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Original article

# Magnetic stimulation of the upper trapezius muscles in patients with migraine – A pilot study

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ABSTRACT

*Background:* Repetitive peripheral magnetic stimulation (rPMS) has been applied to musculoskeletal pain conditions. Since recent data show that migraine and tension-type headache (TTH) might be closely related to peripheral muscular pain in the neck and shoulder region (supporting the concept of the trigemino-cervical complex (TCC)), this pilot study explores the acceptance of rPMS to the upper trapezius muscles in migraine (partly in combination with TTH).

*Methods:* We used rPMS to stimulate active myofascial trigger points (aTrPs) of the upper trapezius muscles in 20 young adults suffering from migraine. Acceptance was assessed by a standardized questionnaire, whereas self-rated effectiveness was evaluated by headache calendars and the Migraine Disability Assessment (MIDAS). Algometry was performed to explore the local effect of rPMS on the muscles.

*Results:* Acceptance of rPMS was shown in all subjects without any adverse events, and rPMS had a statistically significant impact on almost every parameter of the headache

*Abbreviations:* DMKG, German Migraine and Headache Society; MIDAS, Migraine Disability Assessment; PPT, Pressure Pain Threshold; rPMS, Repetitive Peripheral Magnetic Stimulation; sTMS, Single-pulse Transcranial Magnetic Stimulation; TCC, Trigemino-Cervical Complex; TES, Transcutaneous Electric Stimulation; aTrP, Active Myofascial Trigger Point; TTH, Tension-type Headache; VAS, Visual Analogue Scale.

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calendar and MIDAS. Among others, the number of migraine attacks ($p < 0.001$) and migraine intensity ($p = 0.001$) significantly decreased regarding pre- and post-stimulation assessments. Accordingly, 100.0% of subjects would repeat the stimulation, while 90.0% would recommend rPMS as a treatment option for migraine.

*Conclusions:* rPMS might represent a promising tool to alleviate migraine symptoms within the context of myofascial pain. This might be due to stimulation-dependent modulation of the peripheral sensory effect within the TCC in migraine. However, sham-controlled studies with larger and more homogeneous cohorts are needed to prove a potential beneficial effect.

**Ethics Committee Registration Numbers**: 356-14 and 447/14



## 1. Introduction

Migraine has been ranked the sixth most disabling disorder worldwide since 1990.[1] In this context, recurrent headaches represent one of the most common complaints in adolescents and young adults. Both migraine and tension-type headache (TTH) belong to the complex of primary headaches, and they already show a high but still increasing prevalence among children and adolescents.[2,3] Compared to TTH and unspecific headaches, the prevalence of migraine is relatively low in children (7.5%, 6-months prevalence), but it is experienced as the most disabling and most recurrent type of headache.[4] Furthermore, additional pain symptoms (e.g., back pain) are significantly more common in children suffering from migraine.[4] In this context, several studies indicate that at least certain subtypes of headaches seem to be strongly connected to neck and shoulder pain.[5–10] Approximately twice as many adolescents with recurrent headache reported muscular pain in these regions when compared to healthy subjects in a recent investigation among German students, and muscular pain was shown to be more common in subjects suffering from migraine than in those suffering from TTH.[8]

A widely accepted hypothesis regarding the underlying pathologic mechanism is the concept of the trigemino-cervical complex (TCC).[11–13] This concept represents the idea of a partial convergence in sensory nociceptive afferent input from the upper cervical radices (and from the meninges) in the caudal trigeminal nuclei within the brainstem.[11,12] In line with this hypothesis, migraine-related pain could be partially attributed to nociceptive myofascial inputs that increase cortical neuronal excitability.[6] Accordingly, Fernandez et al. (2010) reported significantly lower pressure pain thresholds (PPTs) at the upper trapezius muscles in subjects suffering from migraine and chronic TTH, compared to controls.[9] This suggests that peripheral muscle hyperalgesia might trigger central pain perception via cervical-to-trigeminal linking and vice versa. Hence, targeted treatment of the neck and shoulder region might relieve muscle pain, and therefore might also be beneficial in treating migraine itself. In this context, different invasive and non-invasive neuromodulation approaches were described by Diener et al. (2015), although they failed to show beneficial results overall.[14] Thus, new therapy options are urgently needed, since migraine treatments are often unsatisfactory due to a lack of effective and well-tolerated acute and preventive therapies.[14]

However, targeting the upper trapezius muscles in subjects suffering from pain to alleviate symptoms is not a completely new idea. In this context, local therapy of active myofascial trigger points (aTrPs) using anesthetic infiltration has already proven to significantly decrease migraine-related pain. Interestingly, it was shown that the change in pain thresholds of the aTrPs is linearly correlated with migraine reduction, thus supporting the hypothesis of a cervical-to-trigeminal nociceptive link.[6] Moreover, transcutaneous electric stimulation (TES) represents another option for treating the upper trapezius muscles. However, TES has been shown to cause stimulation-related pain by stimulating less deeply and by inducing less muscle torque compared to repetitive peripheral magnetic stimulation (rPMS).[15] Additionally, rPMS has shown longer-lasting effects on myofascial pain compared to TES.[16] Since rPMS is comparatively painless, non-invasive, deeply penetrating, easy to handle, and not characterized by frequent or severe side-effects,[15] it might provide substantial advantages over TES.

