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A Randomized, Sham-Controlled Trial of Repetitive Transcranial Magnetic Stimulation Targeting M1 and S2 in Central Poststroke Pain: A Pilot Trial

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ABSTRACT

Objectives: Central poststroke pain (CPSP), a neuropathic pain condition, is difficult to treat. Repetitive transcranial magnetic stimulation (rTMS) targeted to the primary motor cortex (M1) can alleviate the condition, but not all patients respond. We aimed to assess a promising alternative rTMS target, the secondary somatosensory cortex (S2), for CPSP treatment.

Materials and Methods: This prospective, randomized, double-blind, sham-controlled three-arm crossover trial assessed navigated rTMS (nrTMS) targeted to M1 and S2 (10 sessions, 5050 pulses per session at 10 Hz). Participants were evaluated for pain, depression, anxiety, health-related quality of life, upper limb function, and three plasticity-related gene polymorphisms including Dopamine D2 Receptor (DRD2). We monitored pain intensity and interference before and during stimulations and at one month. A conditioned pain modulation test was performed using the cold pressor test. This assessed the efficacy of the descending inhibitory system, which may transmit TMS effects in pain control.

Results: We prescreened 73 patients, screened 29, and included 21, of whom 17 completed the trial. NrTMS targeted to S2 resulted in long-term (from baseline to one-month follow-up) pain intensity reduction of ≥30% in 18% (3/17) of participants. All stimulations showed a short-term effect on pain (17–20% pain relief), with no difference between M1, S2, or sham stimulations, indicating a strong placebo effect. Only nrTMS targeted to S2 resulted in a significant long-term pain intensity reduction (15% pain relief). The cold pressor test reduced CPSP pain intensity significantly ($p = 0.001$), indicating functioning descending inhibitory controls. The homozygous *DRD2* T/T genotype is associated with the M1 stimulation response.

Conclusions: S2 is a promising nrTMS target in the treatment of CPSP. The *DRD2* T/T genotype might be a biomarker for M1 nrTMS response, but this needs confirmation from a larger study.

Keywords: Central poststroke pain, conditioned pain modulation, CPM, CPSP, *DRD2*, pain genetics, primary motor cortex, secondary somatosensory cortex, transcranial magnetic stimulation

Conflict of Interest: Eija Kalso has received personal fees for participation in advisory board meetings of Pfizer and Orion Pharma, unrelated to this work. Dr. Juhani Ojala reports grants from Suomen Lääketieteen Säätiö, outside the submitted work. Dr. Jukka Vanhanen reports grants from the Emil Aaltonen Foundation, grants from state funding for university-level health research,

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INTRODUCTION

Central poststroke pain (CPSP)[1] may follow an ischemic or hemorrhagic cerebrovascular lesion in the central somatosensory system. Among stroke patients, the prevalence of CPSP varies from 1% to 8%.[1–3] In CPSP, the pain and sensory abnormalities are usually contralateral to the cerebrovascular lesion. Diagnosis is confirmed by brain imaging, neurological examination, and excluding other causes for the pain.[1,4]

CPSP is difficult to treat, and only a minority of patients benefit from neuropathic pain (NP) medications.[5] Thus, there is a pressing need for new treatments. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method with level A (definite efficacy) recommendation for NP for high-frequency primary motor cortex (M1) stimulation.[6–9] It is potentially a feasible and safe treatment with only a few contraindications.[10] M1 stimulation probably modulates pain through connections to other brain areas related to pain control[11] and may activate the top-down pain modulatory mechanisms.[12] However, not all patients respond to M1 stimulation and other targets have been tested.[13] Stimulation of the dorsolateral prefrontal cortex gave negative results,[14] while promising results were obtained with stimulation of S2 in patients with orofacial pain.[15] Applying three-dimensional (3D) magnetic resonance imaging (MRI)-based navigation increases target accuracy to a few millimeters.[16]

The efficacy of rTMS, like other interventions used to manage chronic pain, varies greatly. In pharmacological intervention studies, efficacy of the endogenous pain control system assessed with conditioned pain modulation (CPM) has explained some variation in analgesic responses in NP.[17] Genetic factors may also play a role.[18] In addition, several questions regarding rTMS methodology and stimulation parameters, for example, optimal number of pulses, stimulus intensity, and stimulation site, need to be addressed.[19]

The primary aim of this randomized controlled pilot trial was to study whether navigated rTMS (nrTMS) targeted to M1 or S2, as compared with sham stimulation, was effective in the management of CPSP. In addition, we studied the role of CPM using the cold pressor test,[20] and the association of three plasticity-associated gene polymorphisms, Dopamine D2 Receptor (*DRD2*) C > T (rs6277), catechol-O-methyltransferase (*COMT*) G > A (rs4680), and brain-derived neurotrophic factor (*BDNF*) G > A (rs6265),[18,21–23] with the treatment effect. We characterized the participants with questionnaires on pain, mood, health-related quality of life (QoL), hand disability, and patient-generated pain drawings. The functional disability of the hemiparetic upper arm was assessed by the Nine-Hole Peg Test, pinch, and grip strength tests.

MATERIALS AND METHODS

Participants and Clinical Examination

Participants were recruited from the Helsinki Young Stroke[24] and Young Intracerebral Haemorrhage[25] Patient registries, from the Pain Clinic, and the Neurological Outpatient Clinic of the Helsinki University Hospital, and via advertisement in the newsletter of a stroke patient organization.[24,26] The inclusion criteria were CPSP diagnosis, age >18 years, and pain intensity ≥4 on a numerical rating scale (NRS, 0–10; 0 indicating no pain and 10 the worst pain imaginable),[27,28] predominantly in the upper limb. Exclusion criteria were epilepsy, metal in the body, alcohol or drug abuse, inability to communicate, and psychotic symptoms or disease.

