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Non-invasive cortical modulation of experimental pain in migraine

M. Uglem [a,*], P.M. Omland [a], M. Engstrøm [a,b], G.B. Gravdahl [b], M. Linde [a,b], K. Hagen [a,b], T. Sand [a,b]

[a] Norwegian University of Science and Technology, Department of Neuroscience, Trondheim, Norway
[b] St. Olavs Hospital, Department of Neurology and Clinical Neurophysiology, Trondheim, Norway

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HIGHLIGHTS

- The effects of rTMS to S2 on thermal pain thresholds differed between migraineurs and controls.
- The analgesic effects of rTMS to S2 were of low magnitude.
- The results may suggest a hypofunction of the descending pain-modulating system in migraineurs.

ABSTRACT

Objective: To test the hypothesis that secondary somatosensory cortex (S2) is involved in the migraine pathogenesis, by exploring the effect of navigated repetitive transcranial magnetic stimulation (rTMS) to S2 on thermal perception and pain.
Methods: In this blinded sham-controlled case-control study of 26 interictal migraineurs and 31 controls, we measured thermal detection and pain thresholds on the hand and forehead, and pain ratings to heat stimulation on the forearm and temple, after real and sham 10 Hz rTMS.
Results: rTMS increased cold and heat pain thresholds in controls as compared to interictal migraineurs ($p < 0.026$). rTMS decreased forehead and arm pain ratings ($p < 0.005$) and increased hand cool detection thresholds ($p < 0.005$) in both interictal migraineurs and controls.
Conclusions: The effects of rTMS to S2 on thermal pain measures differed significantly between migraine and control subjects, although the effects were generally low in magnitude and not present in pain ratings. However, the lack of cold and heat pain threshold increase in migraineurs may reflect a hypofunction of inhibitory pain modulation mechanisms.
Significance: The expected rTMS-induced cold and heat hypoalgesia was not found among migraineurs, possibly a reflection of reduced intracortical inhibition.

1. Introduction

The migraine pathophysiology is partly unknown, but it is generally accepted that dysfunction of central nervous system (CNS) structures is involved, causing unstable CNS-excitability. This dysfunction could cause migraine attacks by increasing the susceptibility for activation and sensitization of the trigeminovascular pain pathway (Vecchia and Pietrobon, 2012; Noseda and Burstein, 2013).

Many structures are involved in modulation of nociceptive signals before the conscious recognition of pain. The primary somatosensory cortex (S1) and secondary somatosensory cortex (S2) are likely involved in the sensory-discriminative aspects of pain, while the insula and the anterior cingulate cortex are involved in motivational-affective aspects of pain (Xie et al., 2009). S2 may also be involved in modulation of pain (Kuroda et al., 2001; Gojyo et al., 2002). The activation of S2 by experimental pain may be decreased in interictal migraineurs compared to controls (Schwedt et al., 2015).

Repetitive transcranial magnetic stimulation (rTMS) can non-invasively modulate cortical excitability in humans. Although these effects are far from homogeneous, it seems that

Abbreviations: CDT, cool detection threshold; CPT, cold pain threshold; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; HPT, heat pain threshold; M1, primary motor cortex; MEP, motor evoked potentials; rANOVA, repeated measures analysis of variance; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; WDT, warm detection threshold.

* Corresponding author at: Department of Neuroscience, Medisinsk teknisk forskningssenter, N-7491 Trondheim, Norway. Tel.: +47 470 25 765; fax: +47 73 59 87 95.
E-mail address: martin.uglem@ntnu.no (M. Uglem).

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low-frequency rTMS (⩽1 Hz) decreases and high-frequency rTMS (⩾5 Hz) increases excitability (Lefaucheur et al., 2014).

Interictal migraineurs may have lower thermal pain thresholds compared to controls (Schwedt et al., 2011; Engstrom et al., 2013). The pain thresholds may further decrease right before and during migraine attack (Burstein et al., 2000; Sand et al., 2008). More than half of migraineurs experience allodynia closely before a migraine attack in questionnaire-based studies (Mathew et al., 2004; Lipton et al., 2008), and allodynia has been associated with increased responses in the thalamus, insula and S2 (Lorenz and Casey, 2005). Although S2 is partly involved in pain processing, and most likely its modulation, it has not been widely used as a target for pain modulation by rTMS (Mylius et al., 2012). However, in one study navigated high-frequency rTMS to S2 increased heat pain thresholds in healthy subjects, and resulted in a more pronounced and longer lasting alteration compared to stimulation to M1, S1 and dorsolateral prefrontal cortex (DLPFC) (Valmunen et al., 2009).