Furthermore, rPMS has proven to significantly alleviate muscular pain within the upper back[16–18] and lower back,[19] and to be beneficial in treating symptoms related to lumbar spondylosis and peripheral nerve injury, respectively.[20,21] However, it has not yet been used to modulate migraine or migraine-related muscle pain. Since recent literature suggests that there is a strong relationship between migraine and neck and shoulder pain,[7–9] we hypothesize that rPMS could principally represent a useful peripheral neuromodulation approach for migraine. Therefore, this pilot study aims to investigate, as a first step, the acceptance of rPMS to the upper trapezius muscles in young adults suffering from migraine.

## 2. Materials and methods

### 2.1. Ethics

The study was approved by our local ethics committee (registration numbers LMU and TU Munich: 356-14 and

447/14), in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to the investigations.

### 2.2. Participants and experimental protocol

The inclusion criteria for the study were written informed consent, age above 18 years, presence of at least one aTrP on each side in the region of the upper trapezius muscle (according to a certified physiotherapist's examination), migraine (according to an established German-language self-administered headache questionnaire[22,23]), and the absence of other neurological diseases. The headache questionnaire records TTH and cluster headache, in addition to migraine. It was guaranteed that migraine represented the predominant disorder (due to frequency of headache types and self and professional assessment) in subjects with additional positive TTH criteria. The exclusion criteria were age under 18 years, neurological or other severe disorders, previous seizures, pregnancy, and implanted medical devices (e.g., cochlear implant, deep brain stimulation electrodes, metal devices in the stimulation area, and cardiac pacemaker).

The study was designed for a total cohort size of 20 subjects. Volunteers were recruited via an official advertisement on the websites of the two Munich universities, which included a short description of the study's setup and goals, followed by a detailed listing of the inclusion and exclusion criteria. Out of approximately 40 subjects that answered the advertisement, the first 20 volunteers were enrolled. In the case of any dropout, the next subject on the chronological list of responders was asked to take part in the study. Furthermore, a financial expense allowance was provided for each volunteer.

Each subject was instructed to first fill out the standardized headache calendar of the German Migraine and Headache Society (DMKG) on a daily basis over a period of 1 month. At the end of this month, the Migraine Disability Assessment (MIDAS) was applied,[24,25] and a certified physiotherapist was consulted to mark the aTrPs of the upper trapezius muscle prior to rPMS. Then, 6 stimulation sessions over 2 consecutive weeks were scheduled for each participant, which were followed by a 3-month post-stimulation evaluation for migraine using the DMKG headache calendar and the MIDAS again.

### 2.3. Active trigger points and algometry

The identification of aTrPs within the upper trapezius muscles was important to assess the peripheral sensory effects (C1–C3) within the TCC model.[8,10,11] Therefore, aTrPs within the upper trapezius muscles were determined and marked by an experienced physiotherapist for later stimulation.[17] The criteria for an aTrP, such as referred pain, taut band, and jump sign, were carefully considered.[10,26,27] Furthermore, one central point on the deltoid muscle was marked on each side as a reference point for the algometry, since the deltoid muscles were not part of the stimulation area and are not involved in the TCC loop. Comparing the algometry values derived from both deltoid muscles with the values derived from the trapezius muscles should work as a control for unstimulated versus stimulated muscle areas. All of the aTrPs were photographed for documentation and marked with a waterproof pen to ensure accurate algometry and rPMS.

Concerning algometry, the PPT of the marked aTrPs was determined by an algometer according to a previous report.[17] Algometric measurements were conducted prior and subsequent to each stimulation session at the aTrPs of the trapezius muscles and at both deltoid muscles. The PPT was derived from the mean value of three consecutive measurements over one aTrP to increase intra-examiner reliability.[9] In this context, algometry was conducted to identify any possible local effects of rPMS on the stimulated aTrPs. Since the PPT reflects the amount of pressure at the border between the sensation of mere pressure and pressure-related pain, it is a widely used tool to assess local muscle sensitivity.[9] As local hyperalgesia commonly results in lower PPTs,[9,10] we expected an increase in PPTs in case muscle hyperalgesia was alleviated due to the targeted stimulation.[10]

### 2.4. Repetitive peripheral magnetic stimulation

Stimulation by rPMS was performed with the Nexstim eXimia NBS system, version 4.3, in combination with a figure-of-eight stimulation coil (Nexstim Oy, Helsinki, Finland). The figure-of-eight coil induces a comparatively more focal field of stimulation compared to circular coils[28–31] and is therefore most suitable for primarily targeting the aTrPs of the upper trapezius muscles.[16,17] An integrated cooling system prevented the stimulating coil from overheating during repetitive pulse application within a session.