The presence of CPSP was assessed by the same neurologist at all screening visits according to the following grading system: 1) Other likely reasons for pain were excluded; 2) Pain was in a neuroanatomically plausible distribution; 3) There was a history suggestive of stroke; 4) Sensory signs were detected in the painful area; 5) Brain imaging indicated a relevant cerebrovascular lesion and pain had emerged in the plausible area within a year of the stroke event. CPSP was defined as "possible" if 1, 2, and 3 were fulfilled; "probable," if 1, 2, 3, and 4 or 5 were fulfilled; and "definite," if 1, 2, 3, 4, and 5 were fulfilled.[29] Sensory function was assessed by a cotton ball (light touch), a painter's brush (dynamic allodynia), compression by finger (static allodynia), a cocktail stick (sharp sensation), and a metal roller (thermal sensation). The metal roller was dipped into ice-cold water at 4°C for 10–15 sec to reach a temperature of about 8°C or into boiling water for 10–15 sec to reach a temperature of about 45°C before testing the patient. The researcher checked the temperature on herself before examining the patient (to avoid exposing the patient to excessive heat or cold). In addition, participants completed a pain drawing on a body template.

All participants had received pharmacological treatment for NP with insufficient analgesia. Participants continued their former medications, which included no strong opioids. No new medications were introduced during the study. T1-weighted brain MRI using a three-dimensional magnetization-prepared rapid gradient-echo sequence (TI 900 msec, TR 1900 msec, TE 2.47 msec, flip angle

9°, 1.0 mm^3 isotropic voxels) was performed on all participants for planning the nrTMS.

The study protocol was approved by the medical ethics committee of the Helsinki and Uusimaa Hospital District (Register no. 91/13/03/01/14). All participants gave written informed consent. The study protocol was registered on ClinicalTrials.gov (NCT02277912).

Treatment Protocol

This pilot trial was a randomized, double-blind, 2-sequence, 3-period, 3-treatment crossover study with a wash-out period of at least one month. Each participant received nrTMS targeted to primary motor (M1) and secondary somatosensory cortices (S2), as well as sham stimulation. Each target was stimulated every working day for two weeks, with a total of ten sessions per target (Fig. 1).[30,31]

Randomization was performed using a computer program and sealed envelopes. Participants, researchers not involved in the stimulations, and the study nurse were blinded to the treatment allocation.

E-Field Navigated rTMS

Navigated repetitive TMS was delivered with a figure-of-eight coil (diameter 70 mm) NBS 4 (Nexstim Ltd., Helsinki, Finland). The representation area of the abductor pollicis brevis muscle in M1 was first searched from the hand knob area identified from the individual MRI image, contralateral to the side of pain. The motor threshold (MT) of the abductor pollicis brevis was estimated as previously described.[30] The range of the MT values was 20–84% of the maximum stimulator output. The site and coil orientation producing motor-evoked potentials with the highest amplitude were selected as the nrTMS target for M1.

S2 resides in the parietal operculum deep in the Sylvian fissure about 5 cm below and 1 cm anterior to the hand primary somatosensory cortex.[32–34] To activate S2, nrTMS was targeted to the lateral upper lip of the Sylvian fissure corresponding to these coordinates in the individual MRI images, contralateral to the side of pain. The stimulation current was oriented perpendicularly to the Sylvian fissure (Fig. 2). Induced current orientation perpendicular to the central sulcus reveals distinct excitability peaks and lowest motor thresholds for different hand muscle activations.[35] Orientation of stimulation perpendicular to target gyri is also recommended for mapping cortical representations of speech to induce maximum stimulation efficacy in language mapping.[36] Moreover, it standardizes stimulation among individuals.

The nrTMS was applied at 10 Hz during a 50-min period with an intensity of 90% of the MT. Altogether, 5050 pulses per session were given in trains of 101 pulses (10-sec stimulation with a 50-sec intertrain interval). The electric fields induced by the nrTMS ranged from 31 to 127 V/m in the underlying M1 cortex. The corresponding values in the chosen lateral cortical site for S2 ranged from 39 to 109 V/m.

Sham nrTMS was delivered over the M1 cortex by attaching a 75-mm nonconductive plastic block on the coil to increase the coil-to-scalp distance (Fig. 3) and to minimize the electric field induced in the cortex. During sham stimulation, the participant could feel a slight shaking of the coil on the scalp. In order to conceal the visual cues of the nature of the stimulation, the sham block was attached only after the patient was seated in the treatment chair and was detached immediately after the stimulation. Therefore, the patient could not, for example, have a preconception that sham stimulation would be more effective because of a bigger coil. The person administering nrTMS was, however, aware of the stimulation type. The participants, all TMS-naïve, were informed that the three stimulation periods could feel somewhat different.

Demographic Factors, Questionnaires, and Conditioned Pain Modulation

At the research visit, detailed demographic and medical information was obtained from all participants. The same neuroradiologist evaluated stroke sizes (≤1.5 or >1.5 cm) and the intracerebral hemorrhage (ICH) volumes (≤30 or >30 mL) in a categorical way from patient brain MRIs or CTs, using computer-based measurements.

The time points of the clinical evaluations are illustrated in Figure 4. Participants recorded pain intensity (NRS) once per day for a week before and two weeks after each stimulation period. During stimulation periods, pain intensity was assessed immediately before and after each nrTMS session. An experienced research nurse made a structured phone call to all participants one month after each nrTMS treatment to evaluate current pain intensities. In addition, participants were asked to report any adverse events relating to TMS treatment.

To assess other nrTMS effects, participants completed a set of validated questionnaires, underwent examinations for hand motor function, as well as a CPM test,[37] approximately a week before and a week after each treatment period (Fig. 4). The questionnaires comprised the Brief Pain Inventory (BPI, assessing, eg, weekly average pain intensity and pain interference),[38] Disabilities of the

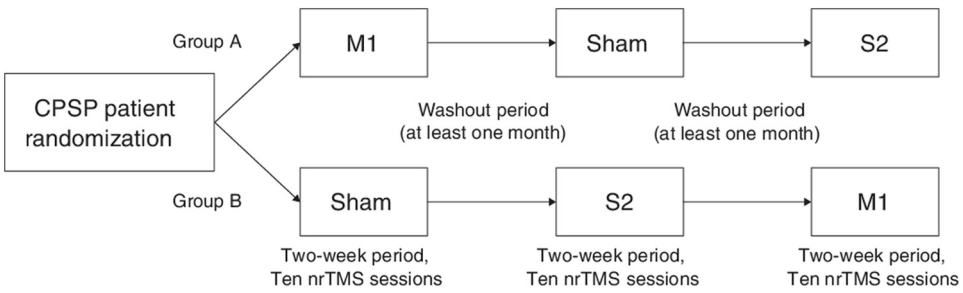

Figure 1. Patient randomization and study protocol. CPSP, central poststroke pain; M1, primary motor cortex; nrTMS, navigated repetitive transcranial magnetic stimulation; S2, secondary somatosensory cortex.

