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Repetitive neuromuscular magnetic stimulation as a novel treatment option in pediatric headache disorders

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List of abbreviations

rNMS	Repetitive neuromuscular magnetic stimulation
mTrP	Myofascial trigger point
UTM	Upper trapezius muscle
FU	Follow-up
TTH	Tension type headache
PTH	Post-traumatic headache
ICHD3	International classification of headache disorder 3rd edition
TCC	Trigemino-cervical complex
CGRP	Calcitonin-gene related peptide
PENS	Percutaneous electrical nerve stimulation
tONS	Transcutaneous occipital nerve stimulation
tSNS	Transcutaneous supraorbital nerve stimulation
tVNS	Transcutaneous vagus nerve stimulation
REN	Remote electrical neuromodulation
PPT	Pressure-pain threshold
KINDL	Revidierter Fragebogen für KINDer und Jugendliche zur Erfassung der gesundheitsbezogenen Lebensqualität
PedMIDAS	Pediatric Migraine Disability Assessment
MRI	Magnetic Resonance Imaging
EMG	Electromyography
TMS	Transcranial magnetic stimulation
fMRI	Functional magnetic resonance imaging

List of publications

Original Articles

2023

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 Using Repetitive Neuromuscular Magnetic Stimulation: A Feasibility Study *Children* 2023, *10*, 1764. Doi:10.3390/children10111764
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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

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Abstracts (Talks/Poster)

2022

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 trapezius 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 reetitive 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.*

1. Contribution to the publications

1.1 Contribution to paper I

Neuromodulation in Pediatric Migraine Using Repetitive Neuromuscular Magnetic Stimulation: A Feasibility Study.

This paper reports the feasibility, safety, and effects of repetitive neuromuscular magnetic stimulation (rNMS) concerning changes in headache and muscular symptoms in pediatric patients affected by migraine. My contribution to this paper comprises my participation in the project preparation, administration, execution, data curation, data analysis, and publication.

The study was conceptualized by my supervisors (Florian Heinen and Michaela Bonfert), Nico Sollmann, and Mirjam Landgraf. The idea was to investigate rNMS in pediatric patients with migraine and muscular involvement in the neck region reflected by the presence of myofascial trigger points (mTrP) in the upper trapezius muscle (UTM). More specifically, we primarily aimed to gain data about the safety, feasibility, and acceptance of this novel migraine treatment modality in a pediatric cohort. Secondarily, clinical effects on the muscular and central level were to be investigated. At the time of study inception, feasibility data and clinical effects had only been reported in two pilot studies including young adults affected by migraine (1-3).

Michaela Bonfert and the medical doctorate student Giada Urban set up the study plan and design and submitted the study protocol to the LMU ethics committee. Together with Michaela Bonfert and Corinna Börner-Schröder, I was responsible for the study administration and project planning.

I prepared the start of the study by setting up meetings to brief all participating parties (physicians, physiotherapists, and psychologists) regarding the study onset. I went through the institution's information system and checked if patients were possible study candidates. To gain the technical experience before the start of the study, I participated in several training sessions to learn the handling of the rNMS device, the handling of the algometer, the documentation of the study visits, and how to identify mTrP previously diagnosed by a physiotherapist.

During the recruitment phase, I attended the weekly outpatient's headache clinic consultations. Together with the responsible pediatricians (Mirjam Landgraf, Iris Hannibal, Kristina Huß) and the physiotherapists (Birgit Klose and Matthias Lechner), I identified potential candidates for study participation. If a possible candidate was considered eligible for study participation, I screened the patients' files for inclusion and exclusion criteria with the help of Corinna Börner-Schröder. The responsible physicians then informed eligible patients regarding the rNMS treatment option and, in case of interest in study participation, the caregiver's and patient's consent was obtained. I created Microsoft Excel data masks for the screening process as well as the inclusion and exclusion criteria and entered data for n=248 screened patients with the help of Corinna Börner-Schröder.

I then contacted eligible patients to hand out a headache diary, in which they would document headache symptoms during a 3-month baseline. Afterwards, I scheduled the treatment appointments consisting of a manual baseline examination of the neck muscles performed by a physiotherapist, six rNMS sessions in the interval of three weeks, and a 3-month follow-up (FU) appointment including another manual examination for every individual participant. With the help of Corinna Börner-Schröder, I conducted all baseline visits, checked baseline questionnaires and headache calendars of each patient for completeness before the first rNMS session. Under

supervision, I performed all n=84 rNMS treatment sessions with the help of the rNMS team (Corinna Börner-Schröder, the doctoral candidates Jacob Staisch and Erik Zaidenstadt, and the neuroscience master student Ari Hauser). Each treatment session included the identification of mTrP and reference points above the UTM and algometry with a handheld analogous algometer above these points. Next, rNMS stimulation of the UTM was performed for 15 min per side, and afterwards algometry was repeated. At the beginning of every single session but especially at the first and the last session, I was responsible for handing out questionnaires to patients and their caregivers to evaluate their satisfaction with treatment. In addition to documenting the rNMS and algometry, we also tracked occurring side effects and adverse events as well as actions taken in case of the occurrence of side effects.

