Aus der

Kinderklinik und Kinderpoliklinik im Dr. von Haunerschen Kinderspital

Klinikum der Ludwig-Maximilians-Universität München

Neuromodulation via repetitive neuromuscular magnetic stimulation (rNMS) targeting the upper trapezius muscles in patients affected by migraine

Dissertation

zum Erwerb des Doctor of Philosophy (Ph.D.)

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität München

vorgelegt von

Corinna Börner

aus

Landsberg/Deutschland

Jahr

2024

Mit Genehmigung der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

Erstes Gutachten:	Prof. Dr. Florian Heinen
Zweites Gutachten:	Dr. Michaela Bonfert
Drittes Gutachten:	Prof. Dr. Michael Meyer
Viertes Gutachten:	Prof. Dr. Jan Senderek

Dekan: Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 07.02.2024

Affidavit

Affidavit

Börner, Corinna
Surname, first name

Lindwurmstr. 4
Street

80337 Munich, Germany
Zip code, town, country

I hereby declare, that the submitted thesis entitled:

Neuromodulation via repetitive neuromuscular magnetic stimulation (rNMS) targeting the upper trapezius muscles in patients affected by migraine

……

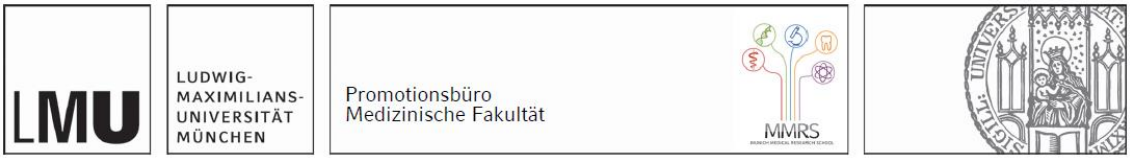
is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

Munich, 04.03.2024
place, date

Corinna Börner
Signature doctoral candidate

Confirmation of congruency



Confirmation of congruency between printed and electronic version of the doctoral thesis

Börner, Corinna

Surname, first name

Lindwurmstr. 4

Street

80337, Munich, Germany

Zip code, town, country

I hereby declare, that the submitted thesis entitled:

Neuromodulation via repetitive neuromuscular magnetic stimulation (rNMS) targeting the upper trapezius muscles in patients affected by migraine

……

is congruent with the printed version both in content and format.

Munich, 04.03.2024

place, date

Corinna Börner

Signature doctoral candidate

Table of content

List of abbreviations

TCC	trigemino-cervical complex
rNMS	repetitive neuromuscular magnetic stimulation
TTH	tension-type headache
PTH	post-traumatic headache
mTBI	mild traumatic brain injury
TrP	myofascial trigger point
UTM	upper trapezius muscle
TNC	trigeminus nucleus caudalis
TVS	trigeminovascular system
CGRP	calcitonin gene-related peptide
PACAP	pituitary adenylate cyclase-activating peptide
CSD	cortical spreading depression
TMS	transcranial magnetic stimulation
tDCS	transcranial direct current stimulation
tONS	transcutaneous occipital nerve stimulation
tVNS	transcutaneous vagus nerve stimulation
tSNS	transcutaneous supraorbital nerve stimulation
REN	remote electrical neurostimulation
PPT	pressure pain threshold

1. Your contribution to the publications

I was the leading person for structuring and implementing the ideas and concepts regarding neuromodulation with repetitive neuromuscular magnetic stimulation for headache disorders within our research group closely supervised by Michaela Bonfert and for coordinating the publications detailed in parts 1.1 to 1.3.

1.1 Contribution to paper I

My contribution to paper I comprises my participation in the entire project planning, project execution, data curation, data analysis, and publication.

The project was conceptualized and the study protocol submitted to the LMU ethics committee by my supervisors (Florian Heinen, Michaela Bonfert), the former clinical head of the headache department of our tertiary pediatric outpatient headache clinic (Mirjam Landgraf), a medical doctoral student (Jacob Staisch), and myself. The project administration was the responsibility of Michaela Bonfert and myself.

The analysis was based on data collected during clinical routine in our tertiary pediatric outpatient headache clinic. Once a patient was diagnosed with a headache disorder with a muscular component (head and neck muscles, trigemino-cervical complex [TCC]) by the physician and physiotherapist, it was my responsibility to offer the repetitive neuromuscular magnetic stimulation (rNMS) treatment to the patient and family. I checked that no contraindications were present and subsequently educated the patient and family about the treatment. If they agreed to treatment, I planned the treatment appointments together with my team of two medical doctoral students (Jacob Staisch, Magdalena Lang) and one neuroscience master student (Ari Hauser).

Together, we have been responsible for treating the patients with rNMS targeted to the upper trapezius muscles (UTM) and documented all relevant details of the rNMS treatments. One rNMS intervention comprised 6 rNMS sessions within 2-3 weeks. Treatment sessions also included the measurement of pressure pain thresholds (PPT) above the UTM before and after each rNMS session. Next to the treatments, we also planned and executed the 3-month follow-up visits of the treated patients. During these visits, changes in headache and muscular symptoms after the rNMS treatment including headache frequency, intensity, and duration were monitored and PPT above the UTM were measured once more.

Preparation of data analysis included the creation of a Microsoft Excel data mask and digitalizing the paper-based rNMS treatment documentations, which was done by Jacob Staisch and myself. After data entry, Jacob Staisch and I analyzed all data using Excel

and SPSS. Data interpretation was done together with my supervisors (Florian Heinen, Michaela Bonfert, Nico Sollmann) and the physicians of our tertiary outpatient pediatric headache clinic (Mirjam Landgraf, Iris Hannibal, Kristina Huß). Data visualization was done by Jacob Staisch, Ari Hauser, and myself.

Our results regarding the clinical and muscular effects of rNMS treatments targeting the UTM were published in paper I. The original manuscript draft was prepared by Jacob Staisch and myself under the supervision of Michaela Bonfert. Moreover, I led the revision process until final acceptance of the manuscript and was responsible for the proofreading process, respectively.

In addition to the publication of paper I, I presented our results at the Kongress für Klinische Neurowissenschaften (DGKN) in March 2022 in Würzburg, Germany. Further, I presented the concept of the rNMS treatment at the 46. Jahrestagung of the Gesellschaft für Neuropädiatrie (GNP) in November 2021 in Salzburg, Austria.

Since Jacob Staisch and I participated equally in most parts of the project and publication process, we decided on a shared-first authorship.

1.2 Contribution to paper II

Regarding paper II, the clinical studies, on which the analyses of this paper are based on, were carried out by Florian Trepte-Freisleder and Tabea Renner under the supervision of Florian Heinen, Nico Sollmann, and Mirjam Landgraf.

Based on these datasets, I had the idea to retrospectively analyze the data regarding baseline factors that may predict better response to rNMS treatment. Since the rNMS treatment is time- and resource-costly, it is clinically meaningful to stratify, which patients may benefit the most from a rNMS intervention. Therefore, I combined and curated the datasets of the two studies and set up a statistical analysis plan.

I conducted all statistical analyses presented in Paper II under the supervision of Nico Sollmann. These included the categorization of participants into responders and non-responders according to a ≥ 25% response criterion of several headache-related outcome measures. Univariate binary logistic regression analyses were used to assess the influence of potential predictors on these headache-related outcome measures. In addition, we used multivariate binary logistic regression analyses to evaluate the combined influence of all potential predictors on the headache-related outcome measures. Together with my team of three medical doctoral students (Giada Urban, Paul Schandelmaier, Magdalena Lang), I compiled tables and figures of the publication.

Initial interpretation of findings was done by Tabea Renner and myself together with Nico Sollmann and Michaela Bonfert. Tabea Renner and I drafted the manuscript under the supervision of Michaela Bonfert and implemented feedback from the co-authors. Further, I led the revision process until final acceptance of the manuscript and was responsible for the proof-reading process.

1.3 Contribution to paper III (Appendix)

My contribution to paper III included the preparation and drafting of the review.

The medical doctoral student Giada Urban conducted the literature search under the supervision of Michaela Bonfert and myself (n = 575 studies identified). Together we reviewed the literature, identified 15 RCT studies to be included in the review and analyzed these studies based on sample size, study design, stimulation protocol, and effectiveness of the intervention (based on headache-related outcomes).

We compiled tables and figures and discussed the findings and implications of the RCTs so far only including adult participants in the light of the child neurologist's perspective.

I drafted the manuscript and incorporated the feedback of all co-authors with the help of Giada Urban and under the supervision of Michaela Bonfert. The revision process until acceptance of the manuscript and the proof-reading process was led by myself.

2. Introductory summary

2.1 Headache Disorders

2.1.1 Epidemiology and clinical picture

Migraine and tension-type headache (TTH) are the most prevalent primary headache disorders. About 14.7% of adults are affected by migraine in Europe and more than one billion worldwide (1-5). Regarding children and adolescents, migraine and TTH were classified as second most disabling conditions in 2019 (4, 6-8). Notably, headache disorders are often underdiagnosed and underrecognized in the pediatric population resulting in the risk of chronification (9-14). Next to primary headache disorders, post-traumatic headache (PTH) plays an important role as a secondary headache disorder, in particular after mild traumatic brain injury (mTBI). While approximately 65% of adults are diagnosed with PTH 3 months after mTBI (15, 16), the reported prevalence of PTH in the pediatric population ranges from 6.8% to 70% (17).

Migraine is a recurrent headache disorder characterized in the adult population by typical migraine attacks with unilateral moderate to severe pain, pulsating pain quality, and attack duration of 4-72 hours (ICHD-3) (18). Next to headaches, symptoms can include nausea, vomiting, photophobia, and phonophobia. In children and adolescents, migraine symptoms may be less distinct in that attacks are shorter and pain location more likely is reported as bilateral. Occasionally, transient neurological symptoms, like visual or sensory symptoms (e.g., flickering visual perception), precede migraine attacks referred to as migraine aura. In contrast, TTH typically presents with headache episodes with mild to moderate intensity and bilateral pain location, pressing/tightening pain quality, and no accompanying autonomic symptoms (ICHD-3) (18). PTH can have a heterogeneous phenotype of migraine-like, TTH-like, daily, and continuous headaches (19-22). In addition, headache disorders of all types and at all ages are often associated with a compelling impact on work or school productivity, participation, social relationships, and quality of life (1-3, 23).

Moreover, a muscular involvement of the neck region is common in patients with headache disorders, and especially migraine (24-27). Importantly, the muscular involvement may be a more frequent accompanying symptom of the headache disorder than for instance nausea and is associated with headache chronicity (26). Muscular involvement can include neck pain or tension, muscular imbalance, hyperalgesia, and myofascial trigger points (TrP) (24, 28-31). TrP are hypersensitive spots within a taut band and manual palpation of these spots leads to referred sensation (32-41). Next to the clinically evident

muscular involvement, advanced muscular MRI imaging (muscle T2 mapping) of the UTM recently demonstrated muscular alterations interpreted most likely as surrogates of muscular neuroinflammation (42, 43).

In the following paragraphs, the focus will be mainly on migraine since one of the two papers deals solely with migraine and literature regarding the underpinnings of TTH and PTH is still scarce to date.

2.1.2 Pathophysiology

Long time, migraine has been perceived as a pain disorder due to its key feature “headache”. This categorization is not congruent to the complex clinical picture of migraine comprising premonitory and post-dromal symptoms before and after the headache, respectively (44). In this context, Andrew Charles (2013) set up the concept to comprehend migraine as a brain state. In this concept, pain and migraine symptoms represent the clinical surrogate of functional and, in case of longstanding existence, structural changes in networks and brain regions that are involved in the processing of nociceptive information translating to atypical pain processing (44). Further, migraine is a complex disorder with an important bidirectional interplay of the central nervous and the peripheral nervous systems. This interplay is evident in realizing the importance of peripheral and central sensitization, and neurogenic inflammation. Within the following paragraphs the most important mechanisms involved in migraine generation and perpetuation are described.

In general, ascending nociceptive information is transmitted to the thalamus, which has bidirectional connections with several cortical regions: the somatosensory cortex, insula, amygdala, and limbic regions. Here, nociceptive inputs are integrated with cognition, emotion, and autonomous symptoms (concept of the **complex pain matrix)** (45-47). Further, the thalamus transfers nociceptive inputs to the **hypothalamus** that itself bilaterally projects to the upper cervical spinal cord/brain stem (trigeminus nucleus caudalis [TNC]/spinal trigeminal nucleus), probably regulating pain thresholds and pain inhibition, and serving as a migraine generator given the oscillating state of brainstem activity (45). Food craving, fatigue, nausea, and yawning are premonitory surrogates of this hypothalamic role (48). The **descending pain modulatory system** comprises projections from the thalamus, hypothalamus, and cortical sites to midbrain and medullary sites (49). Here, the role of the periaqueductal grey and the locus coeruleus in regulating pain inhibition in migraine via modulating the **trigeminovascular system (TVS)** (**top-down inhibition of pain**) has to be highlighted (47, 48).

By now, the **TVS** is regarded as the origin and main pathway of transmission of nociceptive information in migraine (50). Migraine initiation depends on the activation and sensitization of first-order trigeminovascular neurons (located in the trigeminal ganglion) based on the following neuroanatomical features of their afferent fibers (nociception: C fibers, Aδ): (1) innervation of the meninges and their vessels (terminal nerve endings), (2) projection to structures in the central nervous system (central nerve endings in the TNC/spinal trigeminal nucleus), (3) activation of these neurons releases vasoactive peptides (e.g. calcitonin gene-related peptide [CGRP], substance P, pituitary adenylate cyclase-activating peptide [PACAP]) in both directions, that induce inflammatory reactions including vasodilation and plasma extravasation (**neurogenic inflammation**) in the periphery (48, 50, 51). Subsequently, this process discharges and sensitizes second- (upper spinal cord/brain stem) and third-order neurons (thalamus), resulting in the transmission of nociceptive impulses to the somatosensory cortex and other brain regions involved in pain (see complex pain matrix, descending pain modulatory system) (52).

In case of migraine with aura, **cortical spreading depression (CSD)** is interpreted as the electrophysiological pattern of migraine aura and describes “a short-lasting, intense wave of neuronal and glial depolarization that spreads slowly over the cortex”, “followed by a long-lasting inhibition of spontaneous and evoked neuronal activity” (48, 52, 53). This electrophysiological phenomenon is accompanied by alterations in regional cerebral blood flow beginning in the occipital cortex and slowly expanding in frontal direction (53). **CSD initiates the release of inflammatory mediators by microglia activation** (neuropeptides [=neurogenic inflammation] and mast cell degranulation). These neuropeptides (e.g., CGRP) activate the trigeminal Aδ and C afferents in the perivasculature of the meninges and induce thereby an inflow of nociceptive information to the trigeminal ganglion and the TNC/spinal trigeminal nucleus and trigger the **TVS**, as well (50).

Long(er) standing neurogenic inflammation in the context of the **TVS** causes sensitization of meningeal nociceptors and the neurons in the trigeminal ganglion **(peripheral sensitization)**; in turn second- and third-order trigeminovascular neurons in the TNC/spinal trigeminal nucleus and thalamus are sensitized. **Central sensitization** reflects the situation that nociceptors are already activated at lower thresholds and that their receptive field expands. Consequently, noxious stimuli cause amplified, prolonged, and extended responses (**activity dependent central sensitization**). **Neuroplastic and structural adaptations at pain modulatory areas in the spinal cord and the cortex** promote a net descending pain facilitation (activity independent sensitization). While hyperalgesia (increased pain reaction to a usually pain-evoking stimulus) can be considered a clinical surrogate of peripheral sensitization, allodynia (pain reaction to a non-painful stimulus) can be understood as clinical surrogate of central sensitization.

In migraine and TTH, the association of headaches and muscular symptoms / pain can be explained by introducing an additional neuroanatomical pathway – the trigemino-cervical complex (TCC) (50, 52, 54-57). Within the framework of the TCC, muscular involvement of the neck muscles – and of the UTM in particular – represents one of the extracranial peripheral sites involved in pain origination (48, 58): nociceptive and proprioceptive information is transmitted from cervical afferents (C1-C3/4) stemming from the neck musculature to the TNC within the upper cervical spinal cord (54, 56, 57, 59). Here, this information converges with sensory information from the head and face (trigeminal branch I) and is forwarded to the above outlined higher-order pain processing networks in the brain.

Regarding myofascial structures, muscular contraction or strain, ischemia, and inflammation are potent to activate local nociceptors of Aδ and C fibers (57, 60-63). Headaches can be associated to stress as stress can induce increased muscle tension and amplified activity of motor units inducing ischemia-like states in the myofascial tissue. All these mechanisms result in the excretion of mediators that consecutively contribute to an increased responsiveness of the nociceptors (myofascial peripheral sensitization) (57, 60-63). As described above, the myofascial nociception is conveyed to higher-order pain networks via the TCC. Here, the level of sensitization of the second- and higher-order neurons (central sensitization) together with the level of top-down inhibition regulates the extent to that the nociceptive information is transferred. On the myofascial level, vasoactive neurogenic mediators, such as CGRP, are potent to booster peripheral sensitization. These mediators can induce vasodilation and mast cell degradation followed by plasma exudation into the myofascial tissue (57, 60-64). Notably, analogously as described for the TVS, retrograde excretion of CGRP via Aδ and C fibers into the myofascial tissue is likely to be triggered by the afferent nociceptive inflow itself (65). Like a vicious cycle, myofascial peripheral sensitization continuously exaggerates and perpetuates.

In PTH, similar pathophysiological processes to migraine play a key role (21, 66). However, the muscular involvement, especially in the neck region, plays an additional role in PTH due to a whiplash-like component leading to similar muscular symptoms as described for migraine or TTH (21, 67, 68). The role of the neck region in PTH pathophysiology is also supported by studies showing that blocking the greater occipital nerve (cannulating through the UTM) can lead to a reduction in headache symptoms (69, 70).

2.1.3 Treatment

Next to the well-established acute treatment with pain medication or migraine specific medications (10, 71, 72), prevention of headache episodes plays a crucial role within headache care. Prevention of migraine is currently based on an individually tailored

multi-modal approach comprising extensive education, lifestyle management, physiotherapy, relaxation techniques, behavioral therapy, and pharmacotherapy (10, 73, 74). Preventive strategies for TTH and PTH are mainly based on the same concept. Regarding all of the headache disorders, pharmaco-prophylaxis is not a first line treatment since side effects and inappropriate safety data have been reported (75-78). This challenge is even more pronounced for pediatric headache disorders (10, 79). Non-pharmacological treatment options for headache disorders are scarce to date, which is why innovative, non-invasive treatment options are highly warranted (10, 73, 75, 80, 81).

2.2 Neuromodulation

Neuromodulation in terms of neurostimulation is a recent, innovative, non-pharmacological treatment option: The external application of electrical or electro-magnetically induced stimuli aims at the modulation of the function of cerebral or neuromuscular structures by inducing a voltage difference at the stimulation sites (81-84). For migraine, next to central stimulation approaches like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), several peripheral stimulation approaches, that target to neuromuscular structures have been investigated: transcutaneous occipital nerve stimulation (tONS) of the bilateral occipital nerves, transcutaneous vagus nerve stimulation (tVNS) of the cervical or auricular sections of the vagus nerve, transcutaneous supraorbital nerve stimulation (tSNS) of the bilateral supratrochlear and supraorbital nerves, and remote electrical neurostimulation (REN) targeting the cutaneous afferents of the upper arm (81, 85-96). In terms of acute treatment of migraine attacks, tSNS, tVNS, and REN have been found to be effective (81, 86, 97-99). Regarding migraine prophylaxis, effective approaches include tONS and tSNS (81, 100-103). For TTH and PTH, literature is very scarce and specific neuromodulating treatments have not been established yet (66, 104).

2.3 Repetitive neuromuscular magnetic stimulation

Repetitive neuromuscular magnetic stimulation (rNMS) targeting the UTM represents a novel, neuromodulating approach, that was originally developed by our research group under the supervision of Michaela Bonfert and Florian Heinen which will be discussed in the following paragraphs.

2.3.1 Setup and feasibility

Due to the clinically evident muscular component of the headache pathophysiology, rNMS targeting the UTM has been established as a novel, neuromodulating treatment

from bottom up for migraine, TTH, and PTH in our tertiary outpatient headache center. It is hypothesized that the electromagnetic stimulation of the UTM modulates mechanisms involved in peripheral and central sensitization and promotes network reorganization of regions and pathways involved in pain processing via the upper cervical afferents (C1-C3) and the TCC, respectively (50, 52, 105-108). Previous work of our group showed that the rNMS setup was safe, feasible, and well-accepted by patients and caregivers (109-112). Compared to conventional manual physiotherapy, rNMS has the advantage of reaching deeper muscular structures of the UTM. In addition, rNMS is a personalized neurostimulation approach, in that patients can control the stimulation intensity themselves.

