S1/M1 (EM: 6.2, SE: 0.4; $P = 0.001$) and the sham (EM: 5.1, SE: 0.4; $P = 0.0491$) sessions. Also, the BPI interference of pain scores were lower 3 to 5 days after the S2 session (EM: 2.7, SE: 0.5) than before the sessions (EM: 3.6, SE: 0.5; $P = 0.0074$) or after the S1/M1 (EM: 4.0, SE: 0.5; $P = 0.0001$) and sham (EM: 3.4, SE: 0.5; $P = 0.0359$) sessions. At 1 month after S2 stimulation (**Figures 5 and 6**), both the pain intensity and the pain interference scores remained lower than at baseline. Despite these changes in pain intensity and interference, the symptomatic area in the symptom chart did not change.

There was a small but significant reduction in the NePIQol total score (a higher score indicating more interference) 1 month after the S2 stimulation (ES: 79.8, SE: 5.7) as compared with the situation before the treatment (ES: 86.6, SE: 5.7; $P = 0.0031$). No significant changes occurred after the S1/M1 (ES: 85.5, SE: 5.7; $P = 0.6083$) or the sham (ES: 87.0, SE: 5.7; $P = 0.8563$) stimulations.

There were no significant changes in BDI and RAND-36 scores during the study period. Neither the DRD2 957C>T nor the COMT Val/Met polymorphism had any significant effect on treatment response independent of the cortical stimulation site. The side of pain symptoms did not influence the results of the right S2 stimulation as there was no interaction effect between

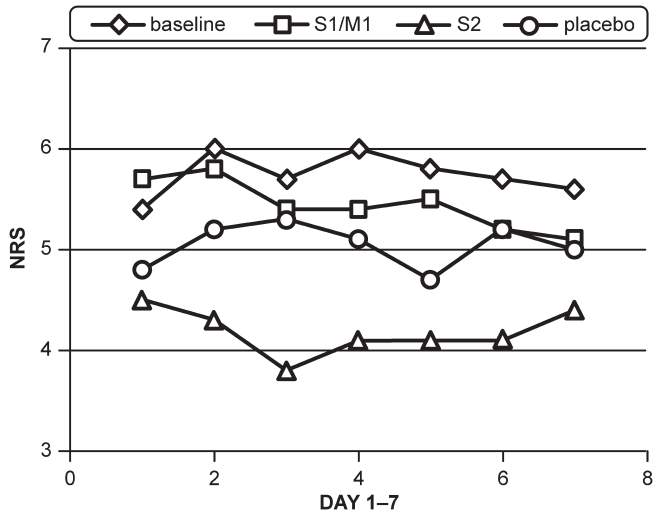

Figure 2. Mean pain intensity (NRS) followed for 7 consecutive days at baseline and after the 3 treatment sessions starting in the evening of the treatment day. Pain intensity on the third day after the stimulation session was significantly lower after S2 stimulation than S1/M1 (0 = 0.0071) or sham ($P = 0.0187$) stimulation.

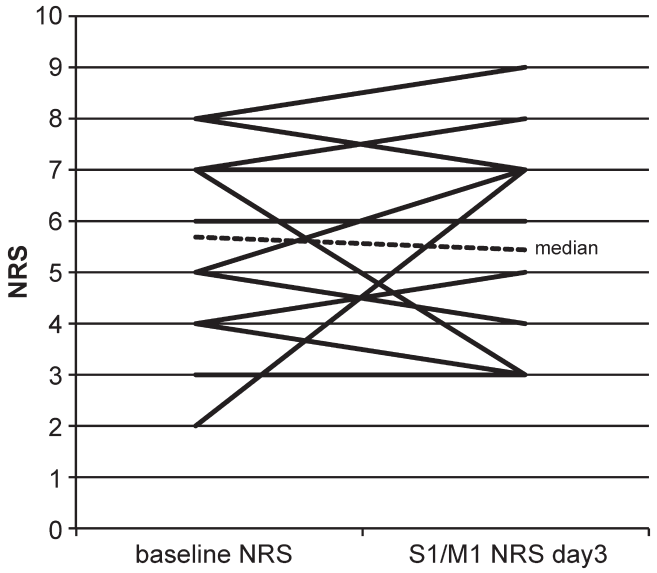

Figure 3. Individual numeric rating scale (NRS) scores at baseline and on the third day after S1/M1 stimulation.

time and the symptomatic side in rmANOVA ($P = 0.6282$, $F_{(14,76)} = 0.84$).

Six of the 16 patients used on-demand nonsteroidal anti-inflammatory drugs for symptoms other than the drug-resistant facial pain, for example, back pain, shoulder pain, and migraine. The consumption of these drugs did not change significantly during the study.