In total, 6 rPMS sessions (3 stimulation days per week over 2 consecutive weeks in 2-day intervals except for the weekend) were scheduled for all of the participants during their symptom-free intervals, meaning that stimulation was always carried out when the subjects were not suffering from a migraine attack. During the stimulation sessions, the participants sat in a comfortable chair with armrests, and both sides were stimulated in consecutive order. The center of the magnetic coil was placed on the aTrP at the spot marked previously. The long axis of the coil was oriented perpendicularly to the anatomical course of the upper trapezius muscle. After careful coil placement, no interspace between the coil and muscle should be visible, in order to ensure close contact and a minimum of coil deviation during stimulation. After appropriate coil positioning was achieved under these premises, the coil handle was fixed using an adjustable coil holder provided by the system. Correct coil positioning was controlled for throughout the session, and it was immediately improved after occasional movements of the participants, if necessary.

Overall, 6000 magnetic pulses were applied to the upper trapezius aTrPs of each side in 15 s trains at 20 Hz, separated by pauses of 30 s. Consequently, the time required to stimulate the aTrP of one side was 15 min. To define the appropriate intensity, we started stimulating at 15% of the system's maximum output and increased the intensity by steps of 5% of the system's maximum output, until the participant perceived local discomfort corresponding to a score of $\geq$5 out of 10 on the visual analogue scale (VAS). The subjects were informed that a score $\geq$5 out of 10 is regarded as the cut-off value between comfortable perception and discomfort. Intensity was

determined at the same aTrP that was targeted during subsequent stimulation on one randomly chosen side. rPMS was then performed at the uncomfortable intensity minus 5% of the system's maximum output to avoid pain. The basics of this approach were demonstrated by Smania and colleagues in their rPMS studies.[16,17]

During the 15 s trains, the shoulder was clearly elevated due to stimulation of the upper trapezius muscle (contraction time/ON), whereas it sank down to its initial position during the 30 s stimulation-free intervals (relaxation time/OFF). All of the participants were instructed to tell the supervisor whether their subjective stimulation perception on the second stimulated side clearly deviated from that of the first side. In such cases, the investigator carefully adjusted the stimulation intensity according to the participant's perception to achieve the same perception on both stimulation sides.

Subsequent to stimulating the aTrPs of both sides, the participants were asked whether the site of stimulation felt unusual (e.g., heat, tingling, numbness) during rest or movement, as well as if the stimulation was pleasant or uncomfortable (according to the VAS), if muscle spasms were observed after stimulation, and whether the participants would be willing to undergo rPMS again. Additionally, three months after the stimulation, each participant was asked whether he/she would personally recommend rPMS as a treatment option for migraine.

### 2.5. *Migraine assessment*

As mentioned before, each participant was asked to complete a standardized headache calendar of the DMKG over a period of 1 month prior to rPMS, which primarily included questions about the occurrence, duration, and intensity of headaches according to the VAS on a daily basis. Furthermore, accompanying symptoms and analgesic drug intake were registered, including a subjective assessment of the analgesic drug's effects. To assess the impact of stimulation on migraine, this questionnaire was repeated over 3 months, starting subsequently after the last stimulation session. Additionally, the MIDAS score, which quantifies migraine-related disability in daily life,[24,25] was appraised before the first and three months after the last rPMS session.

### 2.6. *Statistical analysis*

The algometry values, stimulation questionnaire, DMKG headache calendar, and MIDAS questionnaire were analyzed using descriptive statistics (means, standard deviations, medians, percentages, and total numbers). The differences between pre- and post-stimulation measures were assessed using two-sided Wilcoxon or Chi-square tests. In this context, $p$-values $<0.05$ were considered as statistically significant.

To assess the time effect of rPMS on the upper trapezius muscle over the 6 sessions, mixed log-linear models for 1) measures before the sessions and 2) measures following the sessions were calculated. These models, with algometry values of the upper trapezius muscle as the dependent variable and the number of the sessions as the independent variable, were adjusted for gender and age, and included random effects for individuals to account for similarities in the development of one individual's left and right muscles, as data from both the left and right muscles of all of the individuals were used. Beta coefficients and 95% confidence intervals of these models were given. Differences between the effect of stimulation on the upper trapezius and the deltoid muscles were assessed by including interaction terms between the muscle (trapezius muscle = 1, deltoid muscle = 0) and session in these regression models. The course of the algometry values was displayed using GraphPad Prism (6.04, La Jolla, CA, USA). All of the calculations were performed using R software (3.1.0, The R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

### 3.1. *Subject-related characteristics*

Overall, 22 subjects were enrolled. In 2 subjects, aTrPs were missing or unidentifiable according to the examination of the physiotherapist, which led to replacement by 2 other volunteers to achieve a total cohort size of 20 volunteers with aTrPs and completed procedures. Hence, 19 females and 1 male with a mean age of 23.4 ± 1.8 years (range: 19–27 years) underwent rPMS and were included in data analysis.