2.3.2 Central effects

It was previously shown that rNMS may have a beneficial effect on headache symptoms (e.g., reducing the headache frequency) (109, 110, 112). In paper I of this dissertation we additionally analyzed headache symptoms before and after rNMS treatment of 20 patients receiving 25 rNMS interventions with regard to headache diagnosis, presence of neck pain, and the time frame, in which rNMS was administered (113).

Changes in headache symptoms did not significantly differ between patients with primary headache disorders and posttraumatic headache (headache frequency: $p = 0.191$; minimum headache intensity: $p = 0.679$; maximum headache intensity: $p = 0.770$; headache duration: $p = 0.923$) (113). This may implicate that the response to rNMS treatment was irrespective of the headache diagnosis. However, it is important to note that in the primary headache group, 43% of patients were responders (based on ≥ 25% reduction in headache frequency) and 14% of patients had a reduction in headache frequency of ≥ 75% while in the PTH group, 46% were responders and all patients had a reduction of ≥ 75%.

Similarly, the time frame in which rNMS treatment was administered (< 2x/week, exactly 2x/week, > 2x/week), does not seem to influence the response to rNMS treatment as no significant differences in changes in headache symptoms were observed for the different time frame groups (headache frequency: $p = 0.462$; minimum headache intensity: $p = 0.600$; maximum headache intensity: $p = 0.059$; headache duration: $p = 0.318$) (113). However, receiving rNMS twice a week may be a preferable protocol since 60% of patients were responders (≥ 25%) while only 33% of patients were responders (≥ 25%) when receiving more or less frequent rNMS treatments, respectively.

Regarding the presence of neck pain, the change in headache frequency was found to be significantly higher in patients with neck pain compared to patients without neck pain

($p = 0.032$) (113). In addition, significantly more patients with neck pain (60%) were classified as responders based on a reduction in headache frequency of ≥25% compared to patients without neck pain (20%, $p = 0.048$). This finding fits within the theoretical concept of the TCC since rNMS may have greater effects in patients with more pronounced muscular involvement (i.e., neck pain) of the headache diagnosis (39, 107).

2.3.3 Muscular Effects

Previous work showed beneficial effects in terms of reduction in muscular symptoms in young adults with migraine (111, 112). In paper I of the dissertation, we compared PPT above the UTM before and after rNMS treatment in 17 patients receiving 22 rNMS interventions (data of 3 patients was not available due to a follow-up via telephone) (113). PPT significantly differed before the first rNMS session, before the last rNMS session, and 3 months after rNMS ($p < 0.001$). More specifically, PPT increased from the first to the last rNMS session. From the last rNMS session to 3 months after rNMS, PPT did not significantly change. Thus, muscular hypersensitivity decreased (as reflected by increased PPT) after rNMS treatment and could be sustained until 3 months after treatment. Comparisons of PPT changes between (1) patients with primary headache disorders and posttraumatic headache, (2) patients with and without neck pain, and (3) patients receiving rNMS within different time frames (< 2x/week, exactly 2x/week, > 2x/week) showed no significant interaction effects. Hence, beneficial muscular effects of rNMS do not seem to depend on headache diagnosis, presence of neck pain, or the time frame, in which rNMS was administered.

2.3.4 Possible response predictors

As described previously, rNMS can have beneficial effects on muscular and headache symptoms in pediatric and young adult cohorts with headache disorders (73, 109-113). Nevertheless, some patients respond to rNMS treatment while others do not, and it is not yet known which factors may influence responsiveness to rNMS treatment. In order to evaluate possible response predictors of rNMS, we retrospectively analyzed the data of 30 young adults with migraine who received rNMS targeting the UTM as part of the studies reported by Sollmann et al. (112) and Renner et al. (73, 110, 111).

Several headache characteristics at baseline may predict responsiveness to rNMS treatment: Results showed that responders in terms of a ≥ 25% reduction in headache frequency had a lower mean headache frequency and intensity at baseline and were more often diagnosed with migraine without concurrent TTH (83). Based on these findings, rNMS may have especially beneficial effects when treatment is started during an early disease stage as headache frequency and intensity may still be lower then and the level

of central sensitization is still lower. This should also be considered when offering rNMS treatment to the pediatric cohort.

Responders in terms of a ≥ 25% reduction in analgesic intake frequency had a significantly higher mean baseline headache intensity and higher mean headache frequency with a statistical trend (83). Frequent medication intake likely reflects a higher burden of disease in terms of for instance higher headache frequency or intensity. Thus, responsiveness in terms of reduced medication intake may be associated with lower headache frequency and intensity as beneficial response to rNMS.

With regard to predictive muscular characteristics at baseline, results indicate that responders in terms of a ≥ 25% increase in PPT above the right and left UTM had significantly lower PPT above the right UTM at baseline (83). Supporting the bottom-up approach, rNMS targets the UTM, which feeds sensory information to the TCC, and a high muscular component in terms of muscular hypersensitivity may result in responsiveness to rNMS.

Lastly, technical characteristics may influence responsiveness to rNMS treatment since responders in terms of a ≥ 25% reduction in headache intensity had significantly higher mean stimulation intensities (83). This finding may reflect a dose-effect relationship and comparisons of different stimulation protocols are needed in future to determine the most beneficial technical parameters.

2.4 Future directions

As summarized above, rNMS seems to be a promising, novel, non-invasive, non-pharmacological, neuromodulating treatment for patients affected by headache disorders and is also suited for the pediatric cohort. In this context, rNMS could play a future key role in providing personalized multimodal treatment protocols tailored to the needs of the individual patient. Nevertheless, the above presented evidence is based on (pilot) studies and retrospective analyses with rather small sample sizes and without randomized sham control. Therefore, prospective, randomized, sham-controlled studies are urgently needed to further investigate the effects of rNMS treatment as well as its neurophysiological mechanisms. For this reason, our group set up the currently running MagMig study, that will exactly fill these gaps in research. During my time as PhD, I was involved in the MagMig project creation, preparation of administration (ethic's approval), training of study staff, set-up of the study, patient recruitment, conduction of study appointments/treatments, and data management as well as communication to our study collaborators, the scientific community, and the public.

References

1. Martelletti P, Schwedt TJ, Lanteri-Minet M, Quintana R, Carboni V, Diener HC, et al. My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. J Headache Pain. 2018;19(1):115.

2. Stovner LJ, Nichols E, Steiner TJ, Abd-Allah F, Abdelalim A, Al-Raddadi RM, et al. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2018;17(11):954-76.

3. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. J Headache Pain. 2018;19(1):82.

4. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1204-22.

5. Woldeamanuel YW, Cowan RP. Migraine affects 1 in 10 people worldwide featuring recent rise: A systematic review and meta-analysis of community-based studies involving 6 million participants. J Neurol Sci. 2017;372:307-15.

6. Albers L, von Kries R, Heinen F, Straube A. Headache in school children: is the prevalence increasing? Curr Pain Headache Rep. 2015;19(3):4.

7. Youssef PE, Mack KJ. Episodic and chronic migraine in children. Dev Med Child Neurol. 2020;62(1):34-41.

8. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol. 2010;52(12):1088-97.

9. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia. 2007;27(3):193-210.

10. Bonfert M, Straube A, Schroeder AS, Reilich P, Ebinger F, Heinen F. Primary headache in children and adolescents: update on pharmacotherapy of migraine and tension-type headache. Neuropediatrics. 2013;44(1):3-19.

11. Rho YI, Chung HJ, Lee KH, Eun BL, Eun SH, Nam SO, et al. Prevalence and clinical characteristics of primary headaches among school children in South Korea: a nationwide survey. Headache. 2012;52(4):592-9.

12. Jensen RH. Tension-Type Headache - The Normal and Most Prevalent Headache. Headache. 2018;58(2):339-45.

13. Seshia SS. Mixed migraine and tension-type: a common cause of recurrent headache in children. Can J Neurol Sci. 2004;31(3):315-8.

14. Blume HK. Posttraumatic headache in pediatrics: an update and review. Curr Opin Pediatr. 2018;30(6):755-63.

15. Cnossen MC, van der Naalt J, Spikman JM, Nieboer D, Yue JK, Winkler EA, et al. Prediction of Persistent Post-Concussion Symptoms after Mild Traumatic Brain Injury. J Neurotrauma. 2018;35(22):2691-8.

16. Yilmaz T, Roks G, de Koning M, Scheenen M, van der Horn H, Plas G, et al. Risk factors and outcomes associated with post-traumatic headache after mild traumatic brain injury. Emerg Med J. 2017;34(12):800-5.

17. Shaw L, Morozova M, Abu-Arafeh I. Chronic post-traumatic headache in children and adolescents: systematic review of prevalence and headache features. Pain Manag. 2018;8(1):57-64.

18. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.

19. Kuczynski A, Crawford S, Bodell L, Dewey D, Barlow KM. Characteristics of post-traumatic headaches in children following mild traumatic brain injury and their response to treatment: a prospective cohort. Dev Med Child Neurol. 2013;55(7):636-41.

20. McEvoy H, Borsook D, Holmes SA. Clinical features and sex differences in pediatric post-traumatic headache: A retrospective chart review at a Boston area concussion clinic. Cephalalgia. 2020;40(7):701-11.

21. Howard L, Schwedt TJ. Posttraumatic headache: recent progress. Curr Opin Neurol. 2020;33(3):316-22.

22. Eisenberg MA, Meehan WP, 3rd, Mannix R. Duration and course of post-concussive symptoms. Pediatrics. 2014;133(6):999-1006.

23. Milde-Busch A, Heinrich S, Thomas S, Kuhnlein A, Radon K, Straube A, et al. Quality of life in adolescents with headache: results from a population-based survey. Cephalalgia. 2010;30(6):713-21.

24. Blaschek A, Milde-Busch A, Straube A, Schankin C, Langhagen T, Jahn K, et al. Self-reported muscle pain in adolescents with migraine and tension-type headache. Cephalalgia. 2012;32(3):241-9.

25. Ashina S, Bendtsen L, Lyngberg AC, Lipton RB, Hajiyeva N, Jensen R. Prevalence of neck pain in migraine and tension-type headache: a population study. Cephalalgia. 2015;35(3):211-9.

26. Calhoun AH, Ford S, Millen C, Finkel AG, Truong Y, Nie Y. The prevalence of neck pain in migraine. Headache. 2010;50(8):1273-7.

27. De Marinis M, Accornero N. Recurrent neck pain as a variant of migraine: description of four cases. J Neurol Neurosurg Psychiatry. 1997;62(6):669-70.

28. Blaschek A, Decke S, Albers L, Schroeder AS, Lehmann S, Straube A, et al. Self-reported neck pain is associated with migraine but not with tension-type headache in adolescents. Cephalalgia. 2014;34(11):895-903.

29. Landgraf MN, Ertl-Wagner B, Koerte IK, Thienel J, Langhagen T, Straube A, et al. Alterations in the trapezius muscle in young patients with migraine--a pilot case series with MRI. Eur J Paediatr Neurol. 2015;19(3):372-6.

30. Landgraf MN, Biebl JT, Langhagen T, Hannibal I, Eggert T, Vill K, et al. Children with migraine: Provocation of headache via pressure to myofascial trigger points in the trapezius muscle? - A prospective controlled observational study. Eur J Pain. 2018;22(2):385-92.

31. Landgraf MN, von Kries R, Heinen F, Langhagen T, Straube A, Albers L. Self-reported neck and shoulder pain in adolescents is associated with episodic and chronic migraine. Cephalalgia. 2016;36(8):807-11.

32. Simons DG, Travell JG, Simons LS. Travell & Simons' Myofascial Pain and Dysfunction: Upper half of body: Williams & Wilkins; 1999.

33. Giamberardino MA, Tafuri E, Savini A, Fabrizio A, Affaitati G, Lerza R, et al. Contribution of myofascial trigger points to migraine symptoms. J Pain. 2007;8(11):869-78.

34. Zhuang X, Tan S, Huang Q. Understanding of myofascial trigger points. Chin Med J (Engl). 2014;127(24):4271-7.

35. Fernandez-de-las-Penas C, Alonso-Blanco C, Cuadrado ML, Gerwin RD, Pareja JA. Trigger points in the suboccipital muscles and forward head posture in tension-type headache. Headache. 2006;46(3):454-60.

36. Fernandez-de-las-Penas C, Cuadrado ML, Arendt-Nielsen L, Simons DG, Pareja JA. Myofascial trigger points and sensitization: an updated pain model for tension-type headache. Cephalalgia. 2007;27(5):383-93.

37. Fernandez-de-Las-Penas C, Cuadrado ML, Pareja JA. Myofascial trigger points, neck mobility and forward head posture in unilateral migraine. Cephalalgia. 2006;26(9):1061-70.

38. Fernandez-de-las-Penas C, Dommerholt J. Myofascial trigger points: peripheral or central phenomenon? Curr Rheumatol Rep. 2014;16(1):395.

39. Fernandez-de-las-Penas C, Madeleine P, Caminero AB, Cuadrado ML, Arendt-Nielsen L, Pareja JA. Generalized neck-shoulder hyperalgesia in chronic tension-type headache and unilateral migraine assessed by pressure pain sensitivity topographical maps of the trapezius muscle. Cephalalgia. 2010;30(1):77-86.

40. Luedtke K, Starke W, May A. Musculoskeletal dysfunction in migraine patients. Cephalalgia. 2018;38(5):865-75.

41. Fernandez-de-Las-Penas C, Dommerholt J. International Consensus on Diagnostic Criteria and Clinical Considerations of Myofascial Trigger Points: A Delphi Study. Pain Med. 2018;19(1):142-50.

42. Sollmann N, Mathonia N, Weidlich D, Bonfert M, Schroeder SA, Badura KA, et al. Quantitative magnetic resonance imaging of the upper trapezius muscles - assessment of myofascial trigger points in patients with migraine. J Headache Pain. 2019;20(1):8.

43. Sollmann N, Schandelmaier P, Weidlich D, Borner C, Urban G, Lang M, et al. Patients with episodic migraine show increased T2 values of the trapezius muscles - an investigation by quantitative high-resolution magnetic resonance imaging. Cephalalgia. 2021;41(8):934-42.

44. Charles A. Migraine: a brain state. Curr Opin Neurol. 2013;26(3):235-9.

45. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nat Rev Neurosci. 2013;14(7):502-11.

46. Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: a salience detection system for the body. Prog Neurobiol. 2011;93(1):111-24.

47. Maizels M, Aurora S, Heinricher M. Beyond neurovascular: migraine as a dysfunctional neurolimbic pain network. Headache. 2012;52(10):1553-65.

48. Charles A. The pathophysiology of migraine: implications for clinical management. The Lancet Neurology. 2018;17(2):174-82.

49. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the Trigeminal System in Migraine. Headache. 2019;59(5):659-81.

50. Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R, Moskowitz MA. Migraine and the trigeminovascular system-40 years and counting. Lancet Neurol. 2019;18(8):795-804.

51. Tajti J, Szok D, Majlath Z, Tuka B, Csati A, Vecsei L. Migraine and neuropeptides. Neuropeptides. 2015;52:19-30.

52. Ashina M. Migraine. The New England journal of medicine. 2020;383(19):1866-76.

53. de Vries B, Haan J, van den Maagdenberg A.M.J.M., M.D. F. Migraine; Genetics. In: Michael J. Aminoff RBD, editor. Encyclopedia of the Neurological Sciences (Second Edition): Academic Press; 2014. p. 42-6.

54. Bartsch T, Goadsby PJ. The trigeminocervical complex and migraine: current concepts and synthesis. Curr Pain Headache Rep. 2003;7(5):371-6.

55. Bartsch T. Migraine and the neck: new insights from basic data. Curr Pain Headache Rep. 2005;9(3):191-6.

56. Busch V, Frese A, Bartsch T. [The trigemino-cervical complex. Integration of peripheral and central pain mechanisms in primary headache syndromes]. Schmerz. 2004;18(5):404-10.

57. Ashina S, Mitsikostas DD, Lee MJ, Yamani N, Wang SJ, Messina R, et al. Tension-type headache. Nat Rev Dis Primers. 2021;7(1):24.

58. Dodick DW. A Phase-by-Phase Review of Migraine Pathophysiology. Headache. 2018;58 Suppl 1:4-16.

59. Bartsch T, Goadsby PJ. Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. Brain. 2002;125(Pt 7):1496-509.

60. Ferrari MD, Goadsby PJ, Burstein R, Kurth T, Ayata C, Charles A, et al. Migraine. Nat Rev Dis Primers. 2022;8(1):2.

61. Ashina S, Bendtsen L, Ashina M. Pathophysiology of tension-type headache. Curr Pain Headache Rep. 2005;9(6):415-22.

62. Cathcart S, Winefield AH, Lushington K, Rolan P. Stress and tension-type headache mechanisms. Cephalalgia. 2010;30(10):1250-67.

63. Mense S. The pathogenesis of muscle pain. Curr Pain Headache Rep. 2003;7(6):419-25.

64. Russo AF, Hay DL. CGRP physiology, pharmacology, and therapeutic targets: Migraine and beyond. Physiol Rev. 2022.

65. Messlinger K. The big CGRP flood - sources, sinks and signalling sites in the trigeminovascular system. J Headache Pain. 2018;19(1):22.

66. Ashina H, Porreca F, Anderson T, Amin FM, Ashina M, Schytz HW, et al. Post-traumatic headache: epidemiology and pathophysiological insights. Nat Rev Neurol. 2019;15(10):607-17.

67. Buitenhuis J, de Jong PJ, Jaspers JP, Groothoff JW. Work disability after whiplash: a prospective cohort study. Spine (Phila Pa 1976). 2009;34(3):262-7.

68. Pearce JM. Headaches in the whiplash syndrome. Spinal Cord. 2001;39(4):228-33.

69. Dubrovsky AS, Friedman D, Kocilowicz H. Pediatric post-traumatic headaches and peripheral nerve blocks of the scalp: a case series and patient satisfaction survey. Headache. 2014;54(5):878-87.

70. Seeger TA, Orr S, Bodell L, Lockyer L, Rajapakse T, Barlow KM. Occipital Nerve Blocks for Pediatric Posttraumatic Headache: A Case Series. J Child Neurol. 2015;30(9):1142-6.

71. Oskoui M, Pringsheim T, Holler-Managan Y, Potrebic S, Billinghurst L, Gloss D, et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2019;93(11):487-99.

72. Diener, Förderreuther, Kropp. Therapie der Migräneattacke und Prophylaxe der Migräne, S1-Leitlinie, DGN und DMKG. Deutsche Gesellschaft für Neurologie (Hrsg), Leitlinien für Diagnostik und Therapie in der Neurologie. 2022.

73. Bonfert MV, Borner C, Gerstl L, Hannibal I, Mathonia N, Huss K, et al. [Migraine in childhood and adolescence-neurostimulation as a future innovative approach in terms of a multimodal treatment regimen]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2020;63(7):872-80.

74. Diener HC GCKPea. Therapie Der Migräneattacke Und Prophylaxe Der Migräne, S1 Leitlinie. . Nervenheilkunde. 2018:689-715.

75. Diener H-C, Charles A, Goadsby PJ, Holle D. New therapeutic approaches for the prevention and treatment of migraine. The Lancet Neurology. 2015;14(10):1010-22.

76. Eller M, Goadsby PJ. Migraine: a brain state amenable to therapy. Med J Aust. 2020;212(1):32-9.

77. Locher C, Kossowsky J, Koechlin H, Lam TL, Barthel J, Berde CB, et al. Efficacy, Safety, and Acceptability of Pharmacologic Treatments for Pediatric Migraine Prophylaxis: A Systematic Review and Network Meta-analysis. JAMA Pediatr. 2020;174(4):341-9.

78. Cook C. Acute Treatment of Pediatric Migraine: A Review of the Updated Guidelines. Adv Emerg Nurs J. 2020;42(1):4-12.

79. Oskoui M, Pringsheim T, Billinghurst L, Potrebic S, Gersz EM, Gloss D, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2019;93(11):500-9.

80. Brighina F, Raieli V, Messina LM, Santangelo G, Puma D, Drago F, et al. Non-invasive Brain Stimulation in Pediatric Migraine: A Perspective From Evidence in Adult Migraine. Front Neurol. 2019;10:364.

81. Borner C, Urban G, Beaulieu LD, Sollmann N, Krieg SM, Straube A, et al. The bottom-up approach: Non-invasive peripheral neurostimulation methods to treat migraine: A scoping review from the child neurologist's perspective. Eur J Paediatr Neurol. 2021;32:16-28.

82. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol. 2015;126(6):1071-107.