For data analysis, I set up a Microsoft Excel dataset (Microsoft Office Professional Plus 2016, Microsoft, Redmond, WA, USA) including the details of the physiotherapeutical examinations, the rNMS treatment details, possibly occurred side effects and adverse events, adherence and satisfaction of the patients and their caregivers, algometry measurements, as well as the questionnaire data regarding health-related quality of life and migraine disability. In addition, I analyzed the monthly headache symptoms and medication intake and entered them into the data files. Data analysis was done using SPSS (version 26/27; IBM SPSS Statistics for Windows, Armonk, NY, USA) by Corinna Börner-Schröder and myself. We performed the analysis of the primary outcome parameters adherence, satisfaction, and side effects of the rNMS treatment. Moreover, we analyzed the data regarding changes in headache characteristics, muscular symptoms, health related quality of life and migraine related disability after rNMS treatment and interpreted it with the help of Michaela Bonfert, Mirjam Landgraf, Nico Sollmann, and Florian Heinen.

After data analysis, I prepared the manuscript draft for publication, under the supervision of Corinna Börner-Schröder and Michaela Bonfert. Data visualization was done by myself, Corinna Börner-Schröder, Erik Zaidentadt, Jacob Staisch, and Ari Hauser. After all coauthors sent their respective comments and edited the draft, I accordingly revised the manuscript. Subsequently, Corinna Börner-Schröder, Michaela Bonfert, and I prepared the submission and, in case of revision, worked through the reviewers' comments until the final acceptance in *Children (4)*.

In view of equally shared work regarding the study execution, data analysis, manuscript preparation, and publication process, we decided on a shared first authorship with Corinna Börner-Schröder and myself.

1.2 Contribution to paper II

Repetitive neuromuscular magnetic stimulation in children with headache.

While performing the aforementioned feasibility study, our research team worked on setting up rNMS treatments in the course of the multi-modal treatment approach at the outpatient's headache clinic. Thereby, the aim was to also offer rNMS treatment to children and adolescents with headache disorders comprising migraine, tension type headache (TTH), or post-traumatic headache (PTH), beyond the strict inclusion criteria of the prospective feasibility study.

Together with the physicians and physiotherapists, Jacob Staisch, Corinna Börner-Schröder, and I evaluated which patients of the outpatient's clinic could profit from rNMS within their multi-modal treatment. Possible diagnoses for the treatment modality were migraine, TTH, headache of mixed type (migraine plus TTH), or subacute (defined as >3 weeks post-injury) or persistent (defined as >8 weeks post-injury) PTH. The identified patients were informed and offered rNMS treatment by the responsible physicians. If patients and caregivers gave consent to the rNMS treatment, Jacob Staisch, Corinna Börner-Schröder, and I scheduled six rNMS sessions for every patient. Together with Ari Hauser, we performed all treatment sessions including the rNMS stimulation (with the protocol used in the feasibility study) as well as algometry measurements, documentation of side effects and adverse events, and the administration of questionnaires regarding satisfaction with the treatment. Treatments were supervised by Michaela Bonfert, Mirjam Landgraf and Florian Heinen. Three months after rNMS treatment, a FU visit was planned for every patient. For some of the patients, we scheduled a second rNMS treatment due to good response.

After performing 25 rNMS treatments in children and adolescents with primary headache disorders, the team decided to perform a retrospective analysis of the feasibility and effects of the rNMS treatments in the clinical cohort. Florian Heinen, Michaela Bonfert, Mirjam Landgraf, Corinna Börner-Schröder, and Jacob Staisch conceptualized the project. After ethical approval, data entry was done by Jacob Staisch, Ari Hauser, Corinna Börner-Schröder, and myself. Moreover, I participated in the data analysis and its interpretation. We collected and analyzed data regarding patients' characteristics, headache characteristics, technical stimulation details, feasibility, and adverse events of the treatment, as well as satisfaction with rNMS. The manuscript draft was conceptualized and written by Jacob Staisch, Ari Hauser, Corinna Börner-Schröder, and Michaela Bonfert. I decisively participated in reviewing and editing the manuscript. Together with the other coauthors, I approved the final manuscript before final acceptance and publication in the *European Journal of Pediatric Neurology* (5).

2. Introductory summary

2.1 General introduction

Within the frame of this doctoral thesis, I addressed repetitive neuromuscular magnetic stimulation (rNMS) as a form of neuromodulatory treatment in children and adolescents with headache disorders, which are common neurological disorders in the pediatric population (6, 7). Among the primary headache disorders, TTH has the greatest prevalence in school aged children and adolescents, followed by migraine (8, 9). Another notable disabling headache disorder is defined by the persistence of headache after traumatic brain injury, known as posttraumatic headache (PTH), with a prevalence in the pediatric population ranging from 6.8% to 70% 3 months after a mild traumatic brain injury (10, 11).

As promising data concerning the feasibility, acceptance, and satisfaction already exist for young adults affected by migraine receiving rNMS, our motivation was to collect data about the application of rNMS in children and adolescents to pave the way for rNMS as an established treatment modality in pediatric neurology (1, 3). The main part of this dissertation was the realization of a prospective clinical study for pediatric patients with episodic migraine, which is why I will focus on migraine in the following introduction and to the methods and findings of the respective prospective study in the next paragraphs.

2.2 Migraine epidemiology and diagnosis

The Global Burden of Disease Study declares migraine as one of the most prevalent neurological disorders, with more than one billion people suffering worldwide (6, 12). It is one of the most common headache syndromes in children, with a prevalence of verified migraine in children and adolescents of about 10-20%. The prevalence increases continuously during childhood and adolescence and comes along with a high risk of chronification as well as a high burden of disease. The impact on the children's quality of life, their education, socialization, and family life is significant (8, 13-19). Patients do not only experience the acute pain sensation of migraine attacks but also the direct and indirect psychological and social burden originating from migraine. Despite this high impact on the children's lives, pediatric migraine remains underdiagnosed and insufficiently treated (8, 14, 16).