No serious adverse effects were observed. Active rTMS induced unpleasant contraction of the temporal muscle in 2 patients whose stimulation intensity was particularly high because of high RMT. At the final visit 4 weeks after the last stimulation session, patients were asked: "Which one of the three stimulation sessions you would assume to be the sham stimulation session?" Six patients recognized the sham stimulation, 2 because of the previously mentioned muscle contraction during active rTMS, and 4 because of a distinct (positive) response to the active treatment.

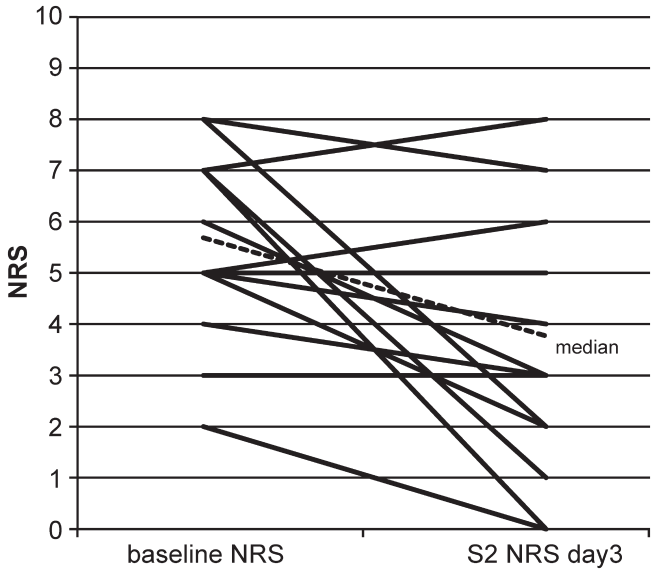

Figure 4. Individual numeric rating scale (NRS) scores at baseline and on the third day after S2 stimulation.

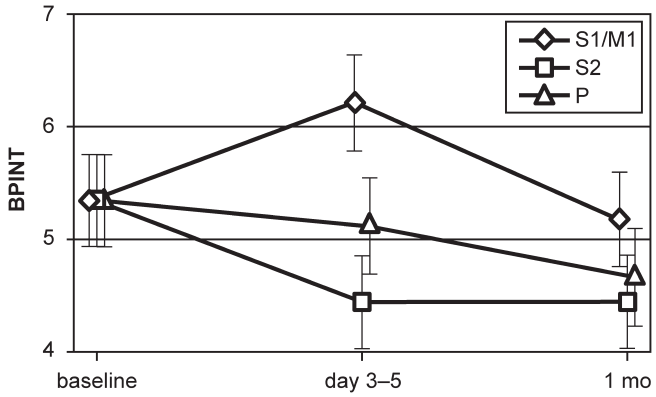

Figure 5. Brief Pain Inventory intensity (BPINT) of pain scores were significantly lower 3 to 5 days after the S2 stimulation session than scores before the sessions ($P = 0.0127$) or after S1/M1 ($P = 0.001$) and placebo ($P = 0.049$) sessions.

4. Discussion

High-frequency rTMS of the right S2 cortex showed a superior analgesic effect on chronic neuropathic orofacial pain when compared with stimulation of the sensorimotor S1/M1 cortex or sham stimulation. Significant improvements were seen in NRS, BPI, and NePIQoL scores which measure pain intensity and its interference with life. No significant changes in mood were seen either in BDI or RAND-36 questionnaires indicating that the analgesic effects were not related or secondary to changes in mood. The effect size of 0.6 with S2 stimulation is similar to the mean weighted effect size of rTMS on depression.[52] When only the patients with more than 30% decrease in NRS score were considered responders, the rr for S2 stimulation was 38%. However, there were many patients receiving some analgesic effect, but it was not enough to be considered responders.

In our previous work,[60] we discovered a significant decrease in thermal pain sensitivity (hypoalgesic effect) of the face after rTMS given to the right S2 cortex in healthy volunteers. Another earlier study[23] showed improvement in chronic visceral pain after right S2

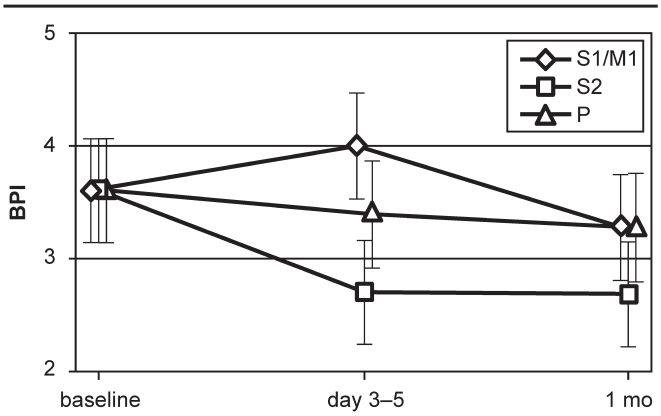

Figure 6. Brief Pain Inventory (BPI) interference of pain scores were significantly lower 3 to 5 days after the S2 stimulation session than before the sessions ($P = 0.0074$) or after the S1/M1 ($P = 0.0001$) and placebo ($P = 0.0359$) sessions.