83. Börner C, Renner T, Trepte-Freisleder F, Urban G, Schandelmaier P, Lang M, et al. Response Predictors of Repetitive Neuromuscular Magnetic Stimulation in the Preventive Treatment of Episodic Migraine. Front Neurol. 2022;13.

84. Moisset X, Pereira B, Ciampi de Andrade D, Fontaine D, Lanteri-Minet M, Mawet J. Neuromodulation techniques for acute and preventive migraine treatment: a systematic review and meta-analysis of randomized controlled trials. J Headache Pain. 2020;21(1):142.

85. Rapoport AM, Bonner JH, Lin T, Harris D, Gruper Y, Ironi A, et al. Remote electrical neuromodulation (REN) in the acute treatment of migraine: a comparison with usual care and acute migraine medications. J Headache Pain. 2019;20(1):83.

86. Yarnitsky D, Dodick DW, Grosberg BM, Burstein R, Ironi A, Harris D, et al. Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. Headache. 2019;59(8):1240-52.

87. Rodrigo D, Acin P, Bermejo P. Occipital Nerve Stimulation for Refractory Chronic Migraine: Results of a Long-Term Prospective Study. Pain Physician. 2017;20(1):E151-E9.

88. de Coo IF, Marin JC, Silberstein SD, Friedman DI, Gaul C, McClure CK, et al. Differential efficacy of non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A meta-analysis. Cephalalgia. 2019;39(8):967-77.

89. Ordas CM, Cuadrado ML, Pareja JA, de-Las-Casas-Camara G, Gomez-Vicente L, Torres-Gaona G, et al. Transcutaneous Supraorbital Stimulation as a Preventive Treatment for Chronic Migraine: A Prospective, Open-Label Study. Pain Med. 2020;21(2):415-22.

90. Starling AJ, Tepper SJ, Marmura MJ, Shamim EA, Robbins MS, Hindiyeh N, et al. A multicenter, prospective, single arm, open label, observational study of sTMS for migraine prevention (ESPOUSE Study). Cephalalgia. 2018;38(6):1038-48.

91. Stilling JM, Monchi O, Amoozegar F, Debert CT. Transcranial Magnetic and Direct Current Stimulation (TMS/tDCS) for the Treatment of Headache: A Systematic Review. Headache. 2019;59(3):339-57.

92. Rapoport AM, Lin T, Tepper SJ. Remote Electrical Neuromodulation (REN) for the Acute Treatment of Migraine. Headache. 2020;60(1):229-34.

93. Reuter U, McClure C, Liebler E, Pozo-Rosich P. Non-invasive neuromodulation for migraine and cluster headache: a systematic review of clinical trials. J Neurol Neurosurg Psychiatry. 2019;90(7):796-804.

94. Tajti J, Szok D, Nyari A, Vecsei L. Therapeutic strategies that act on the peripheral nervous system in primary headache disorders. Expert Rev Neurother. 2019;19(6):509-33.

95. Jurgens TP, Rimmele F. [Neuromodulation in primary headache in the year 2019: is it still up-to-date? : New data on invasive and non-invasive neuromodulation in migraine and cluster headaches]. Schmerz. 2019;33(4):347-67.

96. Halker Singh RB, Ailani J, Robbins MS. Neuromodulation for the Acute and Preventive Therapy of Migraine and Cluster Headache. Headache. 2019;59 Suppl 2:33-49.

97. Chou DE, Shnayderman Yugrakh M, Winegarner D, Rowe V, Kuruvilla D, Schoenen J. Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. Cephalalgia. 2019;39(1):3-14.

98. Hokenek NM, Erdogan MO, Hokenek UD, Algin A, Tekyol D, Seyhan AU. Treatment of migraine attacks by transcutaneous electrical nerve stimulation in emergency department: A randomize controlled trial. Am J Emerg Med. 2021;39:80-5.

99. Tassorelli C, Grazzi L, de Tommaso M, Pierangeli G, Martelletti P, Rainero I, et al. Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized PRESTO study. Neurology. 2018;91(4):e364-e73.

100. Schoenen J, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gérard P, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology. 2013;80(8):697-704.

101. Jiang L, Yuan DL, Li M, Liu C, Liu Q, Zhang Y, et al. Combination of flunarizine and transcutaneous supraorbital neurostimulation improves migraine prophylaxis. Acta Neurol Scand. 2019;139(3):276-83.

102. Liu Y, Dong Z, Wang R, Ao R, Han X, Tang W, et al. Migraine Prevention Using Different Frequencies of Transcutaneous Occipital Nerve Stimulation: A Randomized Controlled Trial. J Pain. 2017;18(8):1006-15.

103. Bono F, Salvino D, Mazza MR, Curcio M, Trimboli M, Vescio B, et al. The influence of ictal cutaneous allodynia on the response to occipital transcutaneous electrical stimulation in chronic migraine and chronic tension-type headache: a randomized, sham-controlled study. Cephalalgia. 2015;35(5):389-98.

104. Lucas S. Posttraumatic Headache: Clinical Characterization and Management. Curr Pain Headache Rep. 2015;19(10):48.

105. Smania N, Corato E, Fiaschi A, Pietropoli P, Aglioti SM, Tinazzi M. Repetitive magnetic stimulation: a novel therapeutic approach for myofascial pain syndrome. J Neurol. 2005;252(3):307-14.

106. Pujol J, Pascual-Leone A, Dolz C, Delgado E, Dolz JL, Aldomà J. The effect of repetitive magnetic stimulation on localized musculoskeletal pain. Neuroreport. 1998;9(8):1745-8.

107. Bartsch T, Goadsby PJ. Central mechanisms of peripheral nerve stimulation in headache disorders. Prog Neurol Surg. 2011;24:16-26.

108. Bartsch T, Goadsby PJ. Increased responses in trigeminocervical nociceptive neurons to cervical input after stimulation of the dura mater. Brain. 2003;126(Pt 8):1801-13.

109. Staisch J, Borner C, Lang M, Hauser A, Hannibal I, Huss K, et al. Repetitive neuromuscular magnetic stimulation in children with headache. Eur J Paediatr Neurol. 2022;39:40-8.

110. Renner T, Sollmann N, Heinen F, Albers L, Trepte-Freisleder F, Klose B, et al. Alleviation of migraine symptoms by application of repetitive peripheral magnetic stimulation to myofascial trigger points of neck and shoulder muscles - A randomized trial. Sci Rep. 2020;10(1):5954.

111. Renner T, Sollmann N, Trepte-Freisleder F, Albers L, Mathonia NM, Bonfert MV, et al. Repetitive Peripheral Magnetic Stimulation (rPMS) in Subjects With Migraine-Setup Presentation and Effects on Skeletal Musculature. Front Neurol. 2019;10:738.

112. Sollmann N, Trepte-Freisleder F, Albers L, Jung NH, Mall V, Meyer B, et al. Magnetic stimulation of the upper trapezius muscles in patients with migraine - A pilot study. Eur J Paediatr Neurol. 2016;20(6):888-97.

113. Börner C, Staisch J, Lang M, Hauser A, Hannibal I, Huß K, et al. Repetitive Neuromuscular Magnetic Stimulation for Pediatric Headache Disorders: Muscular Effects and Factors Affecting Level of Response. Brain Sciences. 2022;12(7):932.

brain sciences

MDPI

Article

Repetitive Neuromuscular Magnetic Stimulation for Pediatric Headache Disorders: Muscular Effects and Factors Affecting Level of Response

Corinna Börner [1,2,3,4,†], Jacob Staisch [1,2,†], Magdalena Lang [1,2], Ari Hauser [1,2], Iris Hannibal [1,2], Kristina Huß [1,2], Birgit Klose [1,2], Matthias F. Lechner [1,2], Nico Sollmann [3,4,5], Florian Heinen [1,2], Mirjam N. Landgraf [1,2] and Michaela V. Bonfert [1,2,*]

1 LMU Hospital, Department of Pediatrics—Dr. von Hauner Children's Hospital, Division of Pediatric Neurology and Developmental Medicine, Ludwig-Maximilians Universität, Lindwurm Str. 4, 80337 Munich, Germany; corinna.boerner@med.lmu.de (C.B.); jacob.staisch@med.uni-muenchen.de (J.S.); magdalena.lang@campus.lmu.de (M.L.); a.hauser@students.uu.nl (A.H.); iris.hannibal@med.uni-muenchen.de (I.H.); kristina.huss@med.uni-muenchen.de (K.H.); birgit.klose@med.uni-muenchen.de (B.K.); matthias.lechner@med.uni-muenchen.de (M.F.L.); florian.heinen@med.lmu.de (F.H.); mirjam.landgraf@med.lmu.de (M.N.L.)

2 LMU Center for Children with Medical Complexity, Dr. von Hauner Children's Hospital, Ludwig-Maximilians Universität, Lindwurm Str. 4, 80337 Munich, Germany

3 Department of Diagnostic and Interventional Neuroradiology, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Ismaninger Str. 22, 81675 Munich, Germany; nico.sollmann@tum.de

4 TUM-Neuroimaging Center, Klinikum rechts der Isar, Technical University of Munich, Ismaninger Str. 22, 81675 Munich, Germany

5 Department of Diagnostic and Interventional Radiology, University Hospital Ulm, Albert-Einstein-Allee 23, 89081 Ulm, Germany

* Correspondence: michaela.bonfert@med.lmu.de

† These authors contributed equally to this work.

Citation: Börner, C.; Staisch, J.; Lang, M.; Hauser, A.; Hannibal, I.; Huß, K.; Klose, B.; Lechner, M.F.; Sollmann, N.; Heinen, F.; et al. Repetitive Neuromuscular Magnetic Stimulation for Pediatric Headache Disorders: Muscular Effects and Factors Affecting Level of Response. *Brain Sci.* **2022**, *12*, 932. https://doi.org/10.3390/brainsci12070932

Academic Editor: Massimiliano Valeriani

Received: 9 June 2022
Accepted: 12 July 2022
Published: 16 July 2022

Abstract: Repetitive neuromuscular magnetic stimulation (rNMS) for pediatric headache disorders is feasible, safe, and alleviates headache symptoms. This study assesses muscular effects and factors affecting response to rNMS. A retrospective chart review included children with headaches receiving six rNMS sessions targeting the upper trapezius muscles. Pressure pain thresholds (PPT) were measured before and after rNMS, and at 3-month follow-up (FU). Mean headache frequency, duration, and intensity within the last 3 months were documented. In 20 patients (14.1 ± 2.7 years), PPT significantly increased from pre- to post-treatment ($p < 0.001$) sustaining until FU. PPT changes significantly differed between primary headache and post-traumatic headache (PTH) ($p = 0.019$–0.026). Change in headache frequency was significantly higher in patients with than without neck pain ($p = 0.032$). A total of 60% of patients with neck pain responded to rNMS (≥25%), while 20% of patients without neck pain responded ($p = 0.048$). 60% of patients receiving rNMS twice a week were responders, while 33% of patients receiving rNMS less or more frequently responded to treatment, respectively. Alleviation of muscular hyperalgesia was demonstrated sustaining for 3 months, which was emphasized in PTH. The rNMS sessions may positively modulate headache symptoms regardless of headache diagnosis. Patients with neck pain profit explicitly well. Two rNMS sessions per week led to the highest reduction in headache frequency.

Keywords: migraine; tension-type headache; post-traumatic headache; neuromodulation; neurostimulation

1. Introduction

Primary headache disorders like migraine and tension-type headache (TTH) are highly prevalent in kids and adolescents, and they represented the second most disabling

conditions in 10- to 24-year-old individuals in 2019 [1–4]. However, these conditions are considerably underdiagnosed [5–9]. Another common entity is post-traumatic headache (PTH) with the heterogeneous character of migraine-like, TTH-like, daily, or continuous headaches [10–14].

In the pathophysiology of these headache disorders, the trigemino-cervical complex (TCC) plays an important role [15,16]. Upper cervical afferents in the neck muscles transmit nociceptive and proprioceptive information to the caudal trigeminal nucleus. There, information is converged with sensory information from trigeminal branches in the head/face area and delivered to pain processing centers in the brain [15,17,18]. Consequently, the TCC represents the key framework of the interplay of peripheral and central mechanisms of pain perception, processing, perpetuation, and sensitization [15,18–20].

Within this concept, muscular involvement accompanying headache disorders comprises reports of neck pain or tension as well as findings during manual palpation of the short neck and upper trapezius muscles (UTM) [21–24]: next to muscular imbalance, restricted range of motion, or hyperalgesia, involvement of these muscles encompasses the presence of myofascial trigger points (mTrP), defined by taut bands, hypersensitive spots, and referred sensation during manual palpation [15,21–35]. In addition, PTH is frequently associated with muscular symptoms due to a whiplash-like component by rotational mechanical forces and a subsequent dysregulation of muscle tone in the neck muscles, which can present with neck pain and similar muscular signs as described for migraine and TTH [12,36–38].

A multimodal therapeutic strategy approaching the burdensome migraine, TTH, and PTH in children, calls for non-invasive, non-pharmacological, safe, and well-accepted treatments [39]. Neurostimulation of the cranial nerves represents one of the currently increasingly investigated approaches in adult neurology [40]. As muscular involvement is frequently diagnosed in pediatric headache disorders, a personalized treatment protocol applying repetitive neuromuscular magnetic stimulation (rNMS) targeting the UTM has been recently developed, demonstrating a feasible and safe set-up process and the effective alleviation of headache symptoms [41]. It is hypothesized that the clinical effects of rNMS in headache patients are achieved through a modulation of central pain processing networks. By electromagnetic stimulation above the UTM, sensory input via the upper cervical afferents (C1-C3) transferring to the TCC is increased by direct and indirect stimulation [42–45].

The aims of this retrospective analysis were (1) to assess the local effects on the (peripheral) muscular level of this rNMS treatment, and (2) to investigate whether the specific headache disorder (primary headache or PTH), the presence of neck pain, and the time frame rNMS is delivered in, may affect the response with regard to muscular and headache symptoms.

2. Materials and Methods

2.1. Ethics

The study was approved by the institutional review board of the medical faculty of the University of Munich (LMU; vote 21-0574).

2.2. Study Design

During chart review, 23 patients were identified, who had a diagnosis of (1) episodic migraine, (2) episodic TTH, (3) mixed-type headache [46], or (4) PTH [14,47] and received rNMS treatment in our outpatient pediatric headache clinic between August 2020 and May 2021. A description of the study design is detailed in Staisch et al. (2022) [41].

2.3. rNMS Intervention

All patients received rNMS delivered by an eMFieldPro system (Zimmer MedizinSysteme GmbH, Neu-Ulm, Germany; CE Nr 0123). Stimulation was targeted to the UTM bilaterally in 6 consecutive sessions during two to three weeks. Each side was stimulated for 15 min consisting of 7420 pulses (20 Hz, 7 s ON time, 10 s OFF time) with a duration of 250 μs by a coil creating a magnetic field of 2.5 T maximum (7.6 cm diameter of the copper winding). The starting side was alternated in each session and the stimulation intensity was individually set to a comfortable level. Detailed descriptions of the rNMS setup and stimulation protocol have been recently published [41].

2.4. PPT Assessments

Before and after each rNMS session, mechanical algometry was performed using a hand-held analogous algometer (Wagner instrument, Greenwich, CT, USA) to determine the patient's pressure pain thresholds (PPT) above the UTM. The PPT is defined as the cut-off weight between the perception of pressure and the perception of pressure-induced pain [31,48]. Patients were seated on a roller stool with their hands resting on their laps. Reference points were marked at 1/3 and 2/3 of the distance from C7 to the acromion above the left and right UTM. The algometer was placed perpendicular on the skin with steadily increasing pressure until the patient indicated that the PPT was reached. Measurements were repeated three times in total, always starting with the lateral point on the right, continuing with the left lateral point, and resuming in the same order with the medial points. This protocol ensured that sufficient time had passed between the three measurements on each reference point [48]. The measurement was performed again during 3-months follow-up (FU) evaluation.

2.5. Headache Characteristics

Headache frequency, headache intensity (minimum and maximum), and headache duration regarding the headaches in the last 3 months were documented before treatment and at FU. Patients were classified according to responder rates (≥25%, ≥50%, ≥75%) based on their relative reduction in headache frequency. While headache changes in the total sample have been previously analyzed [41], this manuscript examines differences in headache changes among subgroups: (1) headache diagnosis, (2) neck pain, and (3) treatment time frame.

2.6. Data Management

Paper-based clinical report forms and customized questionnaires were used to document rNMS interventions and FU examinations. Data were anonymized, entered into Microsoft Excel data sheets (Microsoft Office Professional Plus 2016, Microsoft, Redmond, WA, USA), and plausibility of data was checked by at least two independent analysts. The algometer's maximum pressure was 10 kg/cm^2. If no pain was indicated when that pressure was reached, 10 kg/cm^2 was defined as the PPT [49]. Headache frequency was assessed as headache days per month, headache duration as hours, and headache intensities as 10-point visual analogue scale (VAS).

2.7. Statistical Analysis

Microsoft Excel (Microsoft Office Professional Plus 2016, Microsoft, Redmond, WA, USA) and SPSS (version 25/26; IBM SPSS Statistics for Windows, Armonk, NY, USA) were used for statistics. The level of statistical significance was set at $\alpha = 0.05$. Shapiro–Wilk tests checked for normality of the headache variables and PPT measurements. The Pearson correlation between the time from treatment to FU examinations and the PPT at FU examinations above each reference point were calculated. Since no correlations were observed (left lateral: r = −0.057, left medial: r = 0.084, right medial: r = 0.008, right lateral:

r = 0.052), time from treatment to FU examinations was not considered as a covariate for the following analyses.

Differences in the PPT between pre-, post-, and FU assessments in the total sample were assessed with a repeated-measures analysis of variance (ANOVA). The homogeneity of variances at different time points was assessed by Mauchly's test and was given for all analyses. Bonferroni corrections were used for adjustment for multiple comparisons. Effect sizes were calculated using eta squared.

In addition, the following subgroup analyses were performed: (1) primary headache group vs. PTH group, (2) neck pain group vs. no neck pain group, and (3) different treatment time frame groups (<2x/week, 2x/week, >2x/week). Comparisons of the PPT above each reference point between the groups were calculated with two-way repeated measures ANOVA with time as within-factor and group as between-factor. Bonferroni (within) and Tukey (between) corrections were used for adjustment for multiple comparisons. Differences in the relative change of headache characteristics and the PPT from baseline to FU examinations between the headache diagnosis groups as well as the neck pain groups were assessed using two-samples t-tests and Mann–Whitney U tests. Differences in the relative change in headache characteristics and PPT from baseline to FU examinations between the treatment time frame groups were assessed using one-way ANOVA. Pearson correlations between the time since headache onset or trauma and the relative change in headache frequency were calculated for the headache diagnosis, neck pain, and treatment time frame comparisons. Sample sizes for the comparisons are listed in Table 1.

Table 1. Sample sizes for PPT analysis and subgroup analyses.

Group	n (Patients)	n (Interventions)
Total sample	20	25
PPT analysis (total sample)	17	22
Headache diagnosis analysis		
Primary headaches	13	14
PTH	7	11
Neck pain analysis		
With neck pain	13	15
Without neck pain	7	10
Treatment time frame analysis		
<2x/week	8	9
2x/week	7	10
>2x/week	5	6

Abbreviations: PPT pressure pain threshold, PTH post-traumatic headache.

3. Results

3.1. Subjects

A total of 23 patients completed the rNMS intervention, of whom 5 patients received a second block of rNMS on average 104.2 ± 32.8 days (range: 73–167 days) after the first intervention, resulting in 28 rNMS interventions in total. Two patients were lost to FU and one patient was identified as an outlier based on a late FU as the FU time (210 days after intervention) lied more than 3 standard deviations above the mean FU time of the sample (91.7 ± 26.7 days). Therefore, data from 20 patients receiving 25 rNMS interventions were analyzed. Since three patients received FU examination via telephone calls, data from 17 patients receiving 22 rNMS interventions were included in the PPT analysis. Details on the sample sizes for analysis are given in Table 1.

3.2. Patient and Treatment Characteristics

Patients were on average 14.1 ± 2.7 years old, and 12 patients were females (60%). Diagnoses included migraine without aura and TTH (n = 8, 40%), migraine with aura (n = 2, 10%), migraine without aura (n = 2, 10%), migraine with aura and TTH (n = 1, 5%), and PTH (n = 7, 35%). Acute medication was used by patients in 12 cases (48%) and a pharmacoprophylaxis with magnesium in 11 (44%). In the 3 months before the intervention, physiotherapy was obtained in 12 cases (48%), and was continued during the intervention in 5 (20%). During the 3 months after the intervention, in 4 cases (16%) physiotherapy was continued, and in 5 cases (20%) started. Neck pain as a general complaint besides headaches was indicated 15 times (60%) at the beginning of a rNMS treatment block. For the left UTM, mean stimulation intensity was 25.0% ± 11.6 of the maximum stimulator output and for the right UTM 25.8% ± 11.3 of stimulator output. A detailed description of the study population can be found in Staisch et al. (2022) [41].