Regarding the type of headache, 2 subjects (10.0%) suffered from migraine without aura, whereas 8 subjects (40.0%) had migraine with aura. Furthermore, 4 enrolled volunteers (20.0%) had migraine without aura in combination with TTH, and the remaining 6 subjects (30.0%) were frequently aware of migraine with aura and TTH. None of the volunteers had histories of overusing medication.

### 3.2. *Active trigger points and algometry*

As aforementioned, the physiotherapist successfully determined aTrPs in 20 subjects, whereas no aTrPs were identified in 2 other volunteers, which led to their exclusion from the study. Regarding the short-term comparison of the pre- and post-stimulation algometry values at the aTrPs of the upper trapezius muscle, the average values immediately after stimulation were significantly higher than their counterparts before stimulation, for all except one rPMS session (Table 1).

With respect to the long-term development of pre- and post-stimulation algometry values over the total number of stimulations, both the mean pre- and post-stimulation algometry values increased over the course of the 6 consecutive rPMS sessions (Table 1; Fig. 1A and B). This increase was shown to be statistically significant for both measurements before and subsequent to the stimulation (before stimulation: $\beta = 0.04$ with 95% CI 0.03 to 0.06; after stimulation: $\beta = 0.04$ with 95% CI 0.03 to 0.06). For the algometry values measured before the stimulations, a significantly larger increase was observed in the upper trapezius compared to the deltoid muscle ($\beta = 0.02$ with 95% CI 0.01 to 0.05), whereas no statistically significant difference was revealed for the corresponding post-stimulation values ($\beta = 0.02$ with 95% CI 0.00 to 0.04).

**Table 1 – Short-term comparison of pre- and post-stimulation algometry values. This table provides information about the short-term differences between the pre- and post-stimulation algometry values (in kg) at the active myofascial trigger points (aTrPs) of the upper trapezius muscle. The mean values immediately after stimulation were significantly higher than their counterparts before stimulation, for all except one stimulation session.**

| | Session 1 | | Session 2 | | Session 3 | | Session 4 | | Session 5 | | Session 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | p | Mean (SD) | p | Mean (SD) | p | Mean (SD) | p | Mean (SD) | p | Mean (SD) | p |
| Right side | | | | | | | | | | | | |
| Before stimulation | 2.6 (1.1) | 0.01 | 2.8 (1.2) | <0.001 | 3.2 (1.6) | 0.01 | 3.3 (1.6) | 0.07 | 3.2 (1.6) | <0.001 | 3.4 (1.9) | <0.001 |
| After stimulation | 3.0 (1.6) | | 3.3 (1.5) | | 3.5 (1.7) | | 3.6 (1.9) | | 3.6 (2.2) | | 4.0 (2.0) | |
| Left side | | | | | | | | | | | | |
| Before stimulation | 2.6 (1.1) | 0.02 | 2.8 (1.2) | 0.001 | 2.8 (1.2) | 0.001 | 2.9 (1.3) | 0.004 | 2.9 (1.1) | 0.01 | 3.2 (1.6) | 0.04 |
| After stimulation | 2.9 (1.3) | | 3.2 (1.4) | | 3.1 (1.2) | | 3.2 (1.3) | | 3.5 (1.9) | | 3.6 (2.3) | |

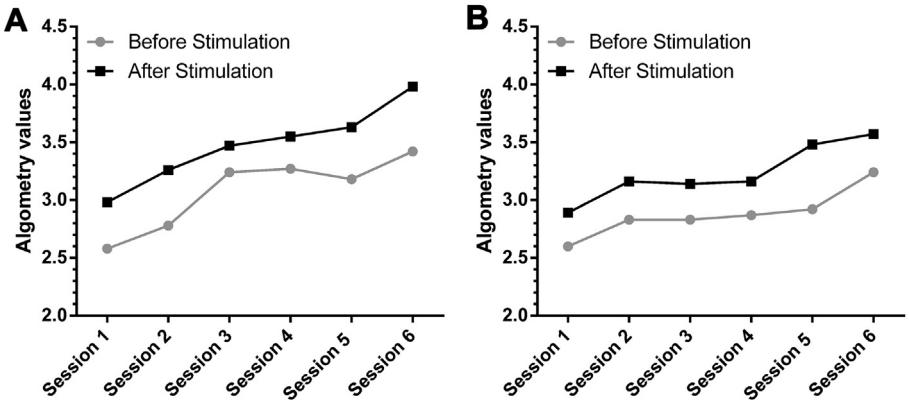


**Fig. 1 – Long-term comparison of pre- and post-stimulation algometry values. This figure visualizes the courses of the mean pre- and post-stimulation algometry values (in kg) for the right (A) and left (B) stimulation sites at the active myofascial trigger points (aTrPs) of the upper trapezius muscle. Exact mean ± standard deviation values are displayed in Table 1.**