stimulation, although in that work only low-frequency stimulation was effective. Based on these findings, we chose the right S2 as the other target for active stimulation. It would have been interesting to include the left S2 cortex as well, but making the study protocol even more demanding could have increased the drop-out rate. The effectiveness of the S2 stimulation could be explained by the location of the cortex close to the insular cortex, which is known to have an important role in pain perception.[6,9,12,24,47–49,55,56,62] Functional connections between the M1, S1, and S2 cortices and the insular cortex have been found, with the S2 connection being especially strong during painful stimulation.[46] rTMS induces metabolic changes both at the site of stimulation and in distant locations probably through cortico–cortical connections and subcortical networks.[59] However, rTMS releases dopamine in the striatum,[34,35,53] and striatal dopamine D2 receptors are involved in the modulation of pain.[27,33] Therefore rTMS may exert its analgesic effect in multiple locations of neuronal networks connected to the S2 stimulation site.

The effects of rTMS on pain intensity NRS scores were mostly short lasting, vanishing within a week after the stimulation. Analgesic effects of a single session have been short lasting also in earlier studies.[40] Longer-lasting effects were observed in BPI and NePIQoL questionnaires, which both measure multiple aspects of pain and its interference on life. This could depend on the alteration in patients' attitude towards pain as suggested earlier.[11,60] However, no significant changes were seen in patients' health-dependent quality of life according to RAND-36 questionnaire. The NePIQoL questionnaire, which is specifically designed to measure quality of life in neuropathic pain, was possibly more suitable for our group of patients with chronic neuropathic orofacial pain.

A slight placebo effect was observed in this study as is common in pain studies. However, the effects of the previous stimulation session did not seem to have an influence on the following placebo session as was found in an earlier study.[4] As is the case in most rTMS studies, the placebo condition was not optimal, but nevertheless, the majority of our patients could not correctly distinguish sham from active stimulations. The S1/M1 stimulation was inefficient or even hyperalgesic in some patients. We decided to include the S1 cortex as the stimulation area because S1 stimulation had shown DRD2 genotype-related efficacy in our previous study with healthy subjects.[32] However, in earlier studies, stimulation of the S1 cortex has been considered inefficient on group-level comparisons[29] or hyperalgesic,[58] which is in line with our present finding. Possibly, the precise navigation of the S1/M1 stimulation to the representation area of the face could also explain some of the poor results, as it has earlier been suggested that the best stimulation target could be the adjacent area rather than the "hotspot" corresponding to the pain.[39] Interestingly, the S1/M1 stimulation induced highly variable effects, from analgesia to hyperalgesia, rendering the group-level efficacy nonsignificant. This variability could not, however, be shown to be dependent on the DRD2 genotype of the patients. In contrast, S2 stimulation induced more uniform hypoalgesic effects regardless of the painful side. Considering the different results from very nearby cortical areas, precise neuronavigation and correct coil positioning seem to be very important as regards the efficacy of rTMS treatment.

In this study, there was a wide variation in the treatment response between individuals, which did not depend either on the specific facial pain diagnosis, the psychiatric diagnosis, or the dopamine system-related genotype. The DRD2 homozygous TT genotype was overrepresented (50%) in our unselected group of patients with neuropathic pain as previously reported,[32] which may have rendered the results of genetic association analyses nonsignificant in this small sample with limited statistical power. Nevertheless, our earlier observations in healthy subjects suggest involvement of DRD2-related genetic factors in rTMS effects on sensory thresholds.[32] However, the underlying mechanism of these hypoalgesic rTMS effects on sensory detection may be, at least partly, different from those contributing to patients' appraisal of their clinical symptoms.

A clear limitation of our study was the small sample size, which is a limitation of many other rTMS studies as well.[37] The study protocol was quite challenging, which complicated recruitment. In addition, patients had a very severe, chronic, and drug-resistant neuropathic pain state. Because of this and old age, many potential participants were not willing or able to take part in the study. However, the diagnoses of neuropathic orofacial pain were carefully performed according to current clinical diagnostic criteria and meticulously confirmed with neurophysiologic and psychophysical examinations. Thus, our patients form a much more pathophysiologically homogenous group than is the case in many previous studies on the treatment of neuropathic pain. This may partly compensate for the small group size. Furthermore, according to the power analysis, the sample size was considered sufficient to detect clinically meaningful changes in pain intensity. Considering current findings indicating a short-lasting effect of a single rTMS session, a multiple session protocol probably would have been more effective, as suggested in some previous studies.[17,36] Based on our findings on the time course of effects with the maximum at day 3, it could be worth examining the effects of multiple sessions separated by 2 to 3 days.

The right S2 cortex seems to be a promising new target for the treatment of drug-resistant neuropathic orofacial trigeminal pain with high-frequency rTMS. This study encourages searching for new efficient stimulation targets in addition to the most commonly applied M1 cortex.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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