3.3. Pressure Pain Thresholds

Comparisons of the PPT above each reference point resulted in significant differences for all reference points over time (left lateral: $p < 0.001$, $\eta^2 = 0.318$; left medial: $p < 0.001$, $\eta^2 = 0.351$; right medial: $p < 0.001$, $\eta^2 = 0.363$; right lateral: $p < 0.001$, $\eta^2 = 0.311$). PPT were increasing from pre- to post-treatment assessments and did not significantly change from post-treatment to FU examinations (Table 2, Figure 1). PPT changes above each reference point over time significantly differed between the primary headache group and the PTH group (left lateral: $p = 0.026$, $\eta^2 = 0.225$; left medial: $p = 0.019$, $\eta^2 = 0.247$; right medial: $p = 0.019$, $\eta^2 = 0.244$; right lateral: $p = 0.020$, $\eta^2 = 0.241$; Table 3, Figure 2). When comparing patients with and without neck pain, no significant differences in PPT changes across time were observed between the groups (left lateral: $p = 0.688$; left medial: $p = 0.807$; right medial: $p = 0.765$; right lateral: $p = 0.520$). Regarding the comparison of different treatment time frames, PPT changes over time did not significantly differ between the three groups (left lateral: $p = 0.146$; left medial: $p = 0.262$; right medial: $p = 0.187$; right lateral: $p = 0.282$).

Table 2. Comparison of PPT above each reference point before the first rNMS session (pre), before the last rNMS session (post), and at FU.

PPT	Test Values			Mean (SD)			Post-Hoc Test
	F	*p*	η2	Pre	Post	FU	*p*
Left lateral	9.77	<0.001 *	0.318	2.00 (1.37)	3.28 (2.21)	2.87 (2.11)	
Pre-post							0.001 *
Pre-FU							0.034 *
Post-FU							0.415
Left medial	11.38	<0.001 *	0.351	1.96 (1.27)	3.17 (1.99)	2.95 (2.11)	
Pre-post							0.002 *
Pre-FU							0.007 *
Post-FU							0.988
Right medial	11.98	<0.001 *	0.363	1.83 (1.26)	3.17 (2.06)	2.95 (2.11)	
Pre-post							0.001 *
Pre-FU							0.004 *
Post-FU							0.788
Right lateral	9.49	<0.001 *	0.311	1.94 (1.37)	3.24 (2.25)	2.81 (2.04)	
Pre-post							0.002 *
Pre-FU							0.020 *
Post-FU							0.510

Differences in PPT above each reference point were analyzed using repeated-measures ANOVAs and Bonferroni post-hoc comparisons. Significant differences at $\alpha = 0.05$ are marked with an asterisk (*). Abbreviations: PPT: pressure pain threshold (in kg), pre: before the first rNMS session, post:

before the last rNMS session, FU: follow-up, rNMS: repetitive neuromuscular magnetic stimulation, SD: standard deviation, F: ANOVA test statistic, η2: effect size eta-squared.

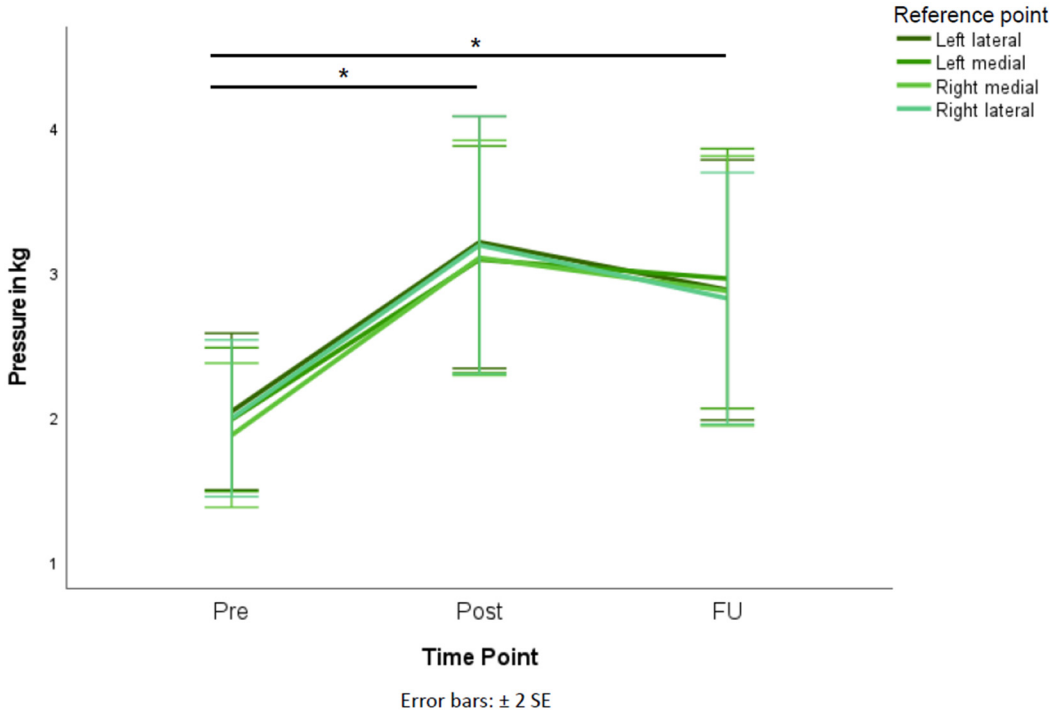


Figure 1. PPT results above each reference point before the first rNMS session (pre), before the last rNMS session (post), and at FU (n = 22 with complete FU). Significant differences are marked with an asterisk (*) and apply to changes at all 4 reference points. Error bars are depicted as ±2 standard errors (SE).

Table 3. Comparison of PPT changes across time between the primary headache group and PTH group.

PPT	Test Values			Mean (SE)		
	F	*p*	η^2	Pre	Post	FU
Left lateral						
Headache diagnosis	5.82	0.026 *	0.225			
Time	10.50	<0.001 *	0.344			
Time * headache diagnosis	2.57	0.089	0.114			
Primary headache				1.49 (0.39)	2.13 (0.58)	2.07 (0.60)
PTH				2.50 (0.39)	4.43 (0.58)	3.68 (0.60)
Left medial						
Headache diagnosis	6.56	0.019 *	0.247			
Time	11.62	<0.001 *	0.368			
Time * headache diagnosis	1.45	0.247	0.068			
Primary headache				1.38 (0.35)	2.13 (0.52)	2.13 (0.60)
PTH				2.54 (0.35)	4.20 (0.52)	3.78 (0.60)
Right medial						
Headache diagnosis	6.47	0.019 *	0.244			
Time	12.66	<0.001 *	0.388			
Time * headache diagnosis	2.19	0.125	0.099			

Primary headache				1.33 (0.36)	2.11 (0.54)	1.93 (0.61)
PTH				2.34 (0.36)	4.22 (0.54)	3.80 (0.61)
Right lateral						
Headache diagnosis	6.34	0.020 *	0.241			
Time	9.94	<0.001 *	0.332			
Time * headache diagnosis	2.00	0.148	0.091			
Primary headache				1.41 (0.39)	2.12 (0.60)	1.97 (0.57)
PTH				2.46 (0.39)	4.37 (0.60)	3.66 (0.57)

Differences in PPT changes above each reference point between groups were analyzed using two-way repeated measures ANOVAs with time as within-factor (pre, post, FU) and group as between-factor (primary headache, PTH). Multiple comparison correction was done using the Bonferroni (within) and Tukey (between) procedures. Significant differences at $\alpha = 0.05$ are marked with an asterisk (*). Abbreviations: PPT: pressure pain threshold (in kg), PTH: post-traumatic headache, pre: before the first rNMS session, post: before the last rNMS session, FU: follow-up, SD: standard deviation, F: ANOVA test statistic, η2: effect size eta-squared.

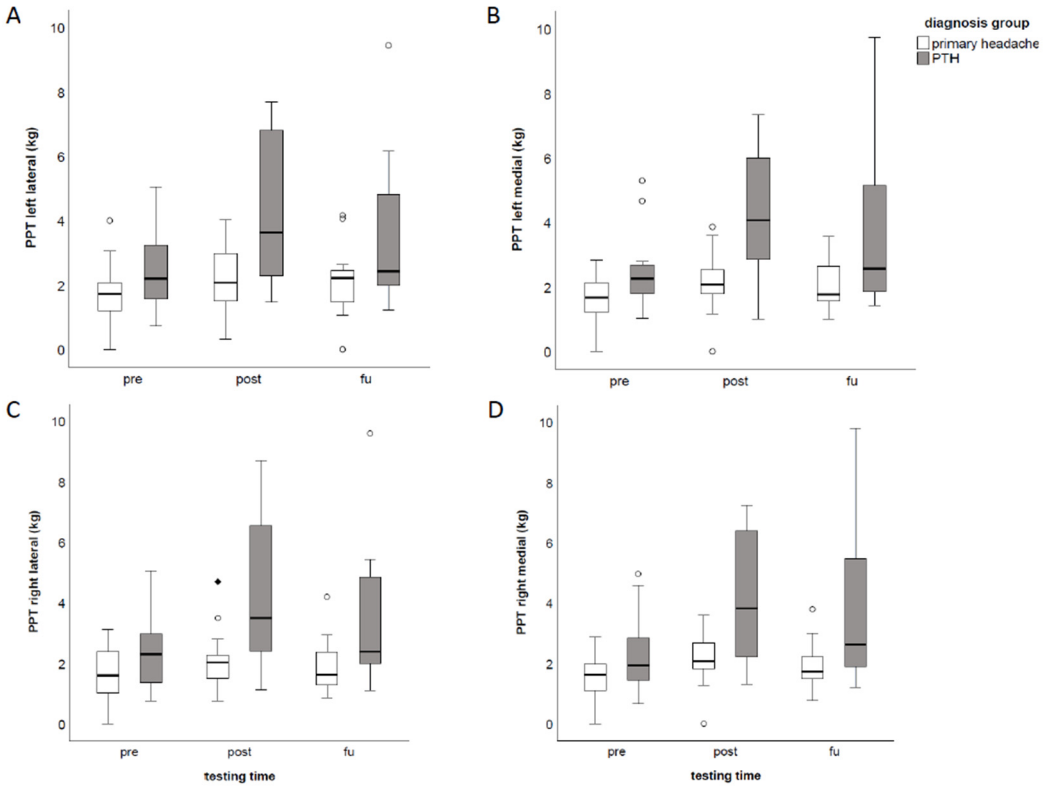


Figure 2. Comparison of PPT changes across time between the primary headache group (white) and PTH group (grey). (**A**) Comparison of PPT above left lateral reference point, (**B**) Comparison of PPT above left medial reference point, (**C**) Comparison of PPT above right lateral reference point, (**D**) Comparison of PPT above right medial reference point. Abbreviations: PPT: pressure pain threshold, PTH: post-traumatic headache, pre: before the first rNMS session, post: before the last rNMS session, FU: follow-up.

3.4. Headache Characteristics

When comparing patients with and without neck pain at baseline, the change in headache frequency was significantly higher in the neck pain group (t = 2.29, $p = 0.032$, confidence interval 0.04–0.89; Figure 3). Changes in headache intensity (minimum: $p = 0.434$; maximum: $p = 0.434$) and duration ($p = 0.511$) did not significantly differ between these groups. No significant differences were observed for the changes in headache characteristics in the headache diagnosis (headache frequency: $p = 0.191$; minimum

headache intensity: $p = 0.679$; maximum headache intensity: $p = 0.770$; headache duration: $p = 0.923$) and treatment time frame comparisons (headache frequency: $p = 0.462$; minimum headache intensity: $p = 0.600$; maximum headache intensity: $p = 0.059$; headache duration: $p = 0.318$).

Regarding the responder rate classification (≥25%, ≥50%, ≥75%), 43% of patients with primary headaches were responders (≥25%) with 14% being classified as 75% responders (Table 4). In the PTH group, 46% of patients were responders and all were categorized as 75% responders. Furthermore, 60% of patients with neck pain responded to rNMS (≥25%), while 20% of patients without neck pain were responders (≥25%, $p = 0.048$). In addition, 60% of patients receiving rNMS twice a week were responders (≥25%), while 33% of patients receiving rNMS less or more than twice a week responded to treatment (≥25%), respectively.

No statistically significant correlation for time since headache onset / time since trauma and the relative mean change in headache frequency was found in the primary headache group ($r = -0.05$, $p = 0.857$), nor in headache frequency in the PTH group ($r = 0.23$; $p = 0.492$; Table 5).

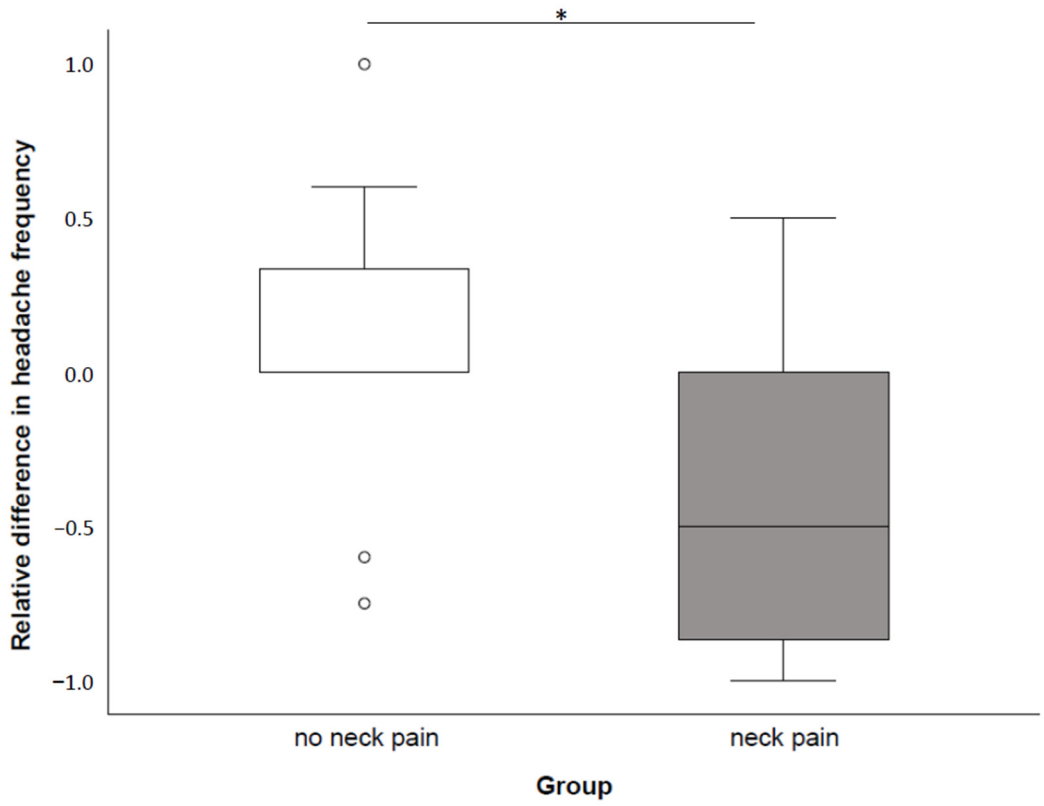


Figure 3. Relative difference in headache frequency (days/month) from baseline to follow up after rNMS intervention in patients with and without neck pain. Significant differences at $\alpha = 0.05$ are marked with an asterisk (*).

Table 4. Classification in responder rates based on the relative headache frequency reduction from pre-assessment to FU for the headache diagnosis, neck pain, and treatment time frame group comparisons.

Responder Rate	Headache Diagnosis Comparison n (%)		Neck Pain Comparison n (%)		Treatment Time Frame Comparison n (%)		
	Primary Headache	PTH	Neck Pain	No Neck Pain	<2x/week	2x/week	>2x/week
75% responder	2 (14.3)	5 (45.6)	6 (40)	1 (10)	2 (22.2)	4 (40)	1 (16.7)
50% responder	5 (35.7)	5 (45.6)	8 (53.3)	2 (20)	2 (22.2)	6 (60)	2 (33.3)

25% responder	6 (42.9)	5 (45.6)	9 (60) *	2 (20) *	3 (33.3)	6 (60)	2 (33.3)
No responder	8 (57)	6 (54.6)	6 (40) *	8 (80) *	6 (66.7)	4 (40)	4 (66.7)

Differences in responder rates between groups were assessed using Chi-square tests. Significant differences at $\alpha = 0.05$ are marked with an asterisk (*).

Table 5. Pearson's correlations between the time since headache onset or trauma and the relative mean change in headache frequency per headache diagnosis, neck pain, and rNMS time frame groups.

Group	Correlation r	*p*
Headache diagnosis groups		
Primary headache [a]	−0.05	0.857
PTH [b]	0.23	0.492
Neck pain groups		
Neck pain [a]	−0.04	0.881
No neck pain [a]	0.34	0.334
Treatment time frame groups		
<2x/week [a]	0.53	0.139
2x/week [a]	−0.03	0.943
>2x/week [a]	0.03	0.955

[a] Correlation using time since headache onset, [b] correlation using time since trauma.

4. Discussion

This retrospective analysis evaluated the muscular effects of rNMS targeting the UTM in children and adolescents with headache disorders. As an additional goal, we investigated whether the type of headache disorder, the presence of neck pain, and the time frame of rNMS affected the change of muscular and headache symptoms.

With regard to muscular effects, muscular hypersensitivity decreased from pre- to post-treatment assessment and was sustained until FU examinations on a lower level than at baseline. No significant differences in PPT changes were found between neck pain and treatment time frame groups, respectively. Thus, the response of the PPT seems not to depend on the presence of neck pain, nor on the time frame rNMS is applicated in. When compared to healthy controls, migraine patients demonstrated a pronounced pressure pain sensitivity translating to a lower PPT in the neck and shoulder region in previous studies [50–52]. Our analysis suggests a higher level of muscular hypersensitivity in pediatric headache patients before the rNMS intervention with a similar or even lower PPT compared to adults with migraine [51]. After rNMS intervention, PPT were comparable to or even higher than the PPT of healthy adults [51]. This finding may underline that with the application of rNMS to UTM, muscular hypersensitivity in headache patients can reach a "healthy" level. As decreased PPT are interpreted as a sign of sensitization of the trigemino-cervical nucleus caudalis [53], rNMS is likely to exert a desensitization effect on the TCC. Our findings regarding PPT are in accordance with previous studies that explored the muscular effects of rNMS in young adults with frequent episodic migraine receiving six rNMS sessions (stimulation protocol: 15 min/side, 20-Hz frequency, 15 s ON time, and 30 s OFF time) [48,54,55]. While a significant increase in the pre- and post-treatment algometry-based PPT was reported over the course of the intervention in the pilot study [55], an increase in PPT was bilaterally observed but only reached statistical significance in the left UTM in a later study [48]. However, PPT were only measured locally, directly above an active mTrP, and no reference points were explored in these previous studies [48,55].

Moreover, the current study investigated the possible impact of headache diagnosis, presence of neck pain, or the treatment time frame on the clinical efficacy of rNMS. No significant differences regarding changes in headache symptoms or responder rates were observed between patients with primary headaches and PTH, thus indicating a similar

response to rNMS irrespective of the distinct headache diagnosis. However, it should be noted that all PTH patients showed at least 75% reduction in headache frequency, which is an important clinical finding on the individual patient's level. Patients with neck pain as a general complaint in addition to their headaches demonstrated a greater reduction in headache frequency than patients without neck pain, with significantly higher responder rates. Following the concept of the TCC, rNMS is expected to have a greater impact on headache characteristics, like headache frequency, in patients with neck pain [31,44]. No significant differences regarding changes in headache symptoms were present between groups of different treatment time frames. However, the highest responder rates were documented in patients receiving rNMS twice per week (60% responders), which is why a treatment protocol with two sessions per week might be preferred.

Neurostimulation by rNMS represents a novel approach to acute and preventive treatment in primary headache disorders. Transcutaneous supraorbital nerve stimulation (tSNS) [56–58], transcutaneous occipital nerve stimulation (tONS) [59,60], and transcutaneous vagus nerve stimulation (tVNS) [61,62] have previously been investigated within this context [40]. Regarding PTH, no adequate treatments have yet been established, which is why treatment of PTH is commonly based on research in primary headache disorders [38,63].