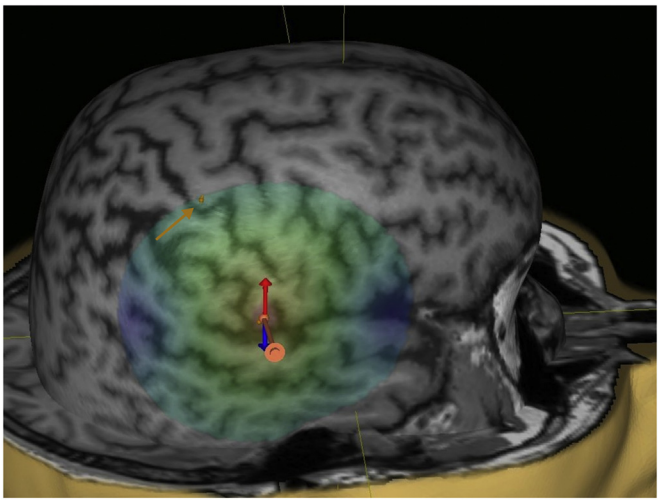

Figure 2. The target of nrTMS for S2 stimulation in the lateral upper lip of the Sylvian fissure. The red arrow gives the orientation of the induced electric current. The hotspot of M1 activation is also displayed in the hand knob of M1 (orange arrow). M1, primary motor cortex; nrTMS, navigated repetitive transcranial magnetic stimulation; S2, secondary somatosensory cortex.

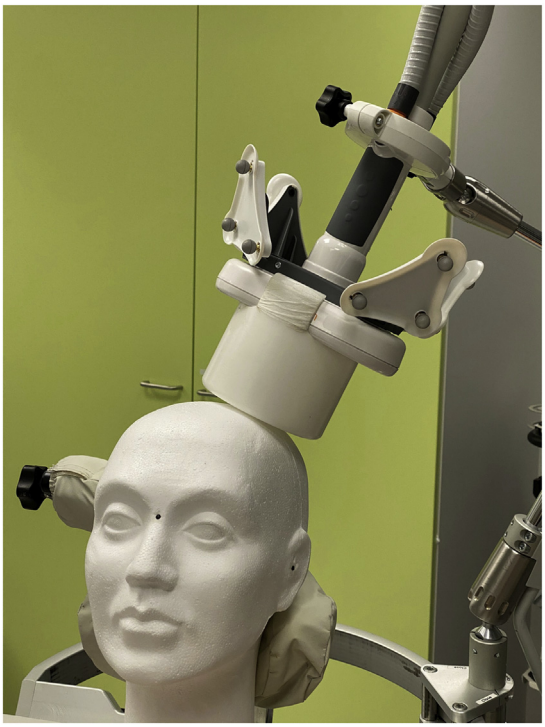

Figure 3. The stimulation coil with a 75-mm-high plastic block for sham stimulation.

Arm, Shoulder, and Hand (DASH),[39] health-related QoL (EQ-5D-3L),[40,41] depression (Beck Depression Inventory, BDI),[42] and anxiety (Pain Anxiety Symptoms Scale [PASS-20]).[43] The examinations for hand function were Nine-Hole PEG,[44] JAMAR (JAMAR hand dynamometer, Sammons Preston Rolyan, Bolingbrook, IL), and Pinch (Mechanical Pinch Gauge, Fabrication Enterprises Inc., Elmsford, NY).[45]

For CPM, the cold pressor test served as the conditioning stimulus. First, the participant reported the current CPSP intensity in the affected hand (NRS). Then, they immersed the healthy hand up to the wrist in the cold-water bath (3°C–4°C) (JULABO USA Inc., Allentown, PA) for as long as tolerated, with a cut-off at 90 sec. Participants reported the intensity of CPSP at withdrawal and at 1, 5, and 15 min afterwards.

Genotyping

Sixteen participants provided blood samples for DNA analysis. DNA was extracted from peripheral blood with the Autopure LS automated DNA purification instrument (Gentra Systems, Inc., Minneapolis, MN). Three plasticity-related single-nucleotide polymorphisms (SNP), *DRD2* C > T (rs6277), *COMT* G > A (rs4680), and *BDNF* G > A (rs6265), were genotyped using capillary sequencing with ABI3730XL DNA Analyzer and BigDye v.3.1 chemistry (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA) at the Institute for Molecular Medicine Finland (FIMM), University of Helsinki.

Statistical Analysis

The short-term primary outcome of nrTMS was defined by NRS_{PRE} (immediately before first stimulation) vs NRS_{POST} (median NRS immediately after each stimulation from all 10 daily sessions) (Fig. 4). This analysis protocol was modified from a previous rTMS study.[46] The percentage of pain relief (PPR) was calculated as $([NRS_{POST} - NRS_{PRE}]/NRS_{PRE}) \times 100\%$. A responder was defined as having a PPR of at least 30%; the responder rate is the percentage of responders. The long-term primary outcome was defined by pain intensity reduction from baseline (the median NRS value of the week prior to nrTMS) to the one-month follow-up.

Normally distributed data were analyzed using a repeated-measures two-way ANOVA (rmANOVA) with two within-subject factors: "Treatment," containing three group levels ("M1," "Sham," and "S2") and "Time," containing two group levels ("Pre" and "Post"). The main hypothesis was tested in the interaction between "Treatment" and "Time." Post hoc tests were performed with paired *t*-tests using Bonferroni's correction; 95% confidence intervals were not adjusted for multiple comparisons. Non-normally distributed within-subject data were analyzed with the Wilcoxon signed-rank test (Bonferroni's correction for multiple comparisons). The effect of different genotypes and various stroke parameters on the PPR were analyzed with the Mann–Whitney *U*-test, and the effect of CPM with paired *t*-test. Pairwise comparisons of the affected and unaffected hand were done with paired *t*-test or Wilcoxon signed-rank test.