**Table 2 – Stimulation questionnaire. The table summarizes the results of the stimulation-related questionnaire, which was assessed subsequently after each stimulation session. Furthermore, it provides the average stimulation intensity values for repetitive peripheral magnetic stimulation (rPMS). There were no statistically significant differences in the intensities of each session ($p = 0.55$).**

| | | |
|---|---|---|
| Paresthesia (% of sessions) | | 22.5 |
| Overall impression (% of sessions) | pleasant | 55.8 |
| | unpleasant | 35.0 |
| | neutral | 9.2 |
| Pain (% of sessions) | | 0.0 |
| Muscle spasm after stimulation (% of sessions) | | 0.0 |
| Repetition (% of subjects) | yes | 100.0 |
| | no | 0.0 |
| Recommendation (% of subjects) | yes | 90.0 |
| | no | 10.0 |
| rPMS intensity (% of maximum output), mean (SD) | Session 1 | 25.2 (3.4) |
| | Session 2 | 25.7 (3.1) |
| | Session 3 | 25.4 (2.9) |
| | Session 4 | 25.8 (3.0) |
| | Session 5 | 26.9 (2.3) |
| | Session 6 | 25.8 (2.8) |

### 3.3. *Repetitive peripheral magnetic stimulation*

Six single sessions of rPMS were feasible for all of the 20 subjects with aTrPs. We did not observe any adverse events within the course of the stimulation. Correspondingly, rPMS was completed in those subjects without any dropouts. Table 2 summarizes the results of our stimulation-related questionnaire as well as the stimulation intensities used for rPMS. There were no statistically significant differences in the stimulation intensities of each session ($p = 0.55$).

### 3.4. *Migraine*

Pre- and post-stimulation assessment of headache was achieved successfully in all of the 20 volunteers that had undergone rPMS of the aTrPs. Table 3 depicts the summarized data of the DMKG headache calendars. There was a statistically significant difference between the pre- and post-stimulation numbers of migraine attacks per month ($p < 0.001$; Table 3). In this context, the potential confounding factor of changed medication during the study was registered by the DMKG headache calendar. However, there was no significant change regarding the type of drug, but intake frequency per month was clearly reduced when comparing the pre- and post-stimulation status ($p = 0.008$; Table 3).

**Table 3 – Headache calendar of the German Migraine and Headache Society (DMKG). Summary of data from the DMKG headache calendar, which was assessed before and after stimulation. There was a statistically significant difference regarding the number of attacks per month ($p < 0.001$) and the intake frequency of analgesic drugs per month ($p = 0.008$) between the pre- and post-stimulation evaluations.**

| | Before stimulation | After stimulation | p |
|---|---|---|---|
| | Mean (SD)<br>Median | | |
| Number of headache episodes (per month) | 7.7 (6.9)<br>5.5 | 5.1 (4.8)<br>4 | <0.001 |
| Duration per headache attack (in hours) | 6.9 (4.6)<br>5.4 | 6.7 (3.2)<br>6 | 0.55 |
| Pain intensity (VAS 1–10) | 4.9 (1.4)<br>5.1 | 4.7 (0.9)<br>4.6 | 0.24 |
| Drug intake (days per month) | 3.8 (2.8)<br>3.5 | 2.6 (1.8)<br>2.3 | 0.008 |

Concerning the MIDAS, the average pain intensity of migraine attacks was significantly lower in the post-stimulation assessment, compared to the data acquired before stimulation ($p = 0.001$; Table 4), and migraine-related disability decreased within the course of rPMS ($p = 0.05$; Table 4). In addition, absences from work or school due to migraine were reduced ($p = 0.01$), and, correspondingly, overall productivity at work or school was significantly improved ($p = 0.003$; Table 4). Besides that, household work was less impaired after stimulation on average ($p = 0.02$; Table 4), and social participation was significantly more frequently possible when comparing the pre- and post-stimulation statuses ($p = 0.004$; Table 4).