In comparison to the above-mentioned techniques that stimulate cranial nerves directly, rNMS is not only safe but also well accepted among patients, which is an important factor especially in the pediatric field [40,41]. The key benefit of rNMS is the muscular approach via the UTM, which is clinically involved in the pathophysiology of headache disorders via the TCC [15,16]. Therefore, the choice of the UTM as a stimulation target can be easily explained to the patients (especially in cases of reported neck pain or muscular symptoms together with headache symptoms), who themselves directly experience the stimulation at the local level and control the treatment by being able to adjust stimulation intensity. Hence, rNMS represents a personalized neurostimulation approach from the bottom-up by simultaneously modulating muscular and central pain processing (network reorganization) [40]. However, studies evaluating the efficacy of rNMS differ in methodology so far, making the use of guidelines for quality improvement of rNMS methods, and thus better comparability of studies, inevitable in the future [64].

Some limitations apply to the current study. First, it reports data collected during everyday routines within our clinical setting. Patients could have received other therapies like physiotherapy or psychological interventions in parallel to the rNMS intervention within the multimodal treatment regimen. As the setting/placebo effects might be increased in the pediatric field and for medical device treatments, this may have influenced the effects as well [65,66]. Thus, future studies with a prospective and controlled design investigating larger patient samples are needed. Second, the period of analyzed rNMS interventions was during the COVID-19 pandemic. Therefore, the life of children and adolescents changed drastically as, among other things, schools were closed from time to time, digital learning time during home schooling strongly increased, and contact with peers and friends were not possible. The possible impact of COVID-19-related lifestyle changes on headaches in our sample cannot be estimated, as lifestyle factors are known to influence headache symptoms [67]. Specifically, for an Italian cohort it has been reported that school closure was related to a reduction in headache frequency and intensity in school children with headaches [68]. Such effects should be taken into consideration by future studies in a controlled setting.

5. Conclusions

Reduced muscular hyperalgesia after rNMS was demonstrated in pediatric patients with headache disorders, which was sustained up to weeks to months. This effect was particularly emphasized in patients with PTH. In addition, rNMS seems to positively modulate headache symptoms regardless of the specific headache diagnosis. Patients with neck pain profit explicitly well from the intervention. Regarding treatment time frame,

two rNMS sessions per week led to the highest reduction in headache frequency. Given the framework of the trigemino-cervical complex, rNMS targeting the UTM most likely acts via neuromodulation of nociceptive processing at the central level.

Author Contributions: Conceptualization, F.H., M.N.L., M.V.B., C.B. and J.S.; methodology and data collection, C.B., J.S., M.L., A.H., M.F.L., B.K. and M.V.B.; formal analysis and data interpretation, C.B., J.S., M.V.B., F.H., M.N.L., I.H., K.H. and A.H.; data curation, C.B., J.S., A.H. and M.V.B.; writing—original draft preparation, C.B., J.S. and M.V.B.; writing—review & editing, C.B., J.S., M.L., A.H., I.H., K.H., B.K., M.F.L., N.S., F.H., M.N.L. and M.V.B.; visualization, C.B., J.S. and A.H.; supervision, M.V.B. and F.H.; project administration, C.B. and M.V.B.; funding Acquisition, M.V.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. MVB's research concerning neuromodulation in migraine is supported by a scholarship from the Bavarian Gender Equality Grant of the Free State of Bavaria, Germany. MVB's research concerning pediatric mTBI is supported by the ZNS-Hannelore Kohl Stiftung, Germany. MVB's and NS's research on rNMS in adult migraine are supported by a research grant from the Deutsche Migräne- und Kopfschmerzgesellschaft (DMKG).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the medical faculty of the University of Munich (LMU; vote 21-0574, 29 June 2021).

Informed Consent Statement: Informed consent was obtained from all subjects and their caregivers prior to rNMS intervention.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to the sensitive character of pediatric clinical data.

Conflicts of Interest: The LMU Center for Children with Medical Complexity is provided by an emFieldPro magnetic stimulator by Zimmer MedizinSysteme GmbH (Neu-Ulm, Germany). N.S. received honoraria from Nexstim Plc (Helsinki, Finland). M.N.L. and F.H. received a grant "Innovationsfonds" of the joint federal committee of health insurance companies (GBA) for a nation-wide study on an early multimodal intervention program for children with migraine. No further conflicts of interest are reported.

References

1. Albers, L.; von Kries, R.; Heinen, F.; Straube, A. Headache in school children: Is the prevalence increasing?. *Curr. Pain Headache Rep.* **2015**, *19*, 4. https://doi.org/10.1007/s11916-015-0477-0.
2. Vos, T.; Lim, S.S.; Abbafati, C.; Abbas, K.M.; Abbasi, M.; Abbasifard, M.; Abbasi-Kangevari, M.; Abbastabar, H.; Abd-Allah, F.; Abdelalim, A.; et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **2020**, *396*, 1204–1222. https://doi.org/10.1016/s0140-6736(20)30925-9.
3. Youssef, P.E.; Mack, K.J. Episodic and chronic migraine in children. *Dev. Med. Child Neurol.* **2020**, *62*, 34–41. https://doi.org/10.1111/dmcn.14338.
4. Abu-Arafeh, I.; Razak, S.; Sivaraman, B.; Graham, C. Prevalence of headache and migraine in children and adolescents: A systematic review of population-based studies. *Dev. Med. Child Neurol.* **2010**, *52*, 1088–1097. https://doi.org/10.1111/j.1469-8749.2010.03793.x.
5. Stovner, L.; Hagen, K.; Jensen, R.; Katsarava, Z.; Lipton, R.; Scher, A.; Steiner, T.; Zwart, J.A. The global burden of headache: A documentation of headache prevalence and disability worldwide. *Cephalalgia* **2007**, *27*, 193–210. https://doi.org/10.1111/j.1468-2982.2007.01288.x.
6. Bonfert, M.; Straube, A.; Schroeder, A.S.; Reilich, P.; Ebinger, F.; Heinen, F. Primary headache in children and adolescents: Update on pharmacotherapy of migraine and tension-type headache. *Neuropediatrics* **2013**, *44*, 3–19. https://doi.org/10.1055/s-0032-1330856.
7. Rho, Y.I.; Chung, H.J.; Lee, K.H.; Eun, B.L.; Eun, S.H.; Nam, S.O.; Kim, W.S.; Kim, Y.O.; Park, H.J.; Kim, H.S. Prevalence and clinical characteristics of primary headaches among school children in South Korea: A nationwide survey. *Headache* **2012**, *52*, 592–599. https://doi.org/10.1111/j.1526-4610.2011.02001.x.
8. Jensen, R.H. Tension-Type Headache—The Normal and Most Prevalent Headache. *Headache* **2018**, *58*, 339–345. https://doi.org/10.1111/head.13067.
9. Seshia, S.S. Mixed migraine and tension-type: A common cause of recurrent headache in children. *Can. J. Neurol. Sci.* **2004**, *31*, 315–318. https://doi.org/10.1017/s0317167100003371.

10. Kuczynski, A.; Crawford, S.; Bodell, L.; Dewey, D.; Barlow, K.M. Characteristics of post-traumatic headaches in children following mild traumatic brain injury and their response to treatment: A prospective cohort. *Dev. Med. Child Neurol.* **2013**, *55*, 636–641. https://doi.org/10.1111/dmcn.12152.
11. McEvoy, H.; Borsook, D.; Holmes, S.A. Clinical features and sex differences in pediatric post-traumatic headache: A retrospective chart review at a Boston area concussion clinic. *Cephalalgia* **2020**, *40*, 701–711. https://doi.org/10.1177/0333102419896754.
12. Howard, L.; Schwedt, T.J. Posttraumatic headache: Recent progress. *Curr. Opin. Neurol.* **2020**, *33*, 316–322. https://doi.org/10.1097/WCO.0000000000000815.
13. Eisenberg, M.A.; Meehan, W.P., 3rd.; Mannix, R. Duration and course of post-concussive symptoms. *Pediatrics* **2014**, *133*, 999–1006. https://doi.org/10.1542/peds.2014-0158.
14. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria For Research; World Health Organization: Geneve, Switzerland, 1993.
15. Bartsch, T.; Goadsby, P.J. The trigeminocervical complex and migraine: Current concepts and synthesis. *Curr. Pain Headache Rep.* **2003**, *7*, 371–376. https://doi.org/10.1007/s11916-003-0036-y.
16. Ashina, M.; Hansen, J.M.; Do, T.P.; Melo-Carrillo, A.; Burstein, R.; Moskowitz, M.A. Migraine and the trigeminovascular system-40 years and counting. *Lancet Neurol.* **2019**, *18*, 795–804. https://doi.org/10.1016/S1474-4422(19)30185-1.
17. Bartsch, T.; Goadsby, P.J. Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. *Brain* **2002**, *125 Pt 7*, 1496–1509. https://doi.org/10.1093/brain/awf166.
18. Busch, V.; Frese, A.; Bartsch, T. The trigemino-cervical complex. Integration of peripheral and central pain mechanisms in primary headache syndromes. *Schmerz* **2004**, *18*, 404–410. https://doi.org/10.1007/s00482-004-0347-x.
19. Fernandez-De-Las-Penas, C.; Arendt-Nielsen, L. Improving understanding of trigger points and widespread pressure pain sensitivity in tension-type headache patients: Clinical implications. *Expert Rev. Neurother.* **2017**, *17*, 933–939. https://doi.org/10.1080/14737175.2017.1359088.
20. Bartsch, T. Migraine and the neck: New insights from basic data. *Curr. Pain Headache Rep.* **2005**, *9*, 191–196. https://doi.org/10.1007/s11916-005-0061-0.
21. Blaschek, A.; Decke, S.; Albers, L.; Schroeder, A.S.; Lehmann, S.; Straube, A.; Landgraf, M.N.; Heinen, F.; von Kries, R. Self-reported neck pain is associated with migraine but not with tension-type headache in adolescents. *Cephalalgia* **2014**, *34*, 895–903. https://doi.org/10.1177/0333102414523338.
22. Landgraf, M.N.; Ertl-Wagner, B.; Koerte, I.K.; Thienel, J.; Langhagen, T.; Straube, A.; von Kries, R.; Reilich, P.; Pomschar, A.; Heinen, F. Alterations in the trapezius muscle in young patients with migraine—A pilot case series with MRI. *Eur. J. Paediatr. Neurol.* **2015**, *19*, 372–376. https://doi.org/10.1016/j.ejpn.2014.12.021.
23. Landgraf, M.N.; von Kries, R.; Heinen, F.; Langhagen, T.; Straube, A.; Albers, L. Self-reported neck and shoulder pain in adolescents is associated with episodic and chronic migraine. *Cephalalgia* **2016**, *36*, 807–811. https://doi.org/10.1177/0333102415610875.
24. Blaschek, A.; Milde-Busch, A.; Straube, A.; Schankin, C.; Langhagen, T.; Jahn, K.; Schroder, S.A.; Reiter, K.; von Kries, R.; Heinen, F. Self-reported muscle pain in adolescents with migraine and tension-type headache. *Cephalalgia* **2012**, *32*, 241–249. https://doi.org/10.1177/0333102411434808.
25. Landgraf, M.N.; Biebl, J.T.; Langhagen, T.; Hannibal, I.; Eggert, T.; Vill, K.; Gerstl, L.; Albers, L.; von Kries, R.; Straube, A.; et al. Children with migraine: Provocation of headache via pressure to myofascial trigger points in the trapezius muscle?—A prospective controlled observational study. *Eur. J. Pain* **2018**, *22*, 385–392. https://doi.org/10.1002/ejp.1127.
26. Simons, D.G.; Travell, J.G.; Simons, L.S. *Travell & Simons' Myofascial Pain and Dysfunction: Upper Half of body*; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 1999.
27. Giamberardino, M.A.; Tafuri, E.; Savini, A.; Fabrizio, A.; Affaitati, G.; Lerza, R.; Di Ianni, L.; Lapenna, D.; Mezzetti, A. Contribution of myofascial trigger points to migraine symptoms. *J. Pain* **2007**, *8*, 869–878. https://doi.org/10.1016/j.jpain.2007.06.002.
28. Zhuang, X.; Tan, S.; Huang, Q. Understanding of myofascial trigger points. *Chin. Med. J.* **2014**, *127*, 4271–4277.
29. Ferracini, G.N.; Florencio, L.L.; Dach, F.; Grossi, D.B.; Palacios-Ceña, M.; Ordás-Bandera, C.; Chaves, T.C.; Speciali, J.G.; Fernández-de-Las-Peñas, C. Musculoskeletal disorders of the upper cervical spine in women with episodic or chronic migraine. *Eur. J. Phys. Rehabil. Med.* **2017**, *53*, 342–350. https://doi.org/10.23736/s1973-9087.17.04393-3.
30. Fernández-de-Las-Peñas, C. Myofascial Head Pain. *Curr. Pain Headache Rep.* **2015**, *19*, 28. https://doi.org/10.1007/s11916-015-0503-2.
31. Fernandez-de-las-Penas, C.; Madeleine, P.; Caminero, A.B.; Cuadrado, M.L.; Arendt-Nielsen, L.; Pareja, J.A. Generalized neck-shoulder hyperalgesia in chronic tension-type headache and unilateral migraine assessed by pressure pain sensitivity topographical maps of the trapezius muscle. *Cephalalgia* **2010**, *30*, 77–86. https://doi.org/10.1111/j.1468-2982.2009.01901.x.
32. Fernandez-de-las-Penas, C.; Cuadrado, M.L.; Arendt-Nielsen, L.; Simons, D.G.; Pareja, J.A. Myofascial trigger points and sensitization: An updated pain model for tension-type headache. *Cephalalgia* **2007**, *27*, 383–393. https://doi.org/10.1111/j.1468-2982.2007.01295.x.
33. Luedtke, K.; Starke, W.; May, A. Musculoskeletal dysfunction in migraine patients. *Cephalalgia* **2018**, *38*, 865–875. https://doi.org/10.1177/0333102417716934.

34. Fernandez-de-las-Penas, C.; Alonso-Blanco, C.; Cuadrado, M.L.; Gerwin, R.D.; Pareja, J.A. Trigger points in the suboccipital muscles and forward head posture in tension-type headache. *Headache* **2006**, *46*, 454–460. https://doi.org/10.1111/j.1526-4610.2006.00288.x.
35. Goadsby, P.J.; Holland, P.R.; Martins-Oliveira, M.; Hoffmann, J.; Schankin, C.; Akerman, S. Pathophysiology of Migraine: A Disorder of Sensory Processing. *Physiol. Rev.* **2017**, *97*, 553–622. https://doi.org/10.1152/physrev.00034.2015.
36. Buitenhuis, J.; de Jong, P.J.; Jaspers, J.P.; Groothoff, J.W. Work disability after whiplash: A prospective cohort study. *Spine (Phila Pa 1976)* **2009**, *34*, 262–267. https://doi.org/10.1097/BRS.0b013e3181913d07.
37. Pearce, J.M. Headaches in the whiplash syndrome. *Spinal Cord* **2001**, *39*, 228–233. https://doi.org/10.1038/sj.sc.3101128.
38. Ashina, H.; Porreca, F.; Anderson, T.; Amin, F.M.; Ashina, M.; Schytz, H.W.; Dodick, D.W. Post-traumatic headache: Epidemiology and pathophysiological insights. *Nat. Rev. Neurol.* **2019**, *15*, 607–617. https://doi.org/10.1038/s41582-019-0243-8.
39. Bonfert, M.V.; Borner, C.; Gerstl, L.; Hannibal, I.; Mathonia, N.; Huss, K.; Rahmsdorf, B.; Kainz, C.; Klose, B.; Koenig, H.; et al. Migraine in childhood and adolescence-neurostimulation as a future innovative approach in terms of a multimodal treatment regimen. *Bundesgesundheitsblatt-Gesundh. Gesundh.* **2020**, *63*, 872–880. https://doi.org/10.1007/s00103-020-03169-w.
40. Borner, C.; Urban, G.; Beaulieu, L.D.; Sollmann, N.; Krieg, S.M.; Straube, A.; Renner, T.; Schandelmaier, P.; Lang, M.; Lechner, M.; et al. The bottom-up approach: Non-invasive peripheral neurostimulation methods to treat migraine: A scoping review from the child neurologist's perspective. *Eur. J. Paediatr. Neurol.* **2021**, *32*, 16–28. https://doi.org/10.1016/j.ejpn.2021.02.008.
41. Staisch, J.; Börner, C.; Lang, M.; Hauser, A.; Hannibal, I.; Huß, K.; Klose, B.; Lechner, M.F.; Sollmann, N.; Heinen, F.; et al. Repetitive neuromuscular magnetic stimulation in children with headache. *Eur. J. Paediatr. Neurol.* **2022**, *39*, 40–48. https://doi.org/10.1016/j.ejpn.2022.04.010.
42. Smania, N.; Corato, E.; Fiaschi, A.; Pietropoli, P.; Aglioti, S.M.; Tinazzi, M. Repetitive magnetic stimulation: A novel therapeutic approach for myofascial pain syndrome. *J. Neurol.* **2005**, *252*, 307–314. https://doi.org/10.1007/s00415-005-0642-1.
43. Pujol, J.; Pascual-Leone, A.; Dolz, C.; Delgado, E.; Dolz, J.L.; Aldomà, J. The effect of repetitive magnetic stimulation on localized musculoskeletal pain. *Neuroreport* **1998**, *9*, 1745–1748. https://doi.org/10.1097/00001756-199806010-00014.
44. Bartsch, T.; Goadsby, P.J. Central mechanisms of peripheral nerve stimulation in headache disorders. *Prog. Neurol. Surg.* **2011**, *24*, 16–26. https://doi.org/10.1159/000323008.
45. Charles, A. The pathophysiology of migraine: Implications for clinical management. *Lancet Neurol.* **2018**, *17*, 174–182. https://doi.org/10.1016/s1474-4422(17)30435-0.
46. ICHD-3 German-Translation-2018. 2018. Available online: https://ichd-3.org/ (accessed on 13 July 2022).
47. Elsevier. *Buck's 2020 ICD-10-CM Hospital Edition E-Book*; Elsevier Health Sciences: Amsterdam, The Netherlands, 2019.
48. Renner, T.; Sollmann, N.; Trepte-Freisleder, F.; Albers, L.; Mathonia, N.M.; Bonfert, M.V.; Konig, H.; Klose, B.; Krieg, S.M.; Heinen, F.; et al. Repetitive Peripheral Magnetic Stimulation (rPMS) in Subjects With Migraine-Setup Presentation and Effects on Skeletal Musculature. *Front. Neurol.* **2019**, *10*, 738. https://doi.org/10.3389/fneur.2019.00738.
49. Lacourt, T., H.J., van Doomen, L. Experimental pressure-pain Assessments: Test-retest reliability, convergence and dimensionality. *Scand. J. Pain* **2012**, *3*, 31–37. https://doi.org/10.1016/j.sjpain.2011.11.010.
50. Barón, J.; Ruiz, M.; Palacios-Ceña, M.; Madeleine, P.; Guerrero, Á., L.; Arendt-Nielsen, L.; Fernández-de-Las-Peñas, C. Differences in Topographical Pressure Pain Sensitivity Maps of the Scalp Between Patients With Migraine and Healthy Controls. *Headache* **2017**, *57*, 226–235. https://doi.org/10.1111/head.12984.
51. Florencio, L.L.; Giantomassi, M.C.; Carvalho, G.F.; Gonçalves, M.C.; Dach, F.; Fernández-de-Las-Peñas, C.; Bevilaqua-Grossi, D. Generalized Pressure Pain Hypersensitivity in the Cervical Muscles in Women with Migraine. *Pain Med.* **2015**, *16*, 1629–1634. https://doi.org/10.1111/pme.12767.
52. Palacios-Cena, M.; Florencio, L.L.; Ferracini, G.N.; Baron, J.; Guerrero, A.L.; Ordas-Bandera, C.; Arendt-Nielsen, L.; Fernandez-de-Las-Penas, C. Women with Chronic and Episodic Migraine Exhibit Similar Widespread Pressure Pain Sensitivity. *Pain Med.* **2016**, *17*, 2127–2133. https://doi.org/10.1093/pm/pnw056.
53. Castien, R.F.; van der Wouden, J.C.; De Hertogh, W. Pressure pain thresholds over the cranio-cervical region in headache: A systematic review and meta-analysis. *J. Headache Pain* **2018**, *19*, 9. https://doi.org/10.1186/s10194-018-0833-7.
54. Renner, T.; Sollmann, N.; Heinen, F.; Albers, L.; Trepte-Freisleder, F.; Klose, B.; Konig, H.; Krieg, S.M.; Bonfert, M.V.; Landgraf, M.N. Alleviation of migraine symptoms by application of repetitive peripheral magnetic stimulation to myofascial trigger points of neck and shoulder muscles—A randomized trial. *Sci. Rep.* **2020**, *10*, 5954. https://doi.org/10.1038/s41598-020-62701-9.
55. Sollmann, N.; Trepte-Freisleder, F.; Albers, L.; Jung, N.H.; Mall, V.; Meyer, B.; Heinen, F.; Krieg, S.M.; Landgraf, M.N. Magnetic stimulation of the upper trapezius muscles in patients with migraine—A pilot study. *Eur. J. Paediatr. Neurol.* **2016**, *20*, 888–897. https://doi.org/10.1016/j.ejpn.2016.07.022.
56. Magis, D.; Sava, S.; d'Elia, T.S.; Baschi, R.; Schoenen, J. Safety and patients' satisfaction of transcutaneous Supraorbital NeuroStimulation (tSNS) with the Cefaly device in headache treatment: A survey of 2,313 headache sufferers in the general population. *J. Headache Pain* **2013**, *14*, 95.
57. Schoenen, J.; Vandersmissen, B.; Jeangette, S.; Herroelen, L.; Vandenheede, M.; Gérard, P.; Magis, D. Migraine prevention with a supraorbital transcutaneous stimulator: A randomized controlled trial. *Neurology* **2013**, *80*, 697–704. https://doi.org/10.1212/WNL.0b013e3182825055.