Possible carry-over effects from previous nrTMS treatments were assessed by comparing the NRS_{PRE} values before each treatment period with the Friedman test. To evaluate the order effect, the change in pain intensity resulting from any of the three treatments was compared between the two sequences (group A vs B) with the Mann–Whitney *U*-test (no correction for multiple comparisons). To handle missing values, we imputed these using the group effect.

Fisher's exact test was used to compare the frequencies of the *DRD2* and *COMT* genotypes with known frequencies in the Finnish population derived from the Sequencing Initiative Suomi (SISu) data resource of 10,490 Finns.[47]

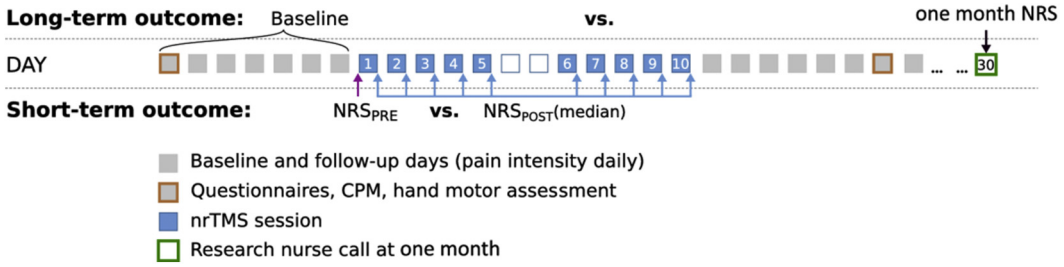

Figure 4. Time points of different evaluations. CPM, conditioned pain modulation; NRS, numeric rating scale; nrTMS, navigated repetitive transcranial magnetic stimulation.

Power calculations were performed with GLIMMPSE.[48] Estimation of CPSP baseline characteristics was based on a previously reported patient cohort with chronic CPSP[24,49] (mean pain intensity 5.3, standard deviation [SD] 2.0). To detect a clinically meaningful 30% pain reduction (corresponding to an effect size of Cohen $d = 0.8$) with a 90% power and two-sided α-level of 5%, the required sample size was 30. Statistical analyses were performed with SPSS software (version 22, IBM Inc., Armonk, NY); $p < 0.05$ was considered significant. The protocol was finalized in May 2013.

RESULTS

The study was performed between September 2013 and October 2015 at the Helsinki University Hospital: 73 patients were prescreened, 29 were screened, and 21 were included in the trial (Fig. S1). Thirteen participants had had an ischemic stroke, two an imaging-negative stroke, and six an ICH (Table 1, Table S1). Stroke sizes and ICH volumes included both large and small lesions (Table 1). Nineteen participants fulfilled definite, and two imaging-negative patients probable, CPSP criteria in CPSP grading.

All 21 participants had difficult-to-treat CPSP with pain NRS ≥4 in the upper arm at the screening visit and insufficient response to regular NP medications. Figure 5 illustrates pain locations from participant pain drawings. Four (all in group B) discontinued the study during or after the first stimulation period and were excluded from the analysis (Fig. 6). Seventeen participants completed the whole protocol. The median wash-out time between different treatment periods was 66 days.

Primary Outcome Measures

All three nrTMS treatments provided short-term pain relief at group level (Fig. 7, Panel A; Table 2). RmANOVA revealed a main effect of "Time" ($p = 0.047$), suggesting that the combined effect of all treatments was significant, with no significant difference between the treatments (rmANOVA interaction "Treatment" × "Time," $p = 0.92$). One month after the nrTMS, treatment effects differed significantly (rmANOVA interaction "Treatment" × "Time," $p = 0.040$) (Fig. 7, Panel B): the post hoc test revealed that the CPSP intensity was significantly lower at one-month follow-up after S2 stimulation than at baseline ($p = 0.042$) (Table 2). The short-term/long-term responder rate was 41%/6% for M1 stimulation, 41%/0% for sham stimulation, and 24%/18% for S2 stimulation, respectively.

The Friedman test did not show any carry-over effect ($p = 0.65$). The analgesic effect of any treatment did not significantly differ between the sequences in short-term (change of NRS in group A vs group B: for S2: −1.9 vs 0.1, $p = 0.27$; for M1: −1.3 vs −0.3, $p = 0.20$;

Table 1. Patient Demographics at Baseline.

Patients	All ($N = 17$)
Sex	
Male	8
Female	9
BMI	26.5 (4.0)
Age at stroke onset, years	48.7 (6.8)
Age at randomization, years	55.8 (7.1)
CPSP duration at randomization, years	5.6 (3.2)
Pain intensity	5.2 (2.3)
Weekly average pain intensity	5.5 (1.5)
Pain interference	6.9 (2.3)
mRS score	2.2 (1.1)
BDI score	15.2 (8.5)
PASS-20 score	38.1 (21.5)
EQ-5D index	0.50 (0.18)
DASH score	45.8 (15.7)
Cerebrovascular lesions	
Ischemic stroke	10
ICH	6
Imaging-negative IS	1
Infarct lesion size	
≤1.5 cm	3
>1.5 cm	7*
ICH volume	
≤30 mL	4
>30 mL	2
Territory	
Anterior	8
Posterior	1
NA	1
Laterality	
Right	9
Left	7
Anatomical location	
Subcortical	7
Subcortical + cortical	6
Cortical	0
Thalamus	5
Basal ganglia	3
Vermis or brainstem	1
M1/S2 lesion	2

Values represent numbers of observations or mean value (standard deviation).
BDI, Beck's Depression Scale; BMI, body mass index; CPSP, central poststroke pain; DASH, Disabilities of Arm, Shoulder, and Hand; EQ-5D index, EuroQol 5 dimensions questionnaire index; ICH, intracerebral hemorrhage; IS, ischemic stroke; mRS, Modified Ranking Scale; NA, not applicable; PASS-20, short version of the Pain Anxiety Symptoms Scale.
*Two patients had multiple strokes.