## 4. Discussion

### 4.1. *rPMS in migraine*

This pilot study was designed to systematically evaluate the acceptance of rPMS on the upper trapezius muscles in young adults suffering from migraine, and it intends to serve as a basis for larger, sham-controlled studies in the future for adolescents and young adults. The impact of our novel approach was primarily assessed by the standardized headache calendar of the DMKG and the MIDAS questionnaire, whereas the local muscle effect was evaluated with repeated algometry

**Table 4 – Results of the Migraine Disability Assessment (MIDAS).**

| | Before stimulation | After stimulation | p |
|---|---|---|---|
| | Mean (SD)<br>Median | | |
| On how many days in the last 3 months did you have any headache? | 16.5 (12.1)<br>12 | 13.8 (15.1)<br>11 | 0.08 |
| On a scale of 0–10, on average, how painful were these headaches? | 5.8 (1.1)<br>5.75 | 4.8 (1.1)<br>5 | 0.001 |
| On how many days in the last 3 months… | | | |
| | Mean (SD)<br>Median | | p |
| a) … did you miss work or school because of your headaches? | 3.8 (6.4)<br>1 | 1.6 (1.9)<br>0 | 0.01 |
| b) … was your productivity at work or school reduced by half or more because of your headaches? | 6.8 (5.2)<br>5 | 3.7 (2.7)<br>3 | 0.003 |
| c) … did you not do household work because of your headaches? | 4.4 (3.2)<br>4 | 2.2 (3.2)<br>1 | 0.02 |
| d) … was your productivity in household work reduced by half or more because of your headaches? | 5.8 (4.7)<br>5 | 4.1 (5.3)<br>3 | 0.08 |
| e) … did you miss family, social or leisure activities because of your headaches? | 5.4 (4.6)<br>3 | 2.9 (2.8)<br>2.5 | 0.004 |
| Grades of disability | | | |
| | % of subjects | | p |
| Non to light impairment | 25.0 | 60.0 | 0.05 |
| Moderate to severe impairment | 75.0 | 40.0 | |

measurements. All of the stimulation sessions were carried out during symptom-free intervals, meaning that rPMS was not applied during a migraine attack.

The results of our pilot study demonstrate that rPMS is technically feasible for application in young adults suffering from migraine, since all of the stimulation sessions were successfully performed without any unintended breaks or adverse events. Furthermore, high acceptance of rPMS among all enrolled subjects was achieved without pain or muscle spasm induction over the course of the rPMS sessions (Table 2), even though a considerably high amount of stimuli close to the individual pain threshold was applied throughout. Correspondingly, 100.0% of the subjects would repeat the trial, and 90.0% would recommend rPMS in treating migraine, according to our questionnaire results (Table 2). Peripheral magnetic field induction has already been applied to treating musculoskeletal pain in a limited number of studies without severe pain induction,[16–19] but the application of this technique in subjects with migraine represents a novel approach. However, it should be emphasized that feasibility was tested in young adults in our pilot study, implicating that an analogous approach in children and adolescents might be needed to further confirm applicability in the context of paediatric neurology.

To evaluate the local muscular hyperalgesia, we assessed the individuals' PPTs on the aTrPs. Thus, we performed algometry with regard to experiences from previous studies.[9,16,17] To guarantee a comparatively high level of standardization and good repeatability, PPTs were derived from the mean value of three consecutive measurements on a marked aTrP.[9] Since we hypothesized that tenderness of the muscle would result in hyperalgesia of the tender region and, therefore, influence the PPT,[9,10] the immediate and long-term increase of algometry values indicates the loosening and alleviation of pain sensitization in the stimulated upper trapezius muscle (Table 1, Fig. 1). Besides migraine, subjects suffering from chronic TTH have repeatedly shown an increase in pericranial muscle tenderness, in combination with lower PPT levels, compared to healthy subjects.[10] Again, this reflects a negative correlation between increasing tenderness and decreasing PPT values, and vice versa. The distinct change in the PPT is in good accordance with the significant improvement in all parameters for evaluating pain that were registered by previous rPMS trials focusing on myofascial pain syndrome, which also primarily targeted the trapezius muscles.[16,17]

Besides positive results regarding technical feasibility and individual acceptance of rPMS, a beneficial effect on migraine itself was shown. However, the mechanism distinctly underlying the alleviation of muscular hyperalgesia is out of the scope of the present investigation. Based on our data, we speculate that the direct interaction with peripheral intramuscular nervous structures and the afferent central input could trigger local, spinal, and supraspinal mechanisms of pain modulation and perception.[17] As a potential pathogenic factor for the development of aTrPs, we hypothesize activity-dependent malposition of the shoulder girdle, e.g., static elevation or anterior-shifting of the shoulder muscles. This may distort the upper trapezius muscles through either tensional or shear stress. As a consequence, intramuscular gliding between myofascial structures may be restricted, which most likely will result in myofascial adherence induction.[26] Mobilizing these structures via rPMS might lower the adherence and increase the lacking proprioceptive input to cortical areas.