58. Hamed, N.S. Supraorbital electrical stimulation in management of chronic type tension headache: A randomized controlled study. *Physiother. Theory Pr.* **2018**, *34*, 101–110. https://doi.org/10.1080/09593985.2017.1370751.
59. Liu, Y.; Dong, Z.; Wang, R.; Ao, R.; Han, X.; Tang, W.; Yu, S. Migraine Prevention Using Different Frequencies of Transcutaneous Occipital Nerve Stimulation: A Randomized Controlled Trial. *J. Pain* **2017**, *18*, 1006–1015. https://doi.org/10.1016/j.jpain.2017.03.012.
60. Bono, F.; Salvino, D.; Mazza, M.R.; Curcio, M.; Trimboli, M.; Vescio, B.; Quattrone, A. The influence of ictal cutaneous allodynia on the response to occipital transcutaneous electrical stimulation in chronic migraine and chronic tension-type headache: A randomized, sham-controlled study. *Cephalalgia* **2015**, *35*, 389–398. https://doi.org/10.1177/0333102414544909.
61. Goadsby, P.J.; Grosberg, B.M.; Mauskop, A.; Cady, R.; Simmons, K.A. Effect of noninvasive vagus nerve stimulation on acute migraine: An open-label pilot study. *Cephalalgia* **2014**, *34*, 986–993. https://doi.org/10.1177/0333102414524494.
62. Grazzi, L.; Egeo, G.; Calhoun, A.H.; McClure, C.K.; Liebler, E.; Barbanti, P. Non-invasive Vagus Nerve Stimulation (nVNS) as mini-prophylaxis for menstrual/menstrually related migraine: An open-label study. *J. Headache Pain* **2016**, *17*, 91. https://doi.org/10.1186/s10194-016-0684-z.
63. Lucas, S. Posttraumatic Headache: Clinical Characterization and Management. *Curr. Pain Headache Rep.* **2015**, *19*, 48. https://doi.org/10.1007/s11916-015-0520-1.
64. Schneider, C.; Zangrandi, A.; Sollmann, N.; Bonfert, M.V.; Beaulieu, L.D. Checklist on the Quality of the Repetitive Peripheral Magnetic Stimulation (rPMS) Methods in Research: An International Delphi Study. *Front. Neurol.* **2022**, *13*, 852848. https://doi.org/10.3389/fneur.2022.852848.
65. Oskoui, M.; Pringsheim, T.; Holler-Managan, Y.; Potrebic, S.; Billinghurst, L.; Gloss, D.; Hershey, A.D.; Licking, N.; Sowell, M.; Victorio, M.C.; et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* **2019**, *93*, 487–499. https://doi.org/10.1212/WNL.0000000000008095.
66. Kaptchuk, T.J.; Goldman, P.; Stone, D.A.; Stason, W.B. Do medical devices have enhanced placebo effects?. *J. Clin. Epidemiol.* **2000**, *53*, 786–792. https://doi.org/10.1016/s0895-4356(00)00206-7.
67. Raucci, U.; Boni, A.; Evangelisti, M.; Della Vecchia, N.; Velardi, M.; Ursitti, F.; Terrin, G.; Di Nardo, G.; Reale, A.; Villani, A.; et al. Lifestyle Modifications to Help Prevent Headache at a Developmental Age. *Front. Neurol.* **2020**, *11*, 618375. https://doi.org/10.3389/fneur.2020.618375.
68. Papetti, L.; Loro, P.A.D.; Tarantino, S.; Grazzi, L.; Guidetti, V.; Parisi, P.; Raieli, V.; Sciruicchio, V.; Termine, C.; Toldo, I.; et al. I stay at home with headache. A survey to investigate how the lockdown for COVID-19 impacted on headache in Italian children. *Cephalalgia* **2020**, *40*, 1459–1473. https://doi.org/10.1177/0333102420965139.

frontiers | Frontiers in Neurology

ORIGINAL RESEARCH
published: 28 July 2022
doi: 10.3389/fneur.2022.919623

Response Predictors of Repetitive Neuromuscular Magnetic Stimulation in the Preventive Treatment of Episodic Migraine

Corinna Börner[1,2,3†], Tabea Renner[1†], Florian Trepte-Freisleder[1], Giada Urban[1], Paul Schandelmaier[1], Magdalena Lang[1], Matthias F. Lechner[1], Helene Koenig[1], Birgit Klose[1], Lucia Albers[1,4], Sandro M. Krieg[3,4], Thomas Baum[2], Florian Heinen[1], Mirjam N. Landgraf[1], Nico Sollmann[2,3,5] and Michaela V. Bonfert[1]*

[1] Division of Pediatric Neurology and Developmental Medicine and LMU Center for Children With Medical Complexity, Dr. von Hauner Children's Hospital, LMU Hospital, Ludwig-Maximilians-Universität, Munich, Germany, [2] Department of Diagnostic and Interventional Neuroradiology, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany, [3] TUM-Neuroimaging Center, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany, [4] Department of Neurosurgery, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany, [5] Department of Diagnostic and Interventional Radiology, University Hospital Ulm, Ulm, Germany

OPEN ACCESS

Edited by:
Massimiliano Valeriani, Bambino Gesù Children's Hospital (IRCCS), Italy

Reviewed by:
Marco Russo, IRCCS Local Health Authority of Reggio Emilia, Italy
Luciana Mendonça Barbosa, University of São Paulo, Brazil

***Correspondence:**
Nico Sollmann
nico.sollmann@tum.de

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Headache and Neurogenic Pain, a section of the journal Frontiers in Neurology

Received: *14 April 2022*
Accepted: *21 June 2022*
Published: *28 July 2022*

Citation:
Börner C, Renner T, Trepte-Freisleder F, Urban G, Schandelmaier P, Lang M, Lechner MF, Koenig H, Klose B, Albers L, Krieg SM, Baum T, Heinen F, Landgraf MN, Sollmann N and Bonfert MV (2022) Response Predictors of Repetitive Neuromuscular Magnetic Stimulation in the Preventive Treatment of Episodic Migraine. Front. Neurol. 13:919623. doi: 10.3389/fneur.2022.919623

Background: Repetitive neuromuscular magnetic stimulation (rNMS) of the trapezius muscles showed beneficial effects in preventing episodic migraine. However, clinical characteristics that predict a favorable response to rNMS are unknown. The objective of this analysis is to identify such predictors.

Methods: Thirty participants with a diagnosis of episodic migraine (mean age: 24.8 ± 4.0 years, 29 females), who were prospectively enrolled in two non-sham-controlled studies evaluating the effects of rNMS were analyzed. In these studies, the interventional stimulation of the bilateral trapezius muscles was applied in six sessions and distributed over two consecutive weeks. Baseline and follow-up assessments included the continuous documentation of a headache calendar over 30 days before and after the stimulation period, the Migraine Disability Assessment Score (MIDAS) questionnaire (before stimulation and 90 days after stimulation), and measurements of pain pressure thresholds (PPTs) above the trapezius muscles by algometry (before and after each stimulation session). Participants were classified as responders based on a ≥25% reduction in the variable of interest (headache frequency, headache intensity, days with analgesic intake, MIDAS score, left-sided PPTs, right-sided PPTs). *Post-hoc* univariate and multivariate binary logistic regression analyses were performed.

Results: Lower headache frequency ($P = 0.016$) and intensity at baseline ($P = 0.015$) and a migraine diagnosis without a concurrent tension-type headache component ($P = 0.011$) were significantly related to a ≥25% reduction in headache frequency. Higher headache frequency ($P = 0.052$) and intensity at baseline ($P = 0.014$) were significantly associated with a ≥25% reduction in monthly days with analgesic intake. Lower right-sided PPTs at baseline were significantly related to a ≥25% increase in right-sided

PPTs ($P = 0.015$) and left-sided PPTs ($P = 0.030$). Performance of rNMS with higher stimulation intensities was significantly associated with a ≥25% reduction in headache intensity ($P = 0.046$).

Conclusions: Clinical headache characteristics at baseline, the level of muscular hyperalgesia, and stimulation intensity may inform about how well an individual patient responds to rNMS. These factors may allow an early identification of patients that would most likely benefit from rNMS.

Keywords: headache, migraine, neurostimulation, non-invasive neuromodulation, repetitive peripheral magnetic stimulation, myofascial trigger point, preventive migraine therapy, migraine prevention

INTRODUCTION

Migraine is one of the most prevalent neurological disorders worldwide, with more than one billion affected people in 2016 and a significant impact on health-related quality of life, work productivity, and social relationships (1–3). Migraine is countervailed by a multimodal approach of lifestyle management, psychoeducation, psychotherapeutic intervention, and pharmacotherapy (4–6). Medication for migraine attacks is well-established and widely used; yet, responsiveness to prophylactic treatment varies and treatment adherence is often poor (e.g., due to side effects or insufficient adjustment of dosage) (7, 8). Against this background, innovative non-pharmacological treatment options are highly required (4, 8–10).

Neurostimulation represents a non-pharmacological treatment alternative that has emerged over the recent years (11–14). It aims at modifying the complex processes and interactions in and in-between the central, peripheral, and/or autonomous nervous system through externally applied electrical or magnetically induced stimuli. Several approaches exist, including: transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), occipital nerve stimulation (ONS), transcutaneous supraorbital nerve stimulation (tSNS), transcutaneous vagus nerve stimulation (tVNS), and remote electrical neurostimulation (REN) of cutaneous sensory afferents of the upper arm (10, 15–22).

Furthermore, repetitive neuromuscular magnetic stimulation (rNMS) has been introduced lately, targeting to the neck and shoulder muscles to prevent attacks in episodic migraine (23–25). Specifically, rNMS has been reported to be safe, feasible, well-tolerated, and well-accepted (23–25). Moreover, promising effects of rNMS in terms of a reduction in headache frequency, headache intensity, migraine-associated disability, and muscular hypersensitivity have been reported (23–25). It is hypothesized that rNMS intervenes at the terminal branches of the motor and afferent nerves in the region within the induced electromagnetic field, thus directly and indirectly leading to an increase of proprioceptive sensation (26, 27). The trigemino-cervical complex (TCC) serves as a gateway for this bottom-up approach and its translation to modulate the central mechanisms of nociception (10, 28, 29).

However, rNMS demands a commitment in terms of patient's and therapist's resources. Stimulators are increasingly available on the markets, but, they are still by far more expensive than devices for transcutaneous electrical nerve stimulation (tENS), which limits availability. Therefore, recommending rNMS for migraine prevention anticipates thorough consideration of which patient may benefit the most in the context of an individualized multimodal treatment paradigm. However, no data on the predictors of a treatment response to rNMS nor to any other neurostimulating approach are available. The aim of this study was to assess clinical headache and muscular characteristics as well as technical aspects of the stimulation protocol that are associated with a positive treatment response to rNMS regarding headache frequency, headache intensity, burden of migraine, frequency of analgesic intake, and level of muscular hyperalgesia.

Abbreviations: DMKG, German Migraine and Headache Society; ICHD, international classification of headache disorders; MIDAS, migraine disability assessment; mTrP, myofascial trigger point; ONS, occipital nerve stimulation; PPT, pressure pain threshold; QoL, quality of life; REN, remote electrical neurostimulation; rNMS, repetitive neuromuscular magnetic stimulation; TCC, trigemino-cervical complex; tDCS, transcranial direct current stimulation; tENS, transcutaneous electrical nerve stimulation; TMS, transcranial magnetic stimulation; TTH, tension-type headache; tSNS, transcutaneous supraorbital nerve stimulation; tVNS, transcutaneous vagus nerve stimulation.

METHODS

Ethics

The protocols of the two non-sham-controlled studies that form the basis of the present analyses were approved by the institutional review boards of both universities of Munich. The studies were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Design

For the analysis of response predictors, the baseline, treatment, and follow-up charts of 30 participants who received rNMS to the upper trapezius muscles during two previous prospective non-sham-controlled clinical studies have been reviewed (23–25). The following inclusion criteria were applied during those studies: (1) age between 18 and 35 years, (2) episodic migraine [according to the German version of the headache questionnaire modified according to the International Classification of Headache Disorders (ICHD), 3rd beta edition (30–32)], (3) at least one active myofascial trigger point (mTrP) in one of the upper trapezius muscles (identified by a physiotherapist specialized

in manual palpation of mTrPs), and (4) no metallic implants (e.g., pacemaker, cochlear implants). The following criteria were defined as exclusion criteria: (1) chronic migraine (≥15 headache days per month for >3 months) (30), (2) any neurological disorder except for primary headache, (3) intake of any medication for migraine prophylaxis, and (4) pregnancy.

During the previous studies, each participant underwent six sessions of rNMS in regular intervals during two consecutive weeks (e.g., Monday/Wednesday/Friday or Tuesday/Thursday/Saturday) (23–25). A Nexstim eXimia NBS System with a figure-of-eight stimulation coil was used for rNMS (version 4.3; Nexstim Oy, Helsinki, Finland). Before starting the first rNMS session, the stimulation intensity (% of maximum stimulator output) was determined individually for the trapezius muscles and was kept for both sides for the following sessions. Individual stimulation intensities were set by increasing the intensity in 5% steps until participants reported a discomfortable sensation (defined as a score of 5 on a 0–10 visual analog scale). Next, this intensity was decreased by 5% so that a comfortable and non-painful stimulation over 15 min was possible (23–25). Stimulation targeted to the left and right upper trapezius muscles – focusing on the mTrP with the highest intensity of referred pain—for 15 min per side during each session. Stimulation of each side consisted of 20 bursts with a total of 6.000 stimuli and a 20-Hz frequency. A single burst lasted 15 s and was composed of 300 stimuli, followed by a relaxation time of 30 s.

Baseline and Follow-up Assessments

The German version of the headache questionnaire modified according to the ICHD (3rd beta edition) (30–32), the headache calendar of the German Migraine and Headache Society (DMKG) (33), and the Migraine Disability Assessment Score (MIDAS) questionnaire (34, 35) were applied. The presence of aura symptoms and an association with tension-type headache (TTH) were documented as well.

To evaluate the headache frequency and characteristics, participants were asked to fill in the headache calendar of the DMKG on a daily basis in the 30 days before the first rNMS session. Numerous items of each headache attack like date, trigger mechanisms (stress, relaxation, disturbance of sleep-awake rhythm, or menstruation), intensity, duration, quality, localization, forerunning symptoms (scintillating scotoma, paresthesia, or aphasia), concomitant symptoms (nausea, vomiting, photophobia, phonophobia or odor-sensitivity), drug intake, dosage form, and pain relief were recorded with the help of the calendar. Subsequently, the participants filled in the headache diary during the course of the 30 days after the last rNMS intervention, defined as the follow-up period.

Moreover, participants were advised to fill in the MIDAS questionnaire to evaluate the impairment by headache events in different aspects of daily life before and after the application of rNMS. As the MIDAS questionnaire is evaluating a period of 90 days, this questionnaire had to be completed prior to the first rNMS session (evaluating the 90 pre-interventional days) and 90 days after the last session (evaluating the 90 post-interventional days). Measurements of PPTs were performed with an analog algometer by applying pressure with its rubber tip of 1 cm^2 perpendicularly to the determined mTrPs. The pressure was increased with a velocity of 1 $kg/s/cm^2$ until the local PPT was attained according to the participant. This algometry was conducted three times per side before and after rNMS during each of the six sessions, and the average of each three measurements was calculated afterwards (36, 37). In this context, the PPT was defined as the cut-off value between mere pressure and pressure-induced painful perception (37–41).

Statistical Analysis

SPSS (version 25.0; IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for statistical data analyses. Response to rNMS was investigated by categorizing participants into responders and non-responders according to a ≥25% response criterion for the following outcomes: (1) headache frequency, (2) headache intensity, (3) MIDAS score, (4) days with analgesic intake per month, (5) left-sided PPT, and (6) right-sided PPT. The following potential predictors were evaluated: (1) age, (2) headache type (episodic migraine, episodic migraine with concurrent TTH diagnosis), (3) pre-interventional headache frequency, (4) pre-interventional headache intensity, (5) pre-interventional MIDAS score, (6) pre-interventional days with analgesic intake per month, (7), pre-interventional left-sided PPT, (8) pre-interventional right-sided PPT, and (9) stimulation intensity. Differences between pre- and post-interventional values of predictor variables were assessed using paired *t*-tests.

We performed univariate binary logistic regression analyses to assess the influence of each potential predictor on the outcome variable. To assess whether the regression model is better fitted than a null model, the Omnibus test was used. Further, multivariate binary logistic regression analyses (with a backward elimination approach) were used to evaluate the combined influence of potential predictors on the response (≥25% response rate) to rNMS. The Benjamini-Hochberg procedure with a false discovery rate (FDR) of 10% was used to adjust for multiple testing. The statistical significance for all tests was set at $\alpha = 0.05$.

RESULTS

Thirty participants who received rNMS applied to the bilateral trapezius muscles were included in the analysis. All participants had a diagnosis of episodic migraine, and 10 subjects had an additional diagnosis of concurrent TTH (33.3%). Participants were on average 24.8 ± 4.0 years old (age range: 19–35 years) and 29 of the participants were female (96.7%). Demographics as well as baseline and follow-up characteristics are summarized in **Table 1**.

Response set to a level of ≥25% was achieved in 50% of this cohort ($n = 15$) in terms of decreases in headache frequency, in 13% of participants ($n = 4$) in terms of decreases in headache intensity, in 73% of participants ($n = 22$) in terms of decreases in the MIDAS score, in 50% of participants ($n = 15$) in terms of decreases in monthly days with analgesic intake, and in 53% of participants ($n = 16$) in terms of increases in left-sided PPTs as well as in 60% of participants ($n = 18$) in terms of increases

TABLE 1 | Descriptive statistics of $n = 30$ patients affected by episodic migraine participating in two pilot studies of repetitive neuromuscular magnetic stimulation applied to the trapezius muscles.

	Descriptive Statistics					Paired *t*-Test	
	N	**%**	**Mean**	**SD**	**Range**	**T**	***P*-value**
Age (years)			24.80	3.96	19–35		
Gender							
Female	29	96.70					
Male	1	3.30					
Headache type							
Migraine without TTH	20	66.70					
Migraine with TTH	10	33.30					
Headache frequency (days/month)							
Pre-interventional			8.17	4.50	2–26	2.88	0.007[a]
Post-interventional			6.33	4.38	1–20		
Headache intensity (10-point VAS scale)							
Pre-interventional			5.23	1.37	2.52–7.5	−0.73	0.473
Post-interventional			5.40	1.33	3.00–7.43		
MIDAS score							
Pre-interventional			26.33	13.89	2–58	6.24	<0.001[a]
Post-interventional			15.27	12.30	1–47		
Analgesic intake (days/month)							
Pre-interventional			3.63	2.58	0–8	1.25	0.233
Post-interventional			3.10	2.44	0–9		
PPT left (kg)							
Pre-interventional			2.02	0.89	0.97–4.17	−4.26	<0.001[a]
Post-interventional			2.68	1.16	0.80–5.33		
PPT right (kg)							
Pre-interventional			2.19	0.83	0.87–3.83	−4.10	<0.001[a]
Post-interventional			2.94	1.15	0.63–5.04		
rNMS intensity (% of maximum stimulator output)			24.23	4.66	15–35		

[a]*Results significant at* $\alpha = 0.05$. *TTH, tension-type headache; VAS, visual analog scale; MIDAS, migraine disability assessment; PPT, pressure pain threshold; rNMS, repetitive neuromuscular magnetic stimulation.*

in right-sided PPTs, respectively. The results of the univariate analyses are summarized in **Table 2**.