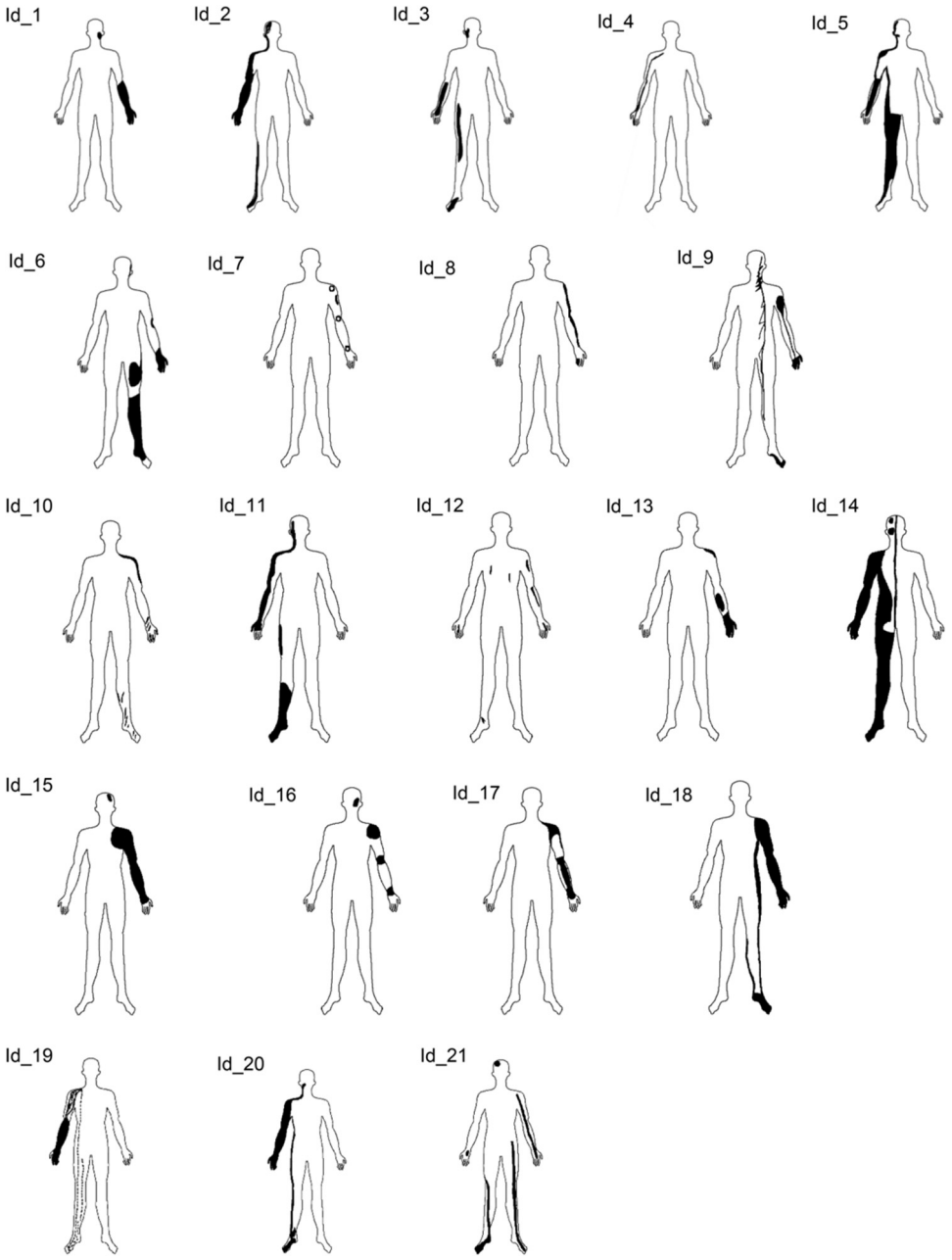

Figure 5. Pain location drawings by the participants.

for sham: −1.2 vs −0.5, $p = 0.57$) or long-term results (S2: −0.95 vs −0.21, $p = 0.38$; M1: −0.25 vs −0.14, $p = 0.42$; sham: 0.1 vs 0.43, $p = 0.65$). The daily NRS recordings during the two-week post-stimulation period were unusable for further analysis due to deficiencies in the collected data.

Secondary Outcome Measures

RmANOVA revealed an interaction of "Treatment" with "Time" in the weekly average pain intensity ($p = 0.001$). Post hoc tests showed that S2 stimulation significantly reduced the weekly average pain intensity score ($p = 0.012$, $N = 16$), whereas M1 ($p > 0.99$) or sham stimulations ($p = 0.060$) did not (Fig. 8, Panel A; Table 2).

All three stimulations reduced pain interference (Fig. 8, Panel B). RmANOVA, main effect of "Time" ($p = 0.002$) suggested that the combined effect of all three was significant, with no significant difference between the treatments (rmANOVA interaction "Treatment" × "Time", $p = 0.38$).

In the CPM tests at baseline, CPSP intensity was significantly lower 1 min after withdrawal of the healthy hand from the water basin (before: mean 5.12 [SD 2.15]; after: mean 4.12 [SD 1.69]: $p = 0.001$) and remained decreased until the end of the 15-min follow-up ($p = 0.003$). The CPM efficacy did not change after any nrTMS treatment.

At baseline, participants presented, on average, mild depression (BDI), high pain-related anxiety (PASS-20), decreased QoL, and

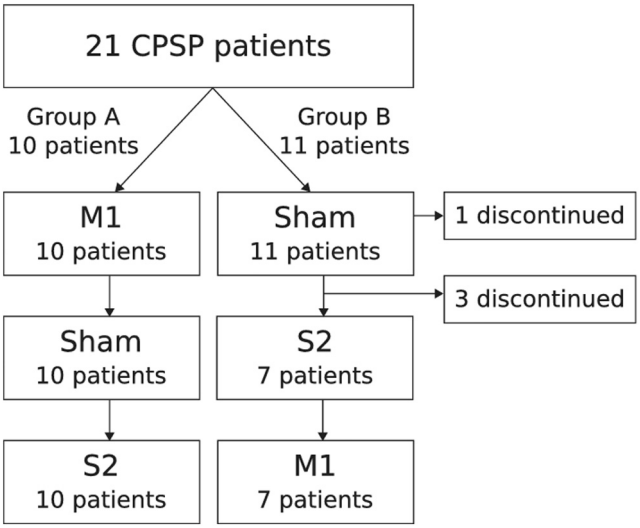

Figure 6. Flow diagram of the trial: intervention allocation.

moderate hand disability (DASH) (Table 1). At group level, these scores did not change significantly after nrTMS treatments (Table S2). In an exploratory analysis, QoL (EQ-5D index and EQ VAS) improved in three out of four S2 responders, in one of seven M1 responders, and in none of seven sham responders.