Migraine can be divided in two important subtypes: migraine *without* aura, which describes a headache syndrome with specific attendant symptoms, and migraine *with* aura, additionally characterized by specific neurological symptoms preceding the headache (13, 20). The diagnostic criteria for migraine are depicted in the international classification of headache disorders version 3 (ICHD 3) (20). In general, it is defined as a recurrent headache disorder manifesting in attacks lasting 4-72h. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or symptoms of hyperexcitability for stimuli like light (photophobia), noise (phonophobia), or odors (osmophobia). At least five attacks fulfilling the typical criteria need to be experienced. When diagnosing migraine *with* aura, at least two attacks of unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are usually followed by a migraine headache and associated migraine symptoms need to be experienced (20).

In children and adolescents, migraine occurring without aura is more frequent. Only 10-20% of pediatric migraine patients experience aura symptoms. The most common symptoms are visual disturbances, followed by sensory symptoms, speech deficits, or motor deficits. Migraine attacks tend to be shorter than in adults, with a duration from 2-72h, and an intensity often milder than adults' migraine. Autonomic symptoms are often seen in pediatric migraine patients, such as nausea, vomiting, or abdominal pain (8, 13, 14, 21-23). Moreover, pediatric migraine can be associated with various comorbidities, such as psychiatric disorders. Depression, epilepsy, anxiety, panic disorders, or specific phobias can come along with migraine. Also, sleep disorders can occur alongside the headache disorder, which poses one of the most frequent headache trigger factors (13, 17, 22, 24).

2.3 Migraine pathophysiology and the role of a muscular involvement

The pathophysiology of migraine is complex and more and more depicted as a functional state of the brain ("migraine is a brain state") with a higher susceptibility for stimuli and therefore a lower threshold of perception – during the attack as well as in-between attacks. So-called *migraine generators* give the rhythm for this undulating level of susceptibility. The lower the threshold, the easier stimuli can trigger migraine attacks (25-31).

Furthermore, a peripheral aspect needs to be considered. Here, the trigemino-cervical complex (TCC) has a major role, which conceptualizes the connection between central and peripheral pathways playing together in migraine pathogenesis. The TCC suggests that the convergence of cervical and dural nociceptive input in the brainstem influences meningeal nociception and affects the peripheral sensitization of the trigemino-cervical neurons. This ascending information is forwarded to specific areas in the brainstem and diencephalon and therefore gets involved in the processing of pain and sensory information up to the sensorimotor cortex (28, 32, 33).

Against this background, the neck region received more attention in research in the recent years as pain in this region is more frequent in migraine patients than in healthy controls. In the course of epidemiological studies, an association between migraine and pain in the neck region was shown (2, 28, 34). 25% of patients suffer from neck pain during a migraine attack, 7% in the prodromal phase (35, 36). In the pediatric population as well, neck pain is often associated with migraine (30). Especially the muscles afferently innervated by C1-3 are affected, such as the Musculi trapezii, Musculi splenii, and Musculi semispinales capitis, which underlines the concept of the TCC (14). Moreover, migraine patients showed a reduced cervical movement and increased mechanical hyperalgesia in clinical trials. These findings were independent from the presence of concomitant neck pain but were correlated with headache duration and headache related disability (37). Thus, the treatment of the involved musculature in patients with migraine gains importance (38, 39).

Furthermore, mTrP are often found in the muscles of patients with migraine (40-42). A mTrP is a spot of tenderness in a skeletal muscle localized in a taut, palpable band. It presents itself as a hypersensitive spot that can mediate a local twitch response when adequately stimulated and cause referred sensation or pain, referred tenderness, motor dysfunction, and autonomic phenomena during palpation (40, 41, 43). It is defined by presenting at least two of the three criteria (1) taut band, (2) hypersensitive spot and (3) referred sensation (44). A mTrP can be categorized as latent if all previously mentioned diagnostic criteria are met, or as an active mTrP, if manual palpation additionally causes the patient's known headache pain (44). The presence of

mTrPs further reflects the above-mentioned muscular involvement in migraine. Considering the often-occurring subjective complaints and the results of the physiotherapeutic examination, targeting the neck musculature to mediate migraine pain sensations from bottom-up is a promising approach (36, 40).

2.4 Therapeutic options in pediatric migraine

Migraine as a complex and impairing neurological disease urges a multimodal therapeutic concept, starting with the education about the disease including for instance the identification of potential trigger factors (e.g., irregular sleep, inappropriate hydration, or stress), acute pain control and, if necessary, preventive treatment (13, 45-47).

Acute treatment options include non-steroidal analgesics given in the early headache phase, such as ibuprofen or paracetamol, and the use of antiemetic drugs, if needed (23, 48). For moderate to severe attacks, migraine-specific medication like triptans should be considered, potentially in combination with long-lasting analgesics as naproxen and a corresponding antiemetic, if needed (13, 14, 23, 47, 49).

Despite the considerable number of pharmacological options to treat acute migraine attacks, the evidence base for prophylactic treatment to reduce the headache frequency is limited, especially regarding pediatric patients (13, 25, 50, 51). In the pediatric setting, most commonly magnesium is recommended, as it has no to only a few side effects. Aside from that, one can consider propranolol as pharmacoprophylaxis in the case of high level of suffering caused by high frequency and/or severe migraine symptoms that lead to restricted participation (45, 48).