The multivariate analyses revealed the following results (**Table 3**): headache type as well as pre-interventional headache frequency and headache intensity were significantly associated with responsiveness in terms of a ≥25% reduction in headache frequency. Responders had on average lower pre-interventional headache frequency (responders: 7.4 ± 3.4 days/month; non-responders: 8.9 ± 5.4 days/month) and intensity (responders: 5.0 ± 1.3 points; non-responders: 5.5 ± 1.5 points on a 10-point visual analog scale). In addition, responders were more often diagnosed with migraine without a concurrent diagnosis of TTH [responders: 12 participants without a TTH diagnosis (80%); non-responders: 8 participants without a TTH diagnosis (53.3%)]. The pre-interventional headache intensity was significantly associated with responsiveness in terms of a ≥25% reduction in monthly days with analgesic intake. The association of pre-interventional headache frequency with responsiveness showed a statistical trend ($P = 0.052$). Responders had on average higher pre-interventional headache frequency (responders: 9.0 ± 5.6 days/month; non-responders: 7.3 ± 3.0 days/month) and intensity (responders: 5.7 ± 1.4 points; non-responders: 4.7 ± 1.1 points on a 10-point visual analog scale).

The pre-interventional right-sided PPT was significantly associated with responsiveness in terms of a ≥25% increase in the right-sided PPTs. Responders had on average lower pre-interventional right-sided PPTs (responders: 2.0 ± 0.9; non-responders: 2.4 ± 0.7). The pre-interventional right-sided PPT was significantly associated with responsiveness in terms of a ≥25% increase in the left-sided PPTs. Responders had on average lower pre-interventional right-sided PPTs (responders: 1.9 ± 0.7; non-responders: 2.6 ± 0.8). Stimulation intensity was significantly associated with responsiveness in terms of a ≥25% reduction in headache intensity. Responders received rNMS with higher stimulation intensities on average (responders: 29.3 ± 4.4% of maximum stimulator output; non-responders: 23.5 ± 4.3% of maximum stimulator output).

TABLE 2 | Results of the univariate analyses of response predictors of repetitive neuromuscular magnetic stimulation applied to the trapezius muscles in patients affected by episodic migraine.

Predictor	Omnibus Test		B	SE	*P*-value	Exp (B)	95% CI [Exp (B)]
	Chi^2	*P*-value					
25% responder rate of headache intensity							
rNMS intensity	6.27	0.012	0.37	0.18	0.046[a]	1.44	1.01–2.07
25% responder rate of MIDAS score							
Headache frequency	4.02	0.045	−0.21	0.13	0.110	0.81	0.63–1.05
Days with analgesic intake/month	3.93	0.048	−0.35	0.19	0.067	0.71	0.49–1.02
25% responder rate of days with analgesic intake							
Headache intensity	4.42	0.035	0.62	0.32	0.053	1.86	0.99–3.48
Days with analgesic intake/month	6.79	0.009	0.42	0.18	0.019[a]	1.52	1.07–2.15
25% responder rate of left-sided PPT							
Right-sided PPT	6.00	0.014	−1.25	0.58	0.030[a]	0.29	0.09–0.89
25% responder rate of right-sided PPT							
rNMS intensity	4.75	0.029	0.20	0.10	0.050[a]	1.22	1.00–1.49

[a]*Results significant at* $\alpha = 0.05$ *and after adjusting for multiple testing using the Benjamini-Hochberg correction with 10% FDR. Only predictors for which the Omnibus test was significant are displayed in this table. B, unstandardized beta (regression coefficient); SE, standard error of the unstandardized beta; Exp(B), expected beta; CI, confidence interval of the expected beta; MIDAS, Migraine Disability Assessment; PPT, pressure pain threshold; rNMS, repetitive neuromuscular magnetic stimulation; FDR, false discovery rate.*

TABLE 3 | Results of the multivariate analyses of response predictors of repetitive neuromuscular magnetic stimulation applied to the trapezius muscles in $n = 30$ patients affected by episodic migraine.

Predictor	B	SE	*P*-value	Exp(B)	95% CI [Exp (B)]
25% responder rate of headache frequency					
Headache type	4.13	1.63	0.011[a]	–	–
Headache frequency	−0.41	0.17	0.016[a]	0.66	0.47–0.93
Headache intensity	−1.41	0.58	0.015[a]	0.25	0.08–0.76
25% responder rate of headache intensity					
rNMS intensity	0.37	0.18	0.046[a]	1.44	1.01–2.07
25% responder rate of days with analgesic intake					
Headache intensity	1.00	0.40	0.014[a]	2.71	1.23–5.99
Headache frequency	0.23	0.12	0.052	1.26	1.00-1.60
25% responder rate of left-sided PPT					
Right-sided PPT	−1.25	0.58	0.030[a]	0.29	0.09–0.89
25% responder rate of right-sided PPT					
Left-sided PPT	2.02	1.07	0.060	7.51	0.92–61.37
Right-sided PPT	−2.83	1.16	0.015[a]	0.06	0.01–0.58
rNMS intensity	0.25	0.14	0.076	1.28	0.97–1.69

[a]*Results significant at* $\alpha = 0.05$ *and after adjusting for multiple testing using the Benjamini-Hochberg correction with 10% FDR. All variables not mentioned in the table were excluded in the prior steps of regression analysis. B, unstandardized beta (regression coefficient); SE, standard error of the unstandardized beta; Exp(B), expected beta; CI, confidence interval of the expected beta; PPT, pressure pain threshold; rNMS, repetitive neuromuscular magnetic stimulation; FDR, false discovery rate.*

No statistically significant predictors were identified for responsiveness in terms of a ≥25% reduction in MIDAS scores ($P > 0.05$).

DISCUSSION

In migraine research, neurostimulation methods are emerging non-invasive, non-pharmacological approaches, for which efficacy data is available but information on clinical baseline characteristics associated with positive treatment response are still lacking (11, 12). This study points at clinical headache and muscular characteristics as well as a technical factor as potential predictors for a beneficial response to rNMS in participants with episodic migraine. Reductions in headache frequency (from 8.17 to 6.33 headache days per month) and in MIDAS scores (from 26.3 reflecting severe disability to 15.3 reflecting moderate disability) were observed after application of rNMS compared to the baseline status, whereas no significant changes were found for headache intensity or duration.

Participants achieving a reduction in headache frequency of at least 25% had on average lower headache frequency, lower headache intensity, and were more often diagnosed with

migraine without a TTH component at baseline. Responsiveness in terms of ≥25% reduction in monthly analgesic intake days was associated with higher mean headache intensity at baseline and higher headache frequency by trend. Regarding muscular involvement, participants achieving a ≥25% increase in right- and left-sided PPTs had on average lower baseline right-sided PPTs. From the technical perspective, participants with a decrease of at least 25% in headache intensity received rNMS with higher mean stimulation intensities. All those findings are in agreement with the current concept of migraine pathophysiology, which includes not only central pain mechanisms but also points at muscular involvement of the neck muscles (7, 42–44). Clinically, particularly the involvement of the upper trapezius muscles has been described more pronounced in migraine than in episodic TTH (45, 46). Supported by muscular imaging by advanced techniques like muscle T2 mapping of the trapezius muscles, the clinical signs might be considered surrogates of muscular neuroinflammation (47, 48). This imaging finding could be seen in line with the framework of the TCC (28, 29).

The level of sensitization and impairment of the nociceptive feedback control systems may eventually be more easily amenable by a tailored treatment approach the lower the baseline headache frequency and intensity are. This may imply to consider a neuromodulatory approach early during the course of disease, before perpetuation of the disorder. With respect to this assumption, a follow-up rNMS study involving patients suffering from chronic migraine would be of interest, as well as long-term follow-up investigations to assess the sustainability of the beneficial effects in different subgroups of patients (e.g., episodic migraine vs. high-frequent episodic migraine vs. chronic migraine). Treating migraine *via* the bottom-up approach allows the modulation of the afferent input to the TCC and, in consequence, of the central pain processing mechanisms (10, 28, 29). Since TTH is associated with different pathophysiological mechanisms, patients with migraine having a concurrent TTH component might respond to rNMS to a lesser extent (49–52).

Patients who are more frequently or more intensely affected by migraine may also use more medication for pain relief. Hence, a decrease of the intake of analgesics is likely to reflect a lower headache frequency and/or intensity as a positive response to rNMS. The better treatment response in patients with a higher level of muscular hyperalgesia supports the concept of the bottom-up approach, as well. In this regard, rNMS targeting the part of the trapezius muscles that is included in the TCC is particularly effective in patients with a high level of muscular involvement. Specifically, the impact of the stimulation intensity on the outcome might reflect a dose-effect relationship. Given the novelty of the rNMS approach, no comparisons of different stimulation protocols have been conducted yet.

Of note, we chose a reduction of ≥25% as responder rate since clinical experience support that responder rates lower than 50% are also clinically meaningful in the context of non-pharmacological preventive treatments (53). This is especially true for the cohort of this study since it involves participants suffering from frequent episodic migraine (up to 26 headache days per month).

Data on the predictors of treatment response to other non-invasive methods of neurostimulation (e.g., TMS, tDCS, or tENS of cranial nerves) for the prevention of migraine is lacking so far. Only one study examined potential predictors for the response to invasive ONS in refractory chronic headache (54). It showed that shorter unilateral headache attacks and prior response to a pharmacologically induced occipital nerve block were associated with a greater likelihood for a positive response to invasive ONS (54).

When interpreting the results of this analysis the following limitations should be respected. First, the sample size is low, which does not allow for an extrapolation to the general population of migraine patients. Second, the analysis relies on data retrieved from not-sham-controlled pilot studies, which is why placebo effects in the context of response level cannot be excluded. Further research is needed to evaluate the association of clinical as well as muscular characteristics and technical aspects to treatment response for neurostimulation therapy. In addition, future studies should investigate rNMS in a higher number of patients as well as in sham-controlled settings to assess and correct for a potential placebo effect. Future studies could for instance assess further predictors like age at onset of migraine, overall duration of migraine (55), number of local spots of muscular hyperalgesia (i.e., mTrPs), fluid biomarkers (e.g., calcitonin gene-related peptide), or biomarkers based on novel muscular imaging methods (e.g., T2 mapping derived from magnetic resonance imaging of the trapezius muscles) (47, 48). Since our results derive from a cohort of young adults with episodic migraine, future studies should include other migraine cohorts as well (e.g., pediatric populations). Further, this study did not assess variables reflecting central sensitization (e.g., allodynia), and it did not systematically assess common comorbidities like depression or anxiety. Future studies should implement such comorbidities in their study design. In addition, different classifications of responsiveness should be considered, for example ≥25% vs. ≥50% response, excellent responders (56), full-length responders, or wearing-off responders (57). Moreover, the establishment of standardized protocols for treatment and for data collection during baseline and follow-up are necessary for reliable data analysis and bias exclusion (55, 58). The identification of potential predictors for the different neurostimulation approaches and for a larger cohort of patients could enable an individually tailored, efficacy-predicting tool (score chart) in a multimodal therapy setting (59).

CONCLUSION

This analysis informs about predictors of treatment response to rNMS applied to the upper trapezius muscle in a cohort of young adults affected by episodic migraine. Findings demonstrate that some clinical headache characteristics at baseline (headache frequency, headache intensity, and headache diagnosis), the level of muscular hyperalgesia expressed by PPTs at baseline, as well as technical aspects during rNMS (stimulation intensity) may deliver information on how well an individual patient may respond to rNMS. These factors may allow early identification of patients who would experience benefits of rNMS based on their initial clinical presentation. This is important as rNMS represents an innovative and promising treatment approach that

is, however, restricted to single headache centers at the current stage, only. Further, to establish a treatment option like rNMS in a cost- and time-efficient manner, the individual counseling on the treatment options in the context of a multimodal regimen should be based on all evidence available.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission TUM & LMU. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TR and FTF conducted the clinical studies on which the analysis of the paper is based on with support of BK and HK and under the supervision of NS, FH, and MNL. CB and NS conducted the statistical analysis with support of TB and LA. CB, TR, MB, NS, SK, MNL, and FH discussed and interpreted the findings and gave their expert opinion with regards to all analyses. CB, TR, and MB drafted the manuscript. GU, PS, and ML compiled tables. All authors reviewed, commented on and contributed to the final manuscript. All authors have agreed to this final version of the article being submitted.

FUNDING

MNL received grants from the Deutsches Zentrum für Luft- und Raumfahrt (DLR-PT). MNL and FH received a grant Innovationsfonds of the joint federal committee of health insurance companies (GBA) for a nation-wide study on an early multimodal intervention program for children with migraine. The work of MB is supported by the Bavarian Gender Equality Grant of the Free State of Bavaria, the German Migraine and Headache Society (DMKG), Germany, and the ZNS-Hannelore-Kohl Stiftung, Germany. The work of NS is supported by the Dr. Ing. Leonhard Lorenz Foundation, the German Migraine and Headache Society (DMKG), and the Joachim Herz Foundation.

REFERENCES

1. Martelletti P, Schwedt TJ, Lanteri-Minet M, Quintana R, Carboni V, Diener HC, et al. My migraine voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. *J Headache Pain.* (2018) 19:115. doi: 10.1186/s10194-018-0946-z
2. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? *J Headache Pain.* (2018) 19:17. doi: 10.1186/s10194-018-0846-2
3. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *J Headache Pain.* (2018) 19:82. doi: 10.1186/s10194-018-0907-6
4. Bonfert M, Straube A, Schroeder AS, Reilich P, Ebinger F, Heinen F. Primary headache in children and adolescents: update on pharmacotherapy of migraine and tension-type headache. *Neuropediatrics.* (2013) 44:3–19. doi: 10.1055/s-0032-1330856
5. Diener H-C, Gaul C, Kropp P. Therapie der Migräneattacke und Prophylaxe der Migräne, S1-Leitlinie. In: *Deutsche Gesellschaft für Neurologie (Hrsg), Leitlinien für Diagnostik und Therapie in der Neurologie*. (2018).
6. Bonfert MV. Primäre Kopfschmerzen bei Kindern und Jugendlichen - Update 2019. *Pädiatrie Up2date*. (2019) 14:71–85. doi: 10.1055/s-0043-115285
7. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol.* (2018) 17:174–82. doi: 10.1016/S1474-4422(17)30435-0
8. Diener H-C, Charles A, Goadsby PJ, Holle D. New therapeutic approaches for the prevention and treatment of migraine. *Lancet Neurol.* (2015) 14:1010–22. doi: 10.1016/S1474-4422(15)00198-2
9. Brighina F, Raieli V, Messina LM, Santangelo G, Puma D, Drago F, et al. Non-invasive brain stimulation in pediatric migraine: a perspective from evidence in adult migraine. *Front Neurol.* (2019) 10:364. doi: 10.3389/fneur.2019.00364
10. Borner C, Urban G, Beaulieu LD, Sollmann N, Krieg SM, Straube A, et al. The bottom-up approach: non-invasive peripheral neurostimulation methods to treat migraine: a scoping review from the child neurologist's perspective. *Eur J Paediatr Neurol.* (2021) 32:16–28. doi: 10.1016/j.ejpn.2021.02.008
11. Schoenen J, Roberta B, Magis D, Coppola G. Non-invasive neurostimulation methods for migraine therapy: the available evidence. *Cephalalgia.* (2016) 36:1170–80. doi: 10.1177/0333102416636022
12. Reuter U, McClure C, Liebler E, Pozo-Rosich P. Non-invasive neuromodulation for migraine and cluster headache: a systematic review of clinical trials. *J Neurol Neurosurg Psychiatry.* (2019) 90:796–804. doi: 10.1136/jnnp-2018-320113
13. Vukovic Cvetkovic V, Jensen RH. Neurostimulation for the treatment of chronic migraine and cluster headache. *Acta Neurol Scand.* (2019) 139:4–17. doi: 10.1111/ane.13034
14. Moisset X, Pereira B, Ciampi de Andrade D, Fontaine D, Lanteri-Minet M, Mawet J. Neuromodulation techniques for acute and preventive migraine treatment: a systematic review and meta-analysis of randomized controlled trials. *J Headache Pain.* (2020) 21:142. doi: 10.1186/s10194-020-01204-4
15. Rapoport AM, Bonner JH, Lin T, Harris D, Gruper Y, Ironi A, et al. Remote electrical neuromodulation (REN) in the acute treatment of migraine: a comparison with usual care and acute migraine medications. *J Headache Pain.* (2019) 20:83. doi: 10.1186/s10194-019-1033-9
16. Rapoport AM, Lin T, Tepper SJ. Remote electrical neuromodulation (REN) for the acute treatment of migraine. *Headache.* (2020) 60:229–34. doi: 10.1111/head.13669
17. Yarnitsky D, Dodick DW, Grosberg BM, Burstein R, Ironi A, Harris D, et al. Remote Electrical neuromodulation (REN) relieves acute migraine: a randomized, double-blind, placebo-controlled, multicenter trial. *Headache.* (2019) 59:1240–52. doi: 10.1111/head.13551
18. Rodrigo D, Acin P, Bermejo P. Occipital nerve stimulation for refractory chronic migraine: results of a long-term prospective study. *Pain Physician*. (2017) 20:E151–9. doi: 10.36076/2017.1.E151
19. de Coo IF, Marin JC, Silberstein SD, Friedman DI, Gaul C, McClure CK, et al. Differential efficacy of non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: a meta-analysis. *Cephalalgia.* (2019) 39:967–77. doi: 10.1177/0333102419856607
20. Ordas CM, Cuadrado ML, Pareja JA, de-Las-Casas-Camara G, Gomez-Vicente L, Torres-Gaona G, et al. Transcutaneous supraorbital stimulation as a preventive treatment for chronic migraine: a prospective, open-label study. *Pain Med.* (2020) 21:415–22. doi: 10.1093/pm/pnz119
21. Starling AJ, Tepper SJ, Marmura MJ, Shamim EA, Robbins MS, Hindiyeh N, et al. A multicenter, prospective, single arm, open label, observational study of sTMS for migraine prevention (ESPOUSE study). *Cephalalgia.* (2018) 38:1038–48. doi: 10.1177/0333102418762525