At baseline, grip strength was significantly lower in the affected hand, as measured with JAMAR ($p = 0.008$) and Pinch ($p = 0.007$) tests, and the Nine-Hole PEG performance was worse in the affected hand ($p = 0.016$); nrTMS did not significantly modify the affected or unaffected hand function, as measured with Pinch, JAMAR, or Nine-Hole PEG tests (data not shown).

Subgroup Analysis of Genotypes and Anatomical Location of Stroke

The *DRD2* C > T (rs6277) homozygous T/T genotype was more frequent in our participants than in the general population, but the difference was not significant (44% vs 30%, $p = 0.30$). The M1 stimulation was more effective in participants with the homozygous *DRD2* T/T genotype (median PPR = −36%, interquartile range IR = 40%), than in those with the genotype C/T or C/C (median PPR = 0.0%, IR = 14%, $p = 0.039$). The *DRD2* genotype was not significantly associated with the effect of S2 ($p = 0.42$) or sham stimulation ($p > 0.99$).

The *COMT* (rs4680) A/A genotype was overrepresented in our participants, compared with the general population (62% vs 31%; $p = 0.031$). The *COMT* genotype did not independently associate with the nrTMS outcome. All subjects were homozygous for *BDNF* (rs6265) G, and therefore no subgroup analysis was conducted.

Whether the pain was on the left or right side of the body did not significantly affect the results of the S2 nrTMS ($p = 0.37$). The anatomical location of the stroke, affecting M1 or S2, thalamus, or purely subcortical structures, did not significantly modify the efficacy of the treatments.

Adverse Events

In general, adverse events associated with nrTMS stimulation were mild and transient: headache (1 participant during M1, 4 during sham, 3 during S2), tiredness (2 M1, 2 sham, 3 S2), paresthesia (2 M1, 3 sham, 3 S2), transient increase of pain (2 M1, 2 sham, 3 S2), collapse (1 M1), increased spasticity (2 S2), and dizziness (1 S2).

DISCUSSION

In this randomized placebo-controlled pilot trial, we tested a novel target, S2 contralateral to the painful side, for nrTMS in CPSP patients, comparing this with M1 and sham stimulation. S2 stimulation significantly reduced the weekly average pain intensity, as well as the long-term pain intensity at one month, compared with baseline, while M1 and sham did not. The short-term effect on pain intensity or pain interference did not significantly differ among the three conditions. CPM reduced CPSP intensity, suggesting that descending inhibitory controls were intact. The *DRD2* rs6277 genotype was significantly associated with the M1 effect,

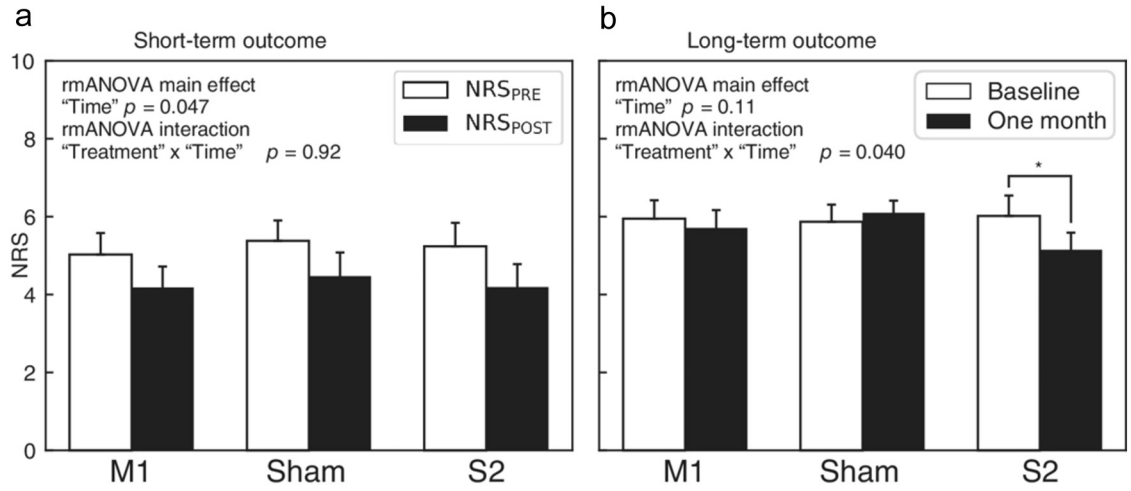

Figure 7. Pain intensity (NRS) immediately after (short-term outcome) and one month after (long-term outcome) nrTMS treatments with different targets: M1, Sham, and S2. M1, primary motor cortex; NRS, numeric rating scale; nrTMS, navigated repetitive transcranial magnetic stimulation; S2, secondary somatosensory cortex. *$p < 0.05$.

Table 2. Results of Primary Outcome Measures (Pain Intensity, NRS 1–10) and Secondary Outcome Measures (Weekly Average Pain Intensity and Pain Interference) with nrTMS Applied to Different Targets.