To test the hypothesis that S2-excitability is involved in the migraine pathogenesis, it would be of interest to compare the effects of navigated rTMS to S2 on thermal pain thresholds and suprathreshold pain ratings in interictal migraineurs compared to healthy controls, since alteration of nociception may be a more clinically relevant measure than measures of motor cortex excitability. In addition, we studied the effect of rTMS on thermal detection thresholds (as secondary variables) to look for unspecific effects on the sensory system. As far as we know, this is the first study exploring the effect of navigated rTMS to S2 in migraineurs (Moisset et al., 2015).

2. Methods

In this blinded sham-controlled case-control study, we measured thermal perception and pain thresholds and ratings from prolonged noxious heat stimulation before and after high-frequency rTMS to S2. Migraineurs kept a headache diary for four weeks before and after the examinations in order to determine the relationship between migraine attacks and the examination day. Measurements were classified as interictal when they were performed more than one day before attack onset or more than one day after the attack ended.

2.1. Subjects

Forty-three migraineurs and 34 healthy controls participated in the study. Participants were students and employees recruited through an Intranet advertisement within our university. Migraineurs were included by neurologists according to the ICHD-II criteria for migraine with and without aura (Headache Classification Subcommittee of the International Headache Society, 2004). Included subjects should have between two and six migraine attacks per month and no more than ten days with migraine per month. Symptomatic, but not prophylactic, migraine medications were allowed.

Exclusion criteria were coexisting frequent episodic (1–14 days/month for healthy controls and 7–14 days/month for migraineurs) or chronic (>15 days/month) tension-type headache, neurological or psychiatric diseases, sleep disorders, active infectious diseases, connective tissue diseases, metabolic, endocrine or neuromuscular diseases, other clinically relevant painful conditions including recent injuries, malignancy, previous craniotomy or cervical spine surgery, heart disease, cardiopulmonary or cerebrovascular diseases, pregnancy, medication for acute or chronic pain, antipsychotics, antidepressants, anticonvulsants or other drugs that may influence neuronal, vascular or muscular function, alcohol or drug abuse, ferromagnetic implants and prophylactic allergy treatment.

Nine subjects were excluded (six with migraine); five due to technical difficulties with the magnetic coil, two due to sleepiness (one interictal and one postictal migraineur), one due to technical difficulties with the thermal test equipment, and one because we were unable to determine resting motor threshold (RMT). Migraineurs who were classified by the headache diary to be either ictal ($n = 3$), preictal ($n = 7$) or postictal ($n = 1$) were excluded prior to statistical analysis. Twenty-six interictal migraineurs and 31 healthy controls were finally included (Table 1). The Regional Committees for Medical and Health Research Ethics approved the protocol and all subjects gave their written informed consent. Migraineurs and controls received an equivalent of $ 80 to cover expenses.

2.2. Procedure

Magnetic resonance imaging scans (3-T Siemens Trio MRI scanner, T1 weighted 3D sequence) were acquired before the neurophysiological procedure. All participants were examined at the same time of day and were told to avoid exercise, smoking and caffeine-containing beverages the morning before examination to reduce the influence of factors that may affect the effect of rTMS (Ridding and Ziemann, 2010). The examination consisted of determination of RMT, baseline thermal tests before rTMS and new thermal tests after real and sham rTMS. Both real and sham rTMS were applied on all participants in a randomized order with 45 min between the first and second rTMS session.

2.2.1. Navigated transcranial magnetic stimulation

The stimulation setup consisted of a figure-of-eight shaped coil with biphasic pulse of 280 μs duration (MCF-B65 Butterfly Coil, MagVenture A/S, Farum, Denmark), a magnetic stimulator (MagPro

Table 1
Demographic and clinical data.

	Healthy controls ($n = 31$)	Interictal migraineurs ($n = 26$)
Age mean (SD) [range], years	30 (10) [19–56]	27 (8) [20–51]
BMI mean (SD), kg/m^2	24 (6)	24 (6)
Women, *n* (%)	26 (84)	23 (88)
Days since 1st day of last menstrual period, mean (SD)	18 (13)	17 (18)
MwoA, MA + MwoA, MA, *n* (%)	NA	15 (58), 4 (15), 7 (27)
Years with headache mean (SD) [range]	NA	13 (8) [2–34]
Migraine days/month mean (SD) [range], 0–4[a]	NA	1.5 (0.6) [1–3]
Migraine intensity mean (SD) [range], 1–4[b]	NA	2.6 (0.6) [1–3]
Headache duration mean (SD) [range], hours[c]	NA	11 (14) [1–60]

[a] Migraine days/month: 0: <1/month, 1: 1–3/month, 2: 4–7/month, 3: 8–14/month, 4: >14/month.
[b] Migraine intensity: 1: mild, 2: moderate, 3: severe, 4: extreme.
[c] Average duration of an attack with or without use of symptomatic medication. MwoA = migraine without aura. MA + MwoA = some attacks with and some without aura (both diagnoses according to ICHD-III). MA = migraine with aura (in 100% of attacks). NA = not applicable.