22. Stilling JM, Monchi O, Amoozegar F, Debert CT. Transcranial magnetic and direct current stimulation (TMS/tDCS) for the treatment of headache: a systematic review. *Headache.* (2019) 59:339–57. doi: 10.1111/head.13479
23. Sollmann N, Trepte-Freisleder F, Albers L, Jung NH, Mall V, Meyer B, et al. Magnetic stimulation of the upper trapezius muscles in patients with migraine—a pilot study. *Eur J Paediatr Neurol.* (2016) 20:888–97. doi: 10.1016/j.ejpn.2016.07.022
24. Renner T, Sollmann N, Heinen F, Albers L, Trepte-Freisleder F, Klose B, et al. Alleviation of migraine symptoms by application of repetitive peripheral magnetic stimulation to myofascial trigger points of neck and shoulder muscles—a randomized trial. *Sci Rep.* (2020) 10:5954. doi: 10.1038/s41598-020-62701-9
25. Renner T, Sollmann N, Trepte-Freisleder F, Albers L, Mathonia NM, Bonfert MV, et al. Repetitive peripheral magnetic stimulation (rPMS) in subjects with migraine-setup presentation and effects on skeletal musculature. *Front Neurol.* (2019) 10:738. doi: 10.3389/fneur.2019.00738
26. Beaulieu LD, Schneider C. Repetitive peripheral magnetic stimulation to reduce pain or improve sensorimotor impairments: a literature review on parameters of application and afferents recruitment. *Neurophysiol Clin.* (2015) 45:223–37. doi: 10.1016/j.neucli.2015.08.002
27. Beaulieu LD, Schneider C. Effects of repetitive peripheral magnetic stimulation on normal or impaired motor control. A review. *Neurophysiol Clin.* (2013) 43:251–60. doi: 10.1016/j.neucli.2013.05.003
28. Bartsch T, Goadsby PJ. The trigeminocervical complex and migraine: current concepts and synthesis. *Curr Pain Headache Rep.* (2003) 7:371–6. doi: 10.1007/s11916-003-0036-y
29. Bartsch T, Goadsby PJ. Central mechanisms of peripheral nerve stimulation in headache disorders. *Prog Neurol Surg.* (2011) 24:16–26. doi: 10.1159/000323008
30. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. *Cephalalgia*. (2018) 38:1–211. doi: 10.1177/0333102417738202
31. Fritsche G, Hueppe M, Kukava M, Dzagnidze A, Schuerks M, Yoon MS, et al. Validation of a German language questionnaire for screening for migraine, tension-type headache, and trigeminal autonomic cephalgias. *Headache.* (2007) 47:546–51. doi: 10.1111/j.1526-4610.2007.00758.x
32. Yoon MS, Obermann M, Fritsche G, Slomke M, Dommes P, Schilf C, et al. Population-based validation of a German-language self-administered headache questionnaire. *Cephalalgia.* (2008) 28:605–8. doi: 10.1111/j.1468-2982.2008.01560.x
33. Jensen R, Tassorelli C, Rossi P, Allena M, Osipova V, Steiner T, et al. A basic diagnostic headache diary (BDHD) is well-accepted and useful in the diagnosis of headache. A multicentre European and Latin American study. *Cephalalgia.* (2011) 31:1549–60. doi: 10.1177/03331024 11424212
34. Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: the migraine disability assessment (MIDAS) questionnaire. *Headache*. (2001) 41:854–61. doi: 10.1046/j.1526-4610.2001.01156.x
35. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the migraine disability assessment (MIDAS) questionnaire to assess headache-related disability. *Neurology*. (2001) 56(6 Suppl 1):S20–8. doi: 10.1212/WNL.56.suppl_1.S20
36. Smania N, Corato E, Fiaschi A, Pietropoli P, Aglioti SM, Tinazzi M. Therapeutic effects of peripheral repetitive magnetic stimulation on myofascial pain syndrome. *Clin Neurophysiol.* (2003) 114:350–8. doi: 10.1016/S1388-2457(02)00367-X
37. Caminero AB, Cuadrado ML, Arendt-Nielsen L, Pareja JA. Generalized neck-shoulder hyperalgesia in chronic tension-type headache and unilateral migraine assessed by pressure pain sensitivity topographical maps of the trapezius muscle. *Cephalalgia.* (2010) 30:77–86. doi: 10.1111/j.1468-2982.2009.01901.x
38. Baron J, Ruiz M, Palacios-Cena M, Madeleine P, Guerrero AL, Arendt-Nielsen L, et al. Differences in topographical pressure pain sensitivity maps of the scalp between patients with migraine and healthy controls. *Headache.* (2017) 57:226–35. doi: 10.1111/head.12984
39. Florencio LL, Giantomassi MC, Carvalho GF, Goncalves MC, Dach F, Fernandez-de-Las-Penas C, et al. Generalized pressure pain hypersensitivity in the cervical muscles in women with migraine. *Pain Med.* (2015) 16:1629–34. doi: 10.1111/pme.12767
40. Grossi DB, Chaves TC, Gonçalves MC, Moreira VC, Canonica AC, Florencio LL, et al. Pressure pain threshold in the craniocervical muscles of women with episodic and chronic migraine: a controlled study. *Arq Neuropsiquiatr.* (2011) 69:607–12. doi: 10.1590/S0004-282X2011000500007
41. Palacios-Cena M, Lima Florencio L, Natalia Ferracini G, Baron J, Guerrero AL, Ordas-Bandera C, et al. Women with chronic and episodic migraine exhibit similar widespread pressure pain sensitivity. *Pain Med.* (2016) 17:2127–33. doi: 10.1093/pm/pnw056
42. Akerman S, Romero-Reyes M, Holland PR. Current and novel insights into the neurophysiology of migraine and its implications for therapeutics. *Pharmacol Ther.* (2017) 172:151–70. doi: 10.1016/j.pharmthera.2016.12.005
43. Dodick DW. A phase-by-phase review of migraine pathophysiology. *Headache.* (2018) 58 Suppl 1:4–16. doi: 10.1111/head.13300
44. Puledda F, Messina R, Goadsby PJ. An update on migraine: current understanding and future directions. *J Neurol.* (2017) 264:2031–9. doi: 10.1007/s00415-017-8434-y
45. Blaschek A, Decke S, Albers L, Schroeder AS, Lehmann S, Straube A, et al. Self-reported neck pain is associated with migraine but not with tension-type headache in adolescents. *Cephalalgia.* (2014) 34:895–903. doi: 10.1177/0333102414523338
46. Landgraf MN, von Kries R, Heinen F, Langhagen T, Straube A, Albers L. Self-reported neck and shoulder pain in adolescents is associated with episodic and chronic migraine. *Cephalalgia.* (2016) 36:807–11. doi: 10.1177/0333102415610875
47. Sollmann N, Mathonia N, Weidlich D, Bonfert M, Schroeder SA, Badura KA, et al. Quantitative magnetic resonance imaging of the upper trapezius muscles—assessment of myofascial trigger points in patients with migraine. *J Headache Pain.* (2019) 20:8. doi: 10.1186/s10194-019-0960-9
48. Sollmann N, Schandelmaier P, Weidlich D, Borner C, Urban G, Lang M, et al. Patients with episodic migraine show increased T2 values of the trapezius muscles—an investigation by quantitative high-resolution magnetic resonance imaging. *Cephalalgia.* (2021) 41:934–42. doi: 10.1177/0333102421996374
49. Jensen R. Mechanisms of tension-type headache. *Cephalalgia.* (2001) 21:786–9. doi: 10.1046/j.0333-1024.2001.00251.x
50. Krusz JC. Tension-type headaches: what they are and how to treat them. *Prim Care*. (2004) 31:293–311. doi: 10.1016/j.pop.2004.02.004
51. de Tommaso M, Fernandez-de-Las-Penas C. Tension type headache. *Curr Rheumatol Rev.* (2016) 12:127–39. doi: 10.2174/1573397112666151231113625
52. Jay GW, Barkin RL. Primary headache disorders- part 2: tension-type headache and medication over use headache. *Dis Mon.* (2017) 63:342–67. doi: 10.1016/j.disamonth.2017.05.001
53. Tassorelli C, Diener HC, Dodick DW, Silberstein SD, Lipton RB, Ashina M, et al. Guidelines of the international headache society for controlled trials of preventive treatment of chronic migraine in adults. *Cephalalgia.* (2018) 38:815–32. doi: 10.1177/0333102418758283
54. Miller S, Watkins L, Matharu M. Predictors of response to occipital nerve stimulation in refractory chronic headache. *Cephalalgia.* (2018) 38:1267–75. doi: 10.1177/0333102417728747
55. Barbanti P, Ferroni P. Onabotulinum toxin A in the treatment of chronic migraine: patient selection and special considerations. *J Pain Res.* (2017) 10:2319–29. doi: 10.2147/JPR.S113614
56. Alpuente A, Gallardo VJ, Torres-Ferrus M, Alvarez-Sabin J, Pozo-Rosich P. Short and mid-term predictors of response to onabotulinumtoxin A: real-life experience observational study. *Headache.* (2020) 60:677–85. doi: 10.1111/head.13765
57. Quintas S, Garcia-Azorin D, Heredia P, Talavera B, Gago-Veiga AB, Guerrero AL. Wearing off response to onabotulinumtoxin A in chronic migraine: analysis in a series of 193 patients. *Pain Med.* (2019) 20:1815–21. doi: 10.1093/pm/pny282
58. Schneider C, Zangrandi A, Sollmann N, Bonfert MV, Beaulieu LD, r PMSCG. Checklist on the quality of the repetitive peripheral magnetic stimulation (rPMS) methods in research: an international delphi study. *Front Neurol.* (2022) 13:852848. doi: 10.3389/fneur.2022.852848
59. Kisler LB, Weissman-Fogel I, Coghill RC, Sprecher E, Yarnitsky D, Granovsky Y. Individualization of migraine prevention: a randomized

controlled trial of psychophysical-based prediction of duloxetine efficacy. *Clin J Pain.* (2019) 35:753–65. doi: 10.1097/AJP.0000000000000739

Conflict of Interest: The Division of Pediatric Neurology and Developmental Medicine, Dr. von Hauner Children's Hospital, LMU Hospital, Munich Germany is provided by an emFieldPro magnetic stimulator by Zimmer MedizinSysteme GmbH (Neu-Ulm, Germany). NS and SK received honoraria from Nexstim Plc (Helsinki, Finland). SK received honoraria from Brainlab AG (Munich, Germany), Spineart (Frankfurt, Germany), Ulrich Medical (Ulm, Germany), Zeiss Meditec (Jena, Germany), and Medtronic (Dublin, Ireland).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Appendix A: Paper III

Reference:

Börner C, Urban G, Beaulieu LD, Sollmann N, Krieg S, Straube A, Renner T, Schandelmaier P, Lang M, Lechner M, Vill K, Gerstl L, Heinen F, Landgraf M, Bonfert M. The bottom-up approach: Non-invasive peripheral neurostimulation methods to treat migraine: A scoping review from the child neurologist's perspective. European Journal of Paediatric Neurology, 32, 16-28. Doi: 10.1016/j.ejpn.2021.02.008

Link:

https://www.ejpn-journal.com/article/S1090-3798(21)00040-4/abstract

Acknowledgements

First, I would like to express my sincere gratitude to Sandro Krieg, who was my supervisor during my Master's internship and raised my special interest in the field of magnetic stimulation. He was the one introducing me to his colleague Florian Heinen and his team. Only thanks to this connection, I met Florian Heinen and Michaela Bonfert and got the chance to apply for a PhD in Medical Research.

Therefore, my greatest "Thank you" certainly goes to my supervisors Florian Heinen, Michaela Bonfert, and Nico Sollmann for supporting me throughout my whole PhD time. I am very grateful for all the opportunities they gave me during my PhD to further develop my research skills, gain experience in project and team administration, learn more about political tasks, and extend my personal network at scientific meetings and conferences.

I would also like to extend my thanks to all the students in our research team (Giada Urban, Magdalena Lang, Jacob Staisch, Ari Hauser, Erik Zaidenstadt, Amelie Amann, Maximilian Frohnmüller, Thomas Lachhammer, Theresa Pfeifer, Emese Palagyi, Paulina Kolorz, Paula Behrendt) and all co-authors, without whom the projects and publications entailed in my PhD thesis would not have been possible.

The same applies to the whole clinical team of the MUC – iSPZ Hauner including physicians, physiotherapists, psychologists, nurses, social workers, and administrative staff who are responsible for the great support that patients with headache disorders and their families receive in the MUC – iSPZ Hauner.

Finally, I would also like to thank my partner Axel Schröder, my family, and all my friends who gave me emotional support during my PhD journey whenever I needed it.

List of publications

A) Original Articles

2023

Grosse L, Späh M, **Börner C**, Schnabel J, Meuche A, Parzefall B, Breuer U, Warken B, Sitzberger A, Hösl M, Heinen F, Berweck S, Schröder S, Bonfert M. Addressing gross motor function by functional repetitive neuromuscular magnetic stimulation targeting to the gluteal muscles in children with bilateral spastic cerebral palsy. *Accepted in Frontiers in Neurology.*

Sollmann N, Schandelmaier P, Weidlich D, Stelter J, Joseph GB, **Börner C**, Schramm S, Beer M, Zimmer C, Landgraf M, Heinen F, Karampinos D, Baum T, Bonfert M. Headache frequency and neck pain are associated with trapezius muscle T2 in tension-type headache among young adults. *Accepted in Journal of Headache and Pain.*

Grosse L, Schnabel J, **Börner C**, Späh M, Meuche A, Parzefall B, Sollmann N, Breuer U, Warken B, Sitzberger A, Hösl M, Heinen F, Berweck S, Schröder S, Bonfert M. Functional repetitive neuromuscular magnetic stimulation targeting to the gluteal muscles in children with bilateral spastic cerebral palsy – safety, feasibility, and patient-reported outcome. *Under review in Frontiers in Neurology.*

Grosse L, Meuche A, Parzefall B, **Börner C**, Schnabel J, Späh M, Sollmann N, Klich L, Hösl M, Heinen F, Berweck S, Schröder S, Bonfert M. Functional repetitive neuromuscular magnetic stimulation (frNMS) aiming at improving ankle strength in children with upper motor neuron syndrom: an intrasubject controlled pilot study. *Under review in Frontiers in Neurology.*

Börner C, Schröder A, Meyer B, Krieg S, Ille S. Cortical location of language function may differ between various languages while subcortical pathways are similar in patients with left-sided perisylvian brain lesions. *Under review in Brain Sciences.*

Börner C, Lang M, Urban G, Zaidenstadt E, Staisch J, Hauser A, Hannibal I, Huß K, Klose B, Lechner M., Sollmann N, Landgraf M., Heinen F, Bonfert M. Neuromodulation in pediatric migraine: safety, feasibility, and effects of repetitive neuromuscular magnetic stimulation. *Under review in Pain Research and Management.*

2022

Staisch J, **Börner C**, Lang M, Hauser A, Hannibal I, Huß K, Klose B, Lechner M, Sollmann N, Heinen F, Landgraf M, Bonfert M. Repetitive neuromuscular magnetic stimulation in children with headache. *European Journal of Paediatric Headache, 39, 2022, 40-48.* Doi: 10.1016/j.ejpn.2022.04.010

Börner C, Staisch J, Lang M, Hauser A, Hannibal I, Huß K, Klose B, Lechner M, Sollmann N, Heinen F, Landgraf M, Bonfert M. Repetitive neuromuscular magnetic stimulation for pediatric headache disorders: muscular effects and factors affecting level of response. *Brain Sciences, 12, 2022, 932.* Doi: 10.3390/brainsci12070932

Börner C, Renner T, Trepte-Freisleder F, Urban G, Schandelmaier P, Lang M, Lechner M, Koenig H, Klose B, Albers L, Krieg S, Baum T, Heinen F, Landgraf M, Sollmann N, Bonfert M.

Response predictors of repetitive neuromuscular magnetic stimulation in the preventive treatment of episodic migraine. *Frontiers Neurology, 13:919623, 2022*. Doi: 10.3389/fneur.2022.919623

2021

Sollmann N, Schandelmaier P, Weidlich D, **Börner C**, Urban G, Lang M, Koenig H, Lechner M, Zimmer C, Karampinos D, Landgraf M, Heinen F, Baum T, Bonfert M. Patients with episodic migraine show increased T2 values of the trapezius muscles – An investigation by quantitative high-resolution magnetic resonance imaging. *Cephalalgia, 0(0), 2021, 1-9.* Doi: 10.1177/0333102421996374

Bonfert M, Sollmann N, Renner T, **Börner C**, Urban G, Schandelmaier P, Hannibal I, Huß K, Parisi C, Gerstl L, Vill K, Blaschek A, König H, Klose B, Heinen F, Landgraf M, Albers L. Burden of disease and lifestyle habits in adolescents and young adults prone to frequent episodic migraine: A secondary comparative analysis. *Journal of Child Health Care, 0(0), 2021, 1-13.* Doi: 10.1177/13674935211008712

2020

van Dellen E, **Börner C**, Schutte M, van Montfort S, Abramovic L, Boks M, Cahn W, van Haren N, Mandl R, Stam C, Sommer I. Functional brain networks in the schizophrenia spectrum and bipolar disorder with psychosis. *npj Schizophrenia, 6(1), 2020, 1-9.* Doi: https://doi.org/10.1038/s41537-020-00111-6

B) Case Reports

2022

Bonfert M, Meuche A, Urban G, **Börner C**, Breuer U, Warken B, Wimmer C, Strattner H, Müller T, Hösl M, Heinen F, Berweck S, Schröder S. Feasibility of Functional Repetitive Neuromuscular Magnetic Stimulation (frNMS) Targeting the Gluteal Muscle in a Child with Cerebral Palsy: A Case Report. *Physical & Occupational Therapy In Pediatrics, 2022.* Doi: 10.1080/01942638.2022.2138732

C) Reviews

2023

Sollmann N, Hoffmann G, Schramm S, Reichert M, Hernandez Petzsche MR, Strobel J, Nigris L, Kloth C, Rosskopf J, **Börner C**, Bonfert MV, Grön G, Müller HP, Kassubek J, Kreiser K, Koerte IK, Liebl H, Beer AJ, Zimmer C, Beer M, Kaczmarz S. Arterial spin labeling (ASL) in neuroradiological diagnostics – methodological overview and use cases. *Accepted in RöFo.*

Szewczyk A, Ulutas S, Aktürk T, Al-Hassany L, **Börner C**, Cernigliaro F, Kodounis M, Lo Cascio S, Mikolajek D, Onan D, Ragaglini C, Ratti S, Rivera-Mancilla E, Tsanoula S, Villino R, Messlinger K, Maassen Van Den Brink A, de Vries T. Prolactin and oxytocin: potential targets for migraine treatment. *Journal of Headache and Pain, 24(1), 2023, 31.* Doi: 10.1186/s10194-023-01557-6

Schramm S, **Börner C**, Reichert M, Baum T, Zimmer C, Heinen F, Bonfert M, Sollmann N. Functional magnetic resonance imaging in migraine: A systematic review. *Cephalalgia, 43 (2), 2023, 1-55.* Doi: 10.1177/03331024221128278

2020

Bonfert M, **Börner C**, Gerstl L, Hannibal I, Mathonia N, Huß K, Rahmsdorf B, Kains C, Klose B, Koenig H, Urban G, Schandelmaier P, Renner T, Albers L, Krieg S, Sollmann N, Heinen F, Landgraf M. Migräne im Kindes- und Jugendalter – Ausblick auf innovative Behandlungsansätze im Rahmen multimodaler Therapiekonzepte. *Themenheft „Versorgungskonzepte für komplex chronisch somatisch kranke Kinder in Deutschland". Bundesgesundheitsblatt; accepted for publication 12.03.2020.*

Börner C, Urban G, Beaulieu LD, Sollmann N, Krieg S, Straube A, Renner T, Schandelmaier P, Lang M, Lechner M, Vill K, Gerstl L, Heinen F, Landgraf M, Bonfert M. The bottom-up approach: Non-invasive peripheral neurostimulation methods to treat migraine: A scoping review from the child neurologist's perspective. *European Journal of Paediatric Neurology, 32, 16-28.* Doi: 10.1016/j.ejpn.2021.02.008

D) Abstracts (Talks/Posters)

2022

Börner C, Zaidenstadt E, Schramm S, Reichert M, Hauser A, Amann A, Frohnmüller M, Lechner M, Krieg S, Heinen F, Landgraf M, Sollmann N, Bonfert M. Neurophysiological mechanisms of neuromodulation via repetitive neuromuscular magnetic stimulation targeting the upper trapezius muscles in migraine patients. *Neurowoche; November 2022, Berlin.*

Börner C, Lang M, Urban G, Staisch J, Hauser A, Amann A, Zaidenstadt E, Frohnmüller M, Hannibal I, Huß K, Klose B, Lechner M, Sollmann N, Landgraf M, Heinen F, Bonfert M. Clinical efficacy of repetitive neuromuscular magnetic stimulation in pediatric episodic migraine. *Neurowoche; November 2022, Berlin.*

Börner C, Lang M, Urban G, Staisch J, Hauser A, Frohnmüller M, Hannibal I, Huß K, Kruse S, Klose B, Lechner M, Sollmann N, Landgraf M, Heinen F, Bonfert M. Effects of repetitive neuromuscular magnetic stimulation targeting the upper trapezius muscles in children and adolescents with episodic migraine. *International Conference of Clinical Neurophysiology (ICCN); September 2022, Geneva.*

Lang M, **Börner C**, Urban G, Staisch J, Hauser A, Frohnmüller M, Hannibal I, Huß K, Kruse S, Klose B, Lechner M, Sollmann N, Landgraf M, Heinen F, Bonfert M. Safety of, adherence to, and satisfaction with repetitive neuromuscular magnetic stimulation in children and adolescents with episodic migraine. *International Conference of Clinical Neurophysiology (ICCN); September 2022, Geneva.*

Börner C, Staisch J, Hauser A, Lang M, Frohnmüller M, Hannibal I, Huß K, Kruse S, Klose B, Lechner M, Sollmann N, Landgraf M, Heinen F, Bonfert M. Effects of repetitive neuromuscular magnetic stimulation targeting to the upper trapezi-us muscles in children with headache disorders. *Congress for Clinical Neuroscience (DGKN); March 2022, Würzburg.*

Staisch J, **Börner C**, Hauser A, Lang M, Frohnmüller M, Hannibal I, Huß K, Kruse S, Klose B, Lechner M, Sollmann N, Landgraf M, Heinen F, Bonfert M. Satisfaction with and safety of repetitive neuromuscular magnetic stimulation in children with headache disorders. *Congress for Clinical Neuroscience (DGKN); March 2022, Würzburg.*

2021

Börner C, Hauser A, Staisch J, Lang M, Göttler C, Wagner J, Heinen F, Bonfert M. Clinical Experiences with Repetitive Neuromuscular Magnetic Stimulation in Children with Posttraumatic Headache: A Retrospective Study. *46th Annual Meeting of the Society for Neuropediatrics; November 2021, Salzburg.*

2020

Bonfert M, Schandelmaier P, Weidlich D, Karampinos D, **Börner C**, Urban G, Koenig H, Landgraf M, Baum T, Heinen F, Sollmann N. Alterations in the upper trapezius muscle in migraine patients assessed by quantitative magnetic resonance imaging using T2 mapping. *European Headache Federation Congress, July 2020, Berlin.*