However, it must be taken into account that the use of beta blockers like propranolol is contraindicated in some conditions such as diabetes, bronchial asthma, or atrioventricular block and these conditions are not infrequent in the pediatric population. Additionally, the interference with physical activity must be considered in athletic patients (9, 52). For several other prophylactic drugs (e.g. topiramate, valproate, amitriptyline), relevant side effects or contraindications must be considered, and currently only propranolol is approved for the pediatric use. (9, 14, 50, 53).

New groups of medication like calcitonin-gene related peptide (CGRP) antibodies (Eptinezumab, Fremanezumab, Galcanezumab) and CGRP receptor antibodies (Erenumab) exist (54). These substances are subcutaneously or intravenously administered in intervals of several weeks to months and are superior to placebo in prophylactic therapy of episodic migraine in adult patients. So far, data is still missing for the pediatric population, which is why there is no approval for admission in children and adolescents yet (48, 55). Altogether, it is of increasing importance to evaluate the benefits and side effects of the novel migraine-specific drugs in the pediatric age group, but also the surging non-pharmacological modalities for headache treatment (14, 17, 49).

2.5 Neuromodulation and rNMS

Due to the limiting safety profiles of pharmacological treatment options in the pediatric cohort, there is an increasing demand to develop non-pharmacological, non-invasive methods to complement the multimodal treatment approach of migraine in children and adolescents (14, 17, 49). In that respect, new neuromodulatory techniques may become relevant options for the pediatric population. The term neuromodulation covers techniques to activate, regress, or modulate actions of the peripheral or central nervous system. Neurostimulation is a

neuromodulatory subtype that aims to modulate central and peripheral pain pathways. The peripheral neurostimulation is performed by several invasive or non-invasive devices that electrically or magnetically stimulate the peripheral nervous system (56, 57). Neuromodulation shows a range of promising options, although data of high-quality clinical trials with larger study populations are currently still missing (1, 3, 14, 56, 58, 59).

Besides invasive methods like percutaneous electrical nerve stimulation (PENS), during which needles are inserted in the skin for electrical stimulation, there are several non-invasive approaches to reach a beneficial effect on headache symptoms (56, 57, 59): on the one hand, these include approaches that directly target a specific nerve with electrical stimulation, like transcutaneous occipital nerve stimulation (tONS), transcutaneous supraorbital nerve stimulation (tSNS), or transcutaneous vagus nerve stimulation (tVNS) (58, 60-62). On the other hand, approaches have been applied, in which the electrical stimulation does not act directly on a nerve. Remote electrical neuromodulation (REN) has been applied as acute treatment of migraine attacks by electrical stimulation of the skin afferents that stimulate the pain inhibitory centers. This takes advantage of the analgetic effect of electrical stimulation by 'opening' or 'closing' a gate for pain signal transmission in the brain depending on the activation of neural fibers ('Gate control theory of pain') (58, 63-65).

Next to electrical stimulation, a novel and unique approach is rNMS targeting the muscular component and simultaneously affecting/modulating the central mechanisms. It is the only technique so far targeting both, the central and the muscular migraine mechanisms in the frame of a bottom-up process (14, 58). The concept of rNMS is based on a magnetic coil located directly above the target muscle and its provoked stimulation. This stimulation leads to a painless electric current in the respective body region (66). As a result, motor and afferent nerves depolarize and lead to a muscular contraction via the stimulated 2nd order motor neurons. Additionally, muscle spindles and mechanoreceptors of the muscular tendon unit, the joints, and the skin get activated by the muscle contraction. Terminal sensory nerve fibers of the joint capsules, ligaments, and skin directly get activated as well, which leads to the effect of a higher proprioceptive input to the central nervous system (67, 68). It is hypothesized that this increased inflow can modulate sensorimotor integration and stimulate pain processing pathways (69-71).

The application of rNMS has been reported to be safe, well-tolerated, and well-accepted in two pilot trials with adults affected by migraine (1-3). These previous studies showed high acceptance and promising results, which imply that rNMS could alleviate muscular sensitivity at the stimulated area as well as headache symptoms within the context of the TCC, encouraging us to make this new therapeutic aspect accessible for children and adolescents (2, 3, 72). Moreover, data is missing especially for the pediatric population even though rNMS may have several aspects facilitating the usage in particular for children and adolescents, such as painless application, or the fact that patients can stay dressed while treated. In that respect, the peripheral neuromodulation can be considered as a promising therapeutic method, especially rNMS (4, 5, 73).

2.6 rNMS setup

In the light of the promising results of rNMS in previous investigations, the rNMS intervention at the pediatric outpatient headache clinic was set up. The treatment was applied using an eMFieldPro system (Zimmer Medizinsysteme GmbH, Neu-Ulm, Germany, CE Nr 0123). This system includes a round coil (copper winding with a diameter of 7.6 cm) that generates a

maximum magnetic field of 2.5 T for stimulation. During treatment, the patient laid on a physical examination bench, which was adjusted to a comfortable, relaxing position. The coil was held above the to be treated area of the UTM, that was stimulated on each side for 15 min (20 Hz frequency, 7s ON-time, and 10 s OFF-time) with an intensity that was adjusted on an individual level. Specifically, the intensity was increased so that a muscle contraction was visible, but the intensity was still rated comfortable by the patient on a visual rating scale. The UTM of both sides were stimulated consecutively in each session, alternating the starting side with every session.