Variable	nrTMS target	Pre-treatment: mean (SD)	Post-treatment: mean (SD)	Change: mean (SD)	Change: 95% CI	PPR	Post hoc *p*-value
Short-term outcome: pain intensity	M1	5.0 (2.3)	4.2 (2.2)	−0.9 (1.5)	[−1.6, −0.1]	17%	
	Sham	5.4 (2.1)	4.5 (2.5)	−0.9 (1.9)	[−1.9, −0.1]	17%	
	S2	5.2 (2.5)	4.2 (2.4)	−1.0 (2.8)	[−2.5, −0.4]	20%	
Long-term outcome: pain intensity	M1	5.9 (1.9)	5.7 (1.8)	−0.2 (1.0)	[−0.8, 0.3]	4%	>0.99
	Sham	5.9 (1.8)	6.1 (1.2)	0.2 (1.3)	[−0.4, 0.9]	−4%	>0.99
	S2	6.0 (2.1)	5.2 (1.8)	−0.9 (1.3)	[−1.5, −0.2]	15%	0.042
Weekly average pain	M1	5.0 (1.4)	4.9 (1.8)	−0.1 (1.1)	[−0.7, 0.5]	1%	>0.99
	Sham	5.7 (1.6)	6.3 (1.5)	0.6 (1.0)	[0.1, 1.1]	−10%	0.060
	S2	6.2 (1.8)	4.7 (1.8)	−1.5 (1.8)	[−2.5, −0.5]	24%	0.012
Pain interference	M1	6.2 (2.9)	5.3 (2.5)	−0.9 (2.1)	[−2.0, 0.2]	14%	
	Sham	6.6 (1.9)	6.1 (1.5)	−0.4 (1.6)	[−1.3, 0.4]	7%	
	S2	6.7 (2.1)	5.3 (2.3)	−1.4 (2.0)	[−2.5, −0.4]	21%	

CI, confidence interval; M1, primary motor cortex; NRS, Numeric Rating Scale; nrTMS, navigated repetitive transcranial magnetic stimulation; PPR, percentage of pain relief; SD, standard deviation; S2, secondary somatosensory cortex.

suggesting that the central dopamine system may have a role in the nrTMS effect.

S2, M1, and Sham Stimulation

Previous rTMS studies targeting S2 are scarce. The mechanism for the analgesic action of S2 stimulation may relate to its location close to the insular cortex, which has a pivotal role in pain perception.[50]

In a previous rTMS study targeting S2 in orofacial pain patients, stimulation of the right S2 showed superior analgesic effect to S1/M1 or sham.[15] Participants reported a significant reduction of weekly average pain after S2 stimulation contralateral to the pain site; the side of stimulation did not significantly affect these results. Additionally, at one-month follow-up, S2 stimulation was the only treatment to show significant pain reduction. The novel S2 stimulation target may hold promise for a longer-lasting treatment efficacy.

M1 stimulation has the best level of evidence regarding rTMS in NP, a parallel-to-midline coil orientation being often preferred.[51] For M1 nrTMS, we used a coil orientation that produced motor-evoked potentials with the highest amplitude, that is, perpendicular to the central sulcus, which has also proved beneficial in chronic pain.[52] However, we are not aware of a direct comparison of efficacy between these two coil orientations.

The effect of sham stimulation varies from strong[53] to weak[54] in rTMS studies. Trial setup and stimulation context can induce strong expectations of efficacy and a strong placebo effect,[55] while a weak placebo effect may indicate failure in concealing the sham nature of the stimulation. Furthermore, individual characteristics may cause variation in the placebo response.[56] We did not ask participants to guess whether they had received active stimulation or not, but the notable placebo effect observed supports successful concealing of sham. A placebo effect might also explain why the NRS_{PRE} values, collected at the treatment facilities before the stimulation, were slightly lower than the baseline NRS values (Fig. 7), which participants recorded at home.

In a previous study on the timing of sham stimulation, placebo analgesia differed significantly depending on whether there was a

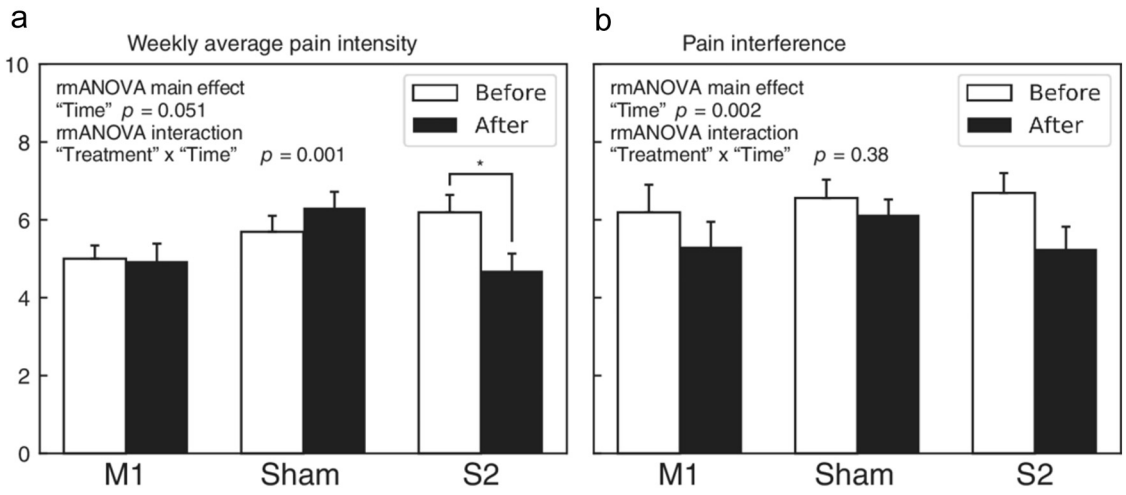

Figure 8. Weekly average pain intensity and pain interference (NRS, numeric rating scale 0–10), compared before and after each treatment (BPI: NRS 0–10). BPI, Brief Pain Inventory questionnaire; M1, primary motor cortex; S2, secondary somatosensory cortex. *$p < 0.05$.

successful or an unsuccessful active rTMS preceding sham.[57] In our study, participants were randomized to have either sham or M1 stimulation first. We noted a trend that all treatments were, to some extent, more effective in group A than in group B, but the difference was non-significant, and the least in sham. Despite these observations, the unbalanced study design prevents a thorough analysis of order, period, and treatment effects separately. Therefore, a possibility exists that the order in which the treatments were given might have modified their efficacy.