Furthermore, the beneficial effect of rPMS might be caused, in particular, by the dynamic character (15 s contraction and 30 s relaxation time) of our stimulation protocol, which seems to effectively solve the pathologic adherence of myofascial structures, as expressed by the significantly changed PPTs captured by the short- and long-term comparisons of the algometry values (Table 1, Fig. 1). This dynamic approach is described in previous rPMS studies[16–19] and is in good accordance with other treatment options, like progressive muscle relaxation, for example. In this context, recent studies have reported a significant alleviation of muscular pain, leading to the assumption that the dynamic design of contraction/relaxation may play an important role.[16–19] Several rPMS studies have identified increased proprioceptive inflow as a relevant factor of central neuroplastic modulation.[15] It is suggested that the intermittent stimulation (ON/OFF protocol) of muscles applied with intensities above the muscular contraction threshold imitates the physiological pattern of contraction/relaxation and generates considerable proprioceptive input to central networks.[15] In this context, such intermittent rPMS seems to modulate local cortical activation levels, which was proven in stroke patients suffering from spasticity in the upper limbs.[32] The patients showed significant improvements in their kinematics and spasticity after treatment with dynamic rPMS (ON/OFF protocol), and later scans revealed a significant increase in neuronal excitability within the superior posterior parietal lobe and the premotor cortex.[32] The positive influence on cortical excitability may reactivate or boost descending pain-inhibiting pathways and contribute to local pain alleviation. Hence, the application of a dynamic rPMS protocol seems favorable, as we expect a local solving effect on muscular adherences and a supraspinal effect by inducing cortical modulation.[15,32] However comparable studies that apply continuous protocols are missing, and systematic comparisons between continuous and intermittent protocols have not yet been evaluated. Furthermore, there is no scientific evidence justifying certain durations of ON and OFF times during an ON/OFF stimulation protocol.[15] Interestingly, Smania et al. (2003) observed a progressive normalization of the pathologic aTrP tissues along a treatment period of ten sessions, indicating a direct effect on the aTrP morphology itself.[17] aTrPs are suspected to sensitize ascending pathways and local nociceptors by liberating allogenic substances.[5,10] In this context, targeting the myofascial tender tissues directly and inducing later cortical modulation may combine to achieve the potentially beneficial effect of rPMS.

Concerning the presumably positive effect of rPMS, the present results extend existing findings and furthermore foster the assumption that rPMS has significant alleviating effects on musculoskeletal pain, as described recently.[18] In this context, Blaschek et al. (2014) reported that local pain was closely associated to migraine, after evaluating questionnaires assessing myofascial pain in the head and neck areas and the incidence of headache in secondary school children.[7] As the PPTs changed, we expected a decline in

migraines, since we suggest that myofascial hyperalgesia in the pericranial and shoulder region and migraine occurrence and intensity are linked to each other. This theory is based on Olesen et al. (1991), who assumed that a prolonged nociceptive input from non-trigeminal, upper-cervical innervated structures (e.g., upper trapezius muscles) results in increased cranial pain perception and therefore is partly responsible for the occurrence and intensity of headaches.[13] Fernández-de-las-Peñas et al. (2010) support this theory by assessing pressure pain topography maps of the trapezius muscle.[9] It turned out that PPT levels are significantly lower within the migraine and chronic TTH group, compared to those of healthy controls, and that, interestingly, within the migraine group, the PPTs of upper and middle trapezius points were lower on the symptomatic side compared to the non-symptomatic side.[9] Significantly lower PPTs on the symptomatic side of an unilateral migraine support the assumption of a cervical-to-trigeminal nociceptive link. As illustrated before, decreased PPTs are correlated with local hyperalgesia,[9,10] which could trigger pain perception in migraine, in case of an existing link. Giamberardino et al. (2007) infiltrated anesthetics in cervical aTrPs, and were able to show a statistically significant increase in PPTs and, simultaneously, a significant decline in migraine pain, with threshold increase and migraine reduction correlating linearly.[6] Bezov et al. (2011), who reviewed pain perception of TTH, reported increased pericranial tenderness in patients suffering from TTH in 17 studies.[5] In this context, they suggest nociceptive cutaneous input as a possible trigger for inducing and maintaining central sensitization and headache chronification.[5]

Overall, the results of our pilot study show statistically significant reductions in migraine occurrence, intensity, frequency of drug intake, and various migraine-related parameters, as assessed by the questionnaires (Tables 3 and 4), whereas algometry values increased (Table 1, Fig. 1). Linking the change of PPTs to the alleviation of migraines, our data are in good accordance with previous findings that suggest a close relationship between migraine and myofascial nociceptive inputs, which may enhance the level of central neuronal excitability.[6] Consequently, the results of our pilot study provide further evidence for the hypothesis regarding the role of the TCC in migraine, which includes peripheral sensory effects. In addition, it provides the first preliminary evidence that rPMS might be a practical clinical tool for effective neuromodulation of migraine.