To assess the safety of the treatment, questionnaires about eventual occurring side effects or adverse events were performed at every session. For the assessment of headache symptoms, questionnaires were used to evaluate frequency, duration, intensity of headache, and medication intake. To quantify the muscular component of the effects, algometry using a hand-held analogous algometer (Wagner Instrument, Greenwich, CT, USA) was performed to determine the pressure pain threshold (PPT) above the whole musculature of the UTM as well as eventual mTrP. To evaluate changes in the whole musculature, two reference points on each side were determined as 1/3 and 2/3 of the distance from the vertebra C7 to the acromion above the left and right UTM.

In the frame of the prospective study, questionnaires concerning lifestyle changes, quality of life (KINDL questionnaire (74)) and migraine related disability (PedMIDAS questionnaire (75)) were processed at the baseline and the FU sessions. Headache characteristics, headache related symptoms, and medication intake were precisely recorded using a headache calendar during the study participation (76). Additionally, physiotherapeutic examinations valuated the presence and evolution of mTrP in the UTM.

2.7 Results

After screening n=248 patients for the prospective study investigating the application of rNMS in children and adolescents with episodic migraine, 20 patients fulfilled all inclusion criteria (8.1%) and completed the baseline period. Due to six dropouts after the baseline period (2.4%), a cohort of n=13 patients with a mean age of 12.2±3.5 years and 92.3% females completed the study protocol. In this trial, rNMS has been reported as safe and feasible with 82.1% of the sessions completed without reported side effects. In the remaining 17.9% of the sessions, side effects occurred, e.g., trembling, tingling, or muscle sore, none of which led to interruption or cessation of the treatment. The adherence rate was 100%. Concerning satisfaction, all subjects and caregivers would recommend the treatment to other migraine patients. 100% of the subjects and 76.9% of the caregivers would repeat the rNMS intervention, three caregivers would not repeat it due to insufficient improvement of their child's headache. In the retrospective analysis of children and adolescents with primary headache disorders treated with rNMS outside of the prospective trial, the number of occurred side effects was comparable (in 22% of the sessions) and satisfaction with the rNMS treatment was confirmed (96.2% of the patients would recommend the treatment) (5).

Muscular examination in the subjects of the prospective trial showed a significant increase of the mean PTT above the UTM of both sides (left UTM: p=0.016, right UTM: p=0.037). The comparison of PPT values after the first and after the sixth treatment did significantly change above the reference points, but not above the TrP (left lateral: pre=2.09 (±0.84), post=3.27 (±2.00), p=0.025; left medial: pre=2.16 (±0.93), post=3.23 (±1.86), p=0.047; right medial: pre=1.98 (±0.79), post=2.99 (±1.67), p=0.046; right lateral: pre=1.97 (±1.12), post=3.31 (±2.02), p=0.013; right TrP:

pre=2.04 (±.73), post=3.18 (±2.18), p=0.073; left TrP: pre=2.03 (±0.72), post=3.52 (±2.33), p=0.052)) (4). The muscular effect in terms of increasing PPT levels above the UTM was confirmed in the retrospective analysis by significantly increased values above all reference points (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: $p<0.001$, $\eta^2=0.311$) (73).

In the analysis of headache characteristics in the cohort of the prospective trial, headache frequency showed a decreasing statistical trend with a numerical decrease of 2.53 days per month from baseline (9.43±5.86 days per month) to FU (6.90±4.53 days per month, t=−1.848, p=0.089). In congruence, a statistically non-significant decreasing trend in medication frequency was registered (from 4.42±2.58 days per month at baseline to 2.73±2.10 days per month at FU (t=1.94, p=0.081))(4). These findings were underlined by the statistically significant reduction of the headache frequency of 6.2 days per month (17.08±11.44 days per month at baseline to 10.88±10.94 at FU; Z=− 2.39; p=0.017) in the retrospective analysis (5).

On the individual level, we could categorize 7 patients as responders with a relative reduction of headache frequency of ≥25%, of which 3 patients showed ≥50%, and 2 patients ≥75% reduction of headache frequency after rNMS treatment. No relevant changes had been shown in headache intensity and duration (4). The retrospective analysis showed comparable findings with 11 patients (44%) categorized as responders with ≥25% relative reduction of headache frequency (5).

The investigation of headache related disability by comparison of PedMIDAS scores before intervention (35.00±23.84) and at FU (20.67±16.83) showed a transition from an average moderate to mild disability level in the course of the study participation (Z=-1.93, p=0.055). Considered at the individual level, three patients experienced “severe” disability, one patient “moderate” disability, and eight patients “mild” disability at baseline. Regarding the transition during the study period, two patients turned to a more severe category, whereas five turned to less severe categories, with one patient even dropping from “severe” to “little to none” disability. Five patients did not change their respective category (4).

By evaluating the health-related quality of life, no significant changes were detected neither in the patients’ questionnaire (baseline=65.23±19.02, FU=67.08±18.04, p=0.675), nor in those answered by the caregivers (baseline=67.27±11.99, FU=69.44±9.64, p=0.320) (4).

2.8 Discussion and future directions

The prospective study performed in the frame of this work investigated rNMS as a non-pharmacological, non-invasive intervention in a cohort of pediatric patients affected by episodic migraine with muscular involvement. It is the first ever prospective clinical trial in children and adolescents with episodic migraine assessing the feasibility of, adherence to, and satisfaction with rNMS. Additionally, headache related symptoms were prospectively investigated for the first time, not only focusing on changes in headache characteristic or muscular impairment, but also assessing burden of migraine and quality of life.