Quality of Life, Stroke Location, and Size

In fibromyalgia patients, rTMS treatment has previously been shown to improve QoL[13] but, in our cohort, QoL did not significantly improve. At group level, none of the nrTMS treatments changed anxiety or mood significantly compared with baseline, suggesting that the analgesic effects were independent of the psychological effects.[58]

Previously, it has been suggested that rTMS treatment for patients with large strokes may need analysis as to whether the gray matter surrounding the lesion is still functional and sufficiently structurally connected to enable effective stimulations.[59,60] In our cohort, we did not find a significant difference in treatment effects based on lesion size or anatomical location. Nevertheless, it is important to consider this possibility in future studies, particularly with lesions of the thalamocortical tract.

Plasticity-Related Gene Polymorphisms

Dopamine D2 receptor binding potential in the striatum may have a key role in central pain modulation.[61] Previous studies have shown that rTMS stimulation to M1 and prefrontal cortex releases dopamine in the striatum.[62,63] Dopaminergic activity is affected by the *DRD2* genotype.[64] Healthy individuals homozygous for the major T-allele of the *DRD2* rs6277 seem to respond to rTMS S1/M1 stimulation more readily than heterozygotes or *CC* homozygotes.[18] In line with this, when nrTMS was targeted to M1, participants with the homozygous *DRD2* T/T genotype were significantly more likely to experience pain relief than those with other genotypes. Due to the small number of participants, this finding remains tentative.

Conditioned Pain Modulation

In line with previous studies,[37] the cold water bath induced a significant pain reduction in participants. These results suggest that endogenous pain inhibitory pathways, which are also needed for a placebo response, are functional in CPSP patients.[65,66]

Strengths of the Trial

We used navigated rTMS to accurately target the stimulation.[67] As pointed out in a recent review,[9] long-term results of S2 stimulation have been awaited. Here we present data encouraging further S2 interventions. Our participants were carefully selected and examined for a diagnosis of CPSP. We assessed the role of three plasticity-related genotypes in the effects of stimulation. CPM was evaluated to analyze the functionality of the descending pain inhibitory system.

Limitations of the Trial

We did not reach the target enrollment of 30 participants, as recruitment proved difficult and the protocol demanding for participants. Thus, statistical analyses were underpowered, and the results should be considered merely indicative.

In bedside testing, thermal sensations were tested by a metal roller. The exact temperature of the metal roller was not tested before administering the test to the patient. However, the cooling and heating of the metal roller were standardized, and the testing was always performed in the same way.

The non-uniform and unbalanced 2-sequence design prevents an exact analysis of order and period effects. Although the effects of nrTMS treatments did not significantly differ between the two randomization groups, we cannot eliminate the possibility of an order effect. A three-arm randomized parallel setup would be preferable, as recommended by Lefaucheur et al.[7] Some questionnaire data were not obtained: in the future, a smartphone-based data collection method might enable more complete datasets. In brain MRI, all but two participants had a brain lesion corresponding to CPSP. As tractography was not performed, we cannot exclude significant dysfunction in connectivity between brain regions, which may have affected the efficacy of TMS.

Defining and stimulating S2 with TMS is more difficult than M1 as S2 resides in the parietal operculum of the Sylvian fissure about 4 cm from the lateral cortical surface.[32–34] The TMS-induced electric field strength diminishes rapidly with increasing distance from the stimulating coil. Our stimulation targeted to S2 created estimated electric fields of 36–109 V/m at the lateral upper lip of the Sylvian fissure. At a 2-cm depth, the field strength, estimated with a standard figure-of-eight coil and a spherical conductor model, is about 36% of the lateral surface value, and about 21% at a depth of 3 cm.[68,69] The threshold for local cortical activation by a single pulse of TMS is estimated to be 50 V/m.[70] The cumulative effect of nrTMS on this threshold is unknown. Nevertheless, it is evident that the lateral area of the upper lip of the Sylvian fissure, considered to harbor the sensory presentation of the larynx and tongue, was stimulated more intensively than was the actual S2 area. We cannot separate the possible effects of this lateral activation and the activation of S2 proper in the effects of nrTMS. DeepTMS with an H-coil might be an interesting option to reach S2 in future trials.[71]

Our sham protocol was suboptimal, and better concealed sham coils are currently available.[7] As we did not ask the patients to guess their group allocation, we cannot directly assess whether blinding was successful. Although the similar short-term effects of sham and active treatments at group level suggest successful blinding, possible unblinding could have affected individual results, most likely diminishing the analgesic effect of sham.

The number of pulses given per session, at 5050, was high, this number being chosen based on the knowledge available in 2013 when our study was planned.

CONCLUSION

For CPSP patients, S2 nrTMS decreased both short-term and long-term pain intensity. S2 contralateral to the pain side shows promise as a stimulation target. The *DRD2* T/T genotype is of interest as a biomarker for a sizeable M1-nrTMS effect, but further studies are needed to confirm this.

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Authorship Statements

Hanna Harno, Eija Kalso, Pantelis Lioumis, Erika Kirveskari, and Jyrki P. Mäkelä designed the study. Pantelis Lioumis and Selja Vaalto designed the TMS protocols, and Pantelis Lioumis did part of the stimulations. Hanna Harno examined and diagnosed all participants. Marko Kangasniemi analyzed the MR images. Juhani Ojala and Jukka Vanhanen conducted stimulations and statistical analyses. All authors participated in data interpreting, writing, and scientific commenting on the manuscript. All authors approved the final version of the manuscript.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1111/ner.13496.

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COMMENT

This article describes a randomized controlled crossover trial to investigate the efficacy of M1- or S2-rTMS in central post-stroke pain (CPSP) compared with sham. The authors evaluated not only pain intensity and interference, but also conditioned pain modulation, depression, quality of life, upper limb motor function, gene polymorphisms, and so on. As the authors mentioned in the article, the pain-relieving effect of M1-rTMS is not sufficient for management of CPSP. Since more effective procedures are required in rTMS therapy, S2 stimulation is quite interesting and promising. However, the study design of this trial could not rule out bias, such as order effect and unblinding; therefore, a parallel trial should be conducted in the future. Furthermore, it is necessary to consider whether S2-rTMS can be useful for clinical practice and which stimulation protocol can be optimal for long-term treatment for CPSP.

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