### 4.2. *Limitations and perspectives*

Although this pilot study provides valuable data regarding rPMS for migraine, we have to keep some limitations in mind. First, the present study was not designed as a randomized sham-controlled investigation. Therefore, a placebo effect cannot be excluded categorically. Although the role of sham control is discussed controversially with regard to magnetic stimulation trials,[33] this restriction implicates that the potential therapeutic effect cannot be distinctly attributed to real stimulation without any doubt. In general, it is possible to use a sham coil by placing a plastic tube between the coil and skin, and thus isolating both from each other.[15,34] Through this setup, characteristic noise and skin contact can be maintained,[15] which makes it difficult for the volunteer to distinguish between real and sham stimulation. However, rPMS leads to clearly visible and perceptible contraction of the muscle, which cannot be experienced when using sham rPMS. Alternatively, a sham condition can be achieved by either reducing stimulation parameters (intensity/frequency), changing the coil orientation, or both.[15] The perception, muscle contraction, and noise experienced still clearly differ from real stimulation when parameters are reduced,[15] making it hard to distinguish between the effects of rPMS and sham stimulation. As another alternative, a muscle that is not included in the TCC could be stimulated with the same parameters as the trapezius muscle to establish a sham condition, which would allow for the perception of muscle contraction and noise. Although all of these potential sham conditions have their inherent restrictions, confirmation of our preliminary results by any form of sham-controlled approach seems to be highly mandatory. Thus, a sham-controlled study should be the next step to be able to draw more definite conclusions that go beyond the level of feasibility and acceptance.

The second limiting factor of our study is the comparatively small size of the cohort, which solely includes young adults with slightly different kinds of migraine headaches. Concerning the heterogeneity of headaches, we made sure that the predominant disorder was migraine by ensuring that the referred pain due to manual stimulation of the aTrPs was exclusively correlated with the known pain perception of migraine. However, as the headache questionnaire also records TTH and cluster headache, some subjects also fulfilled the criteria for TTH. We made sure that, in these subjects, TTH was clearly less frequent and less restrictive in everyday life when compared to migraine. However, upcoming studies with larger cohorts might be able to allow for systematic comparison between different headache forms (migraine, TTH, and other primary headaches) in terms of rPMS effectiveness. Although such an approach is out of the scope of this pilot study, it should be considered in upcoming experiments on the matter. Furthermore, a continuative study enrolling schoolchildren should be set up, since migraine represents a severe impairment among this group and is characterized by high but still increasing prevalence, with a large group of individuals suffering from migraine or other primary headaches at least once a week.[2,3] Although the present study provides encouraging data among young adults, an analogous approach in children and adolescents should be a prerequisite for the successful use of rPMS to the upper trapezius muscle in patient groups of paediatric neurology.

Despite the aforementioned limitations, this pilot study provides first evidence on the acceptance of rPMS in patients with migraine, even demonstrating a subjective positive therapeutic effect (Tables 3 and 4). According to the literature, some studies have already focused on the peripheral application of magnetic stimulation over spinal roots or muscles to reduce spasticity and improve movement dynamics,[15,35] or even have applied rPMS on the trapezius muscle to treat myofascial pain.[16–19]

Moreover, future multimodal approaches could further explore the distinct applicability and effectiveness of rPMS in

migraine. Besides peripheral approaches, current research also focuses on the central application of electric or magnetic fields in order to treat migraine. Against this background, especially single-pulse transcranial magnetic stimulation (sTMS) seems to offer a promising therapy option for acute migraine attacks.[36–39] In a recent sham-controlled study by Lipton et al. (2010), adult patients were instructed to administer sTMS via a portable device during aura symptoms, and this kind of stimulation has proven to be an effective treatment.[38] Interestingly, Andreou et al. (2016) observed that sTMS primarily modulates trigemino-thalamic and thalamo–cortical activity, but it fails to reach trigemino-cervical neurons.[37] Hence, sTMS probably does not affect the TCC directly, although it is supposed to be an important pathophysiologic factor in migraine.[37] Consequently, cortical and peripheral magnetic stimulation could be combined to simultaneously cover the spinal-cortical pathways and modulate the activity within the TCC. After effectiveness of rPMS is finally proven in migraine patients, rPMS could be integrated in an individually-tailored migraine treatment program consisting of different neuromodulatory therapies, which could be further supplemented by pharmaceutical and physical approaches.

## 5. Conclusions

According to the results of this pilot study, rPMS to the upper trapezius muscles is technically feasible and accepted well by patients with migraine. Additionally, a majority of the self-rated parameters in the DMKG headache calendar and MIDAS significantly improved over the course of stimulation, at least in this small series, suggesting that rPMS might represent a promising tool to elucidate and modulate the peripheral sensory effect within the TCC for migraine. Despite relevant limitations, this pilot study could be the basis for placebo-controlled assessments with larger homogenous samples including children and adolescents to prove the therapeutical effect of rPMS in patients with migraine.

## Disclosure

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## Conflict of interest

All of the authors declare that they have no conflict of interest affecting this study or the findings specified in this manuscript.

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