The results show the safety, feasibility, and acceptance of rNMS above the UTM in children and adolescents with migraine (100% adherence rate, no side effects in 82.1% of the sessions and 100% of the patients would repeat and recommend rNMS). The relief in headache symptoms reported by the numerical decrease of headache frequency and medication intake in combination with the number of seven patients (54%) that were qualified as responders experiencing a relief

of at least 25% of headache frequency is significant and in line with the results of the studies involving adult patients (1-4). The same applies to the results of algometry of the UTM pre- and post-intervention, that demonstrated an increase in PTT, reflecting an alleviating effect of the rNMS treatment in muscular hypersensitivity (1, 4). The persistence of this effect until the 3-month FU may indicate that the relieving effect of rNMS on the muscular level can be maintained over a period of time.

The investigation of headache related disability showed a significant reduction in PedMIDAS scores, underlining a beneficial impact of rNMS on the burden of migraine, and being consistent with the significantly improved MIDAS scores in the adult trial (2, 3). These first-time results are clinically meaningful with regard to reduced participation caused by school absenteeism or avoidance of social or physical activities due to migraine symptoms. Regarding the KINDL scores, no reduction was observed during the study. However, it should be considered that baseline KINDL scores were similar to reference values of healthy children, so ceiling effects may have made detection of further improvement difficult (77).

Against the background of the strict inclusion criteria and study protocol, the retrospective analysis gave us the chance to gain mixed cohort clinical data for the pediatric population with other primary headache disorders. The feasibility, safety, and satisfaction of rNMS was confirmed (85.2% adherence rate, no side effects in 78% of the sessions, and 88.5% of patients would repeat rNMS). The lower adherence rate could be explained by different levels of disease burden caused by the different primary headache diseases that were treated, and the resulting differing motivation to repeat the intervention. The alleviating effects of rNMS concerning headache related symptoms were underlined by the statistically significant reduction in headache frequency (numerical reduction of 6.2 days per month) and the comparable responder rate (11 patients categorized as responders) in this analysis. Moreover, the significant increase of PPT above the UTM, implicating the assumed alleviation of muscular impairment, was confirmed (5, 73).

In the process of working with the current data, some limitations were noticed. The small sample size in the prospective study and the non-sham-controlled study design may limit the validity of the findings. As the placebo effect might be increased in the pediatric field, the findings could have been influenced in this way (45, 78). The whole period of rNMS application was during the COVID-19 pandemic. The resulting drastic changes in the children`s daily life might also have influenced their headache symptoms.

The reported changes in headache characteristics and headache related disability together with the potential to alleviate muscular symptoms, are indicative for further investigations in this field and we are empowered to investigate more and to lance further studies concerning the novel treatment method.

We constantly reevaluated the important factors for further prospective trials to counter the afore mentioned limitations. Therefore, we set up a larger study with adult patients affected by high frequent migraine and healthy controls with more than 200 planned subjects (MagMig study, DRKS00024470). The aim is to quantify the muscular and central effects of rNMS in a sham-controlled setting and to evaluate the mechanisms of action of rNMS. Muscular effects are evaluated among others using ultrasound and magnetic resonance tomography (MRT) of the shoulder neck region. For central effects, transcranial magnetic stimulation (TMS), and functional magnetic resonance imaging (fMRI) are among others performed. Until now, I was involved in study planning, conceptualization, set up of ethical approval and study documents.

3. Zusammenfassung (Deutsch)

Die Neuromodulation mittels rNMS ist ein vielversprechender Therapieansatz bei Kopfschmerzerkrankungen (3-5, 14, 56). Neben dem Spannungskopfschmerz und dem Posttraumatischen Kopfschmerz, ist vor allem die Migräne ein häufiges Kopfschmerzsyndrom, das bei pädiatrischen PatientInnen mit einer hohen Prävalenz einhergeht. Insbesondere für Kinder und Jugendliche werden nicht-pharmakologische, nicht-invasive prophylaktische Behandlungen dringend benötigt (8-10, 14).

Die rNMS wurde bereits in Vorarbeiten bei erwachsenen MigränepatientInnen mit mTrP im Schulter-Nacken-Bereich eingesetzt und erfolgversprechende Ergebnisse bezüglich der Kopfschmerzsymptomatik sowie der muskulären Komponente erzielt (1, 3). Um den Weg zur Implementierung dieser nicht-invasiven Therapiemethode auch im pädiatrischen Kollektiv zu ebnen, wurde eine prospektive Studie sowie eine retrospektive Datenanalyse zur Anwendung der rNMS bei Kindern und Jugendlichen mit primären Kopfschmerzerkrankungen durchgeführt (4, 5).

Im Rahmen dieser Dissertationsarbeit wurden Publikationen zur Anwendung von rNMS an der Schulter- und Nackenmuskulatur bei Kindern und Jugendlichen mit episodischer Migräne und mTrP im M. trapezius, sowie bei pädiatrischen PatientInnen mit Migräne, Spannungskopfschmerz und posttraumatischem Kopfschmerz veröffentlicht. Es wurden die Durchführbarkeit, Verträglichkeit, Akzeptanz sowie die klinischen Effekte der rNMS bezogen auf die Kopfschmerzsymptomatik und auf muskulärer Ebene untersucht (4, 5, 73).

Für die prospektive Studie wurden 14 PatientInnen in jeweils sechs rNMS-Sitzungen behandelt, was in einer Gesamtzahl von 84 rNMS-Sitzungen resultierte. Um die Adhärenzrate und die Durchführbarkeit der rNMS zu evaluieren, wurden standardisierte Fragebögen genutzt, die die Zufriedenheit und Verträglichkeit der PatientInnen und ihrer Sorgeberechtigten sowie die Nebenwirkungen während der Intervention erfassen. Kopfschmerzhäufigkeit und -intensität sowie Medikamenteneinnahme wurden mit Hilfe eines Kopfschmerzkalenders der deutschen Gesellschaft für Migräne- und Kopfschmerzerkrankungen erfasst. Muskuläre Effekte wurden mittels physiotherapeutischer Untersuchung und Algometrie am Trapeziusmuskel evaluiert. Zur Beurteilung der Migräne assoziierten Einschränkungen und der Lebensqualität wurden entsprechende Fragebögen ausgefüllt. Es konnte die Akzeptanz, Machbarkeit und Sicherheit der rNMS in der untersuchten Kohorte nachgewiesen werden. Außerdem zeigten sich vielversprechende Ergebnisse hinsichtlich einer reduzierten Kopfschmerzhäufigkeit, Medikamenteneinnahme, reduzierter muskulärer Überempfindlichkeit und Beeinträchtigung durch die Kopfschmerzerkrankung im Alltag (4).

Die retrospektive Analyse erzielte ähnliche Ergebnisse hinsichtlich der Akzeptanz, Sicherheit und Verträglichkeit der Therapiemethode. Auch hier wurden vielversprechende Ergebnisse hinsichtlich der zentralen sowie muskulären Effekte erzielt (5, 73).

Zusammenfassend scheint rNMS als neuro-modulatorischer Ansatz bei pädiatrischer Migräne und anderen Kopfschmerzerkrankungen eine praktikable, gut verträgliche und gut akzeptierte Behandlungsmethode zu sein. Der klinische Effekt von rNMS als pädiatrische Behandlungsmethode ist in zukünftigen, sham-kontrollierten und größer angelegten Studien weitergehend zu bewerten.

4. Abstract

Neuromodulation using rNMS is a promising therapeutic approach for headache disorders (3-5, 14, 56). Besides tension-type headache and post-traumatic headache, migraine in particular is a common headache syndrome that is associated with a high prevalence in pediatric patients. Non-pharmacological, non-invasive prophylactic treatments are urgently needed, especially for children and adolescents (8, 10, 14).

rNMS has already been applied in preliminary studies in adult migraine patients with mTrP in the shoulder-neck area and promising results have been achieved with regard to headache symptoms and the muscular component (1, 3). In order to pave the way for the implementation of this non-invasive therapeutic modality in the pediatric population, a prospective study and a retrospective data analysis regarding the use of rNMS in children and adolescents with primary headache disorders were conducted (4, 5).

This dissertation included publications regarding the use of rNMS targeting the shoulder and neck muscles in children and adolescents with episodic migraine and mTrP in the trapezius muscle, as well as in pediatric patients with migraine, tension-type headache and post-traumatic headache. The feasibility, tolerability, acceptance, and clinical effects of rNMS in relation to headache symptoms and at the muscular level were investigated (4, 5, 73).

For the prospective study, 14 patients were treated in six rNMS sessions, resulting in a total number of 84 rNMS sessions. To evaluate the adherence rate and feasibility of rNMS, standardized questionnaires were used to record the satisfaction and tolerability of the patients and their caregivers as well as the side effects during the intervention. Headache frequency, intensity and medication intake were recorded using a headache calendar from the German Society for Migraine and Headache Disorders. Muscular effects were evaluated by means of physiotherapeutic examination and algometry on the trapezius muscle. Questionnaires were completed to assess migraine-associated disability and quality of life. The acceptance, feasibility, and safety of rNMS was demonstrated. In addition, promising results were shown with regard to reduced headache frequency, medication use, reduced muscular hypersensitivity, and impairment in everyday life due to the headache disorder (4).

The retrospective analysis achieved similar results with regard to the acceptance, safety, and tolerability of the therapeutic approach. Promising results were also achieved in the present analysis with regard to the central and muscular effects (5, 73).

In summary, rNMS as a neuromodulatory treatment method for pediatric migraine and other headache disorders appears to be a practicable, well-tolerated, and well-accepted approach. The clinical effects of rNMS as a pediatric treatment method needs to be further evaluated in future, sham-controlled and larger-scale studies.

5. Paper I

children

MDPI

Communication

Neuromodulation in Pediatric Migraine Using Repetitive Neuromuscular Magnetic Stimulation: A Feasibility Study

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Abstract: Migraine has a relevant impact on pediatric health. Non-pharmacological modalities for its management are urgently needed. This study assessed the safety, feasibility, acceptance, and efficacy of repetitive neuromuscular magnetic stimulation (rNMS) in pediatric migraine. A total of 13 patients with migraine, ≥6 headache days during baseline, and ≥1 myofascial trigger point in the upper trapezius muscles (UTM) received six rNMS sessions within 3 weeks. Headache frequency, intensity, and medication intake were monitored using headache calendars; headache-related impairment and quality of life were measured using PedMIDAS and KINDL questionnaires. Muscular involvement was assessed using pressure pain thresholds (PPT). Adherence yielded 100%. In 82% of all rNMS sessions, no side effects occurred. All participants would recommend rNMS and would repeat it. Headache frequency, medication intake, and PedMIDAS scores decreased from baseline to follow-up (FU), trending towards statistical significance ($p = 0.089$; $p = 0.081$, $p = 0.055$). A total of 7 patients were classified as responders, with a ≥25% relative reduction in headache frequency. PPT above the UTM significantly increased from pre- to post-assessment, which sustained until FU ($p = 0.015$ and 0.026, respectively). rNMS was safe, feasible, well-accepted, and beneficial on the muscular level. The potential to reduce headache-related symptoms together with PPT changes of the targeted UTM may underscore the interplay of peripheral and central mechanisms conceptualized within the trigemino-cervical complex.

Keywords: primary headache; responder rate; neurostimulation; pain pressure threshold; myofascial trigger point

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1. Introduction

Migraine was one of the most prevalent neurological disorders worldwide in 2019 [1]. In children and adolescents, headache disorders are common and frequently associated with a high burden of disease as well [2–4]. Its negative impact on a child's quality of life, participation in school, sports or leisure time activities, and family life is very high [5,6]. Currently, a multi-modal interdisciplinary approach combining education, lifestyle management, behavioral therapy, and physiotherapy is recommended for children

and adolescents affected by migraine [7–13]. Efficient pharmacological treatments for acute migraine attacks are available, whereas pharmaco-prophylaxis plays a secondary role in pediatric patients due to low evidence levels, oftentimes insufficient efficacy, and the risk of side effects [5,14–16]. Whether CGRP antibodies could represent an effective option in the future is currently being evaluated in a randomized clinical trial (https://clinicaltrials.gov/study/NCT03832998 accessed on 20 October 2023). However, data have not yet been published and will only refer to patients affected by chronic migraine. Hence, there is an increasing demand to develop non-pharmacological, non-invasive options as an addition to the contemporary multi-modal approach to pediatric migraine.

Concerning migraine pathophysiology, the trigemino-cervical complex (TCC) plays a major role [17–19], which describes the convergence of central and peripheral mechanisms of pain perception, processing, perpetuation, and sensitization [17]. Within this concept, reports of neck pain as well as findings during manual palpation of the neck and upper trapezius muscles (UTMs, e.g., myofascial trigger points (mTrP) [20–30]) can be interpreted as evidence for muscular involvement in patients with migraine [31,32].

The application of repetitive neuromuscular magnetic stimulation (rNMS) targeting the UTMs has been reported to be a safe and well-tolerated treatment option in adults affected by migraine, with encouraging results regarding the decrease in muscular hyperalgesia and headache symptoms [33–35]. Similar effects were described in an observational analysis among children and adolescents with headache disorders receiving rNMS in a tertiary outpatient headache center [36,37]. Through painless personalized electromagnetic induction, rNMS provokes an electric current in the stimulated body region [38]. This depolarizes motor and afferent nerves causing, among other effects, the muscle to contract. The resulting increased proprioceptive inflow to the central nervous system is hypothesized to modulate sensorimotor integration and pain processing pathways [15,38–42].

This study was designed to investigate the feasibility of the rNMS intervention in a cohort of children and adolescents affected by migraine by assessing the adherence to, safety of, and satisfaction with the treatment in a prospective design for the first time. In addition, the following clinical endpoints were preliminarily evaluated: changes in headache-related symptoms, including the burden of migraine and in quality of life, as well as the immediate local muscular effects of rNMS in terms of changes in pressure pain thresholds (PPT) above the UTMs.

2. Materials and Methods

2.1. Ethics and Study Enrollment

This study was approved by the institutional review board (vote 20-194) and registered in the German Clinical Trials Register (DRKS00022141). It was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and their legal guardians.

2.2. Subjects

Participants were recruited via the outpatient headache center of our university's children's hospital. Inclusion criteria were (1) age 6 to 17 years, (2) a diagnosis of migraine according to the International Classification of Headache Disorders (ICHD 3rd edition) [43], (3) at least six headache days within a 90-day baseline assessment period, and (4) at least one mTrP in one of the UTMs. Regarding mTrP identification, the three standard criteria defining mTrP were carefully checked: (1) a palpable taut band with (2) hypersensitive spots and (3) a referred sensation/pain during manual palpation [22,44]. Exclusion criteria were (1) a diagnosis of familial hemiplegic migraine, (2) any pharmacological migraine prophylaxis except magnesium, (3) any other neurological/psychiatric disorders besides headaches, (4) any serious disease, and (5) contraindications for magnetic stimulation. As mixed-type headache (coexistence of migraine and TTH) is common in children and adolescents, a TTH component was not an exclusion criterion for study participation.

2.3. Prospective Study Design and rNMS Intervention

Enrollment took place consecutively between August 2020 and October 2021, with the last follow-up examination (FU) taking place in January 2022. During a 90-day baseline period, participants recorded the headache frequency and characteristics using a standardized headache calendar [45]. Subsequently, participants entered a 3-week intervention period consisting of 6 rNMS sessions targeting the UTM bilaterally with an eMFieldPro system (Zimmer Medizinsysteme GmbH, Neu-Ulm, Germany, CE Nr 0123). This study used the rNMS method described in the study of Staisch et al. (2022) and may partly reproduce the wording [36] (15 min, 20 Hz, 7 s ON time, 10 s OFF time; Figure 1). After the intervention, a 90-day FU period took place during in which subjects continued using their headache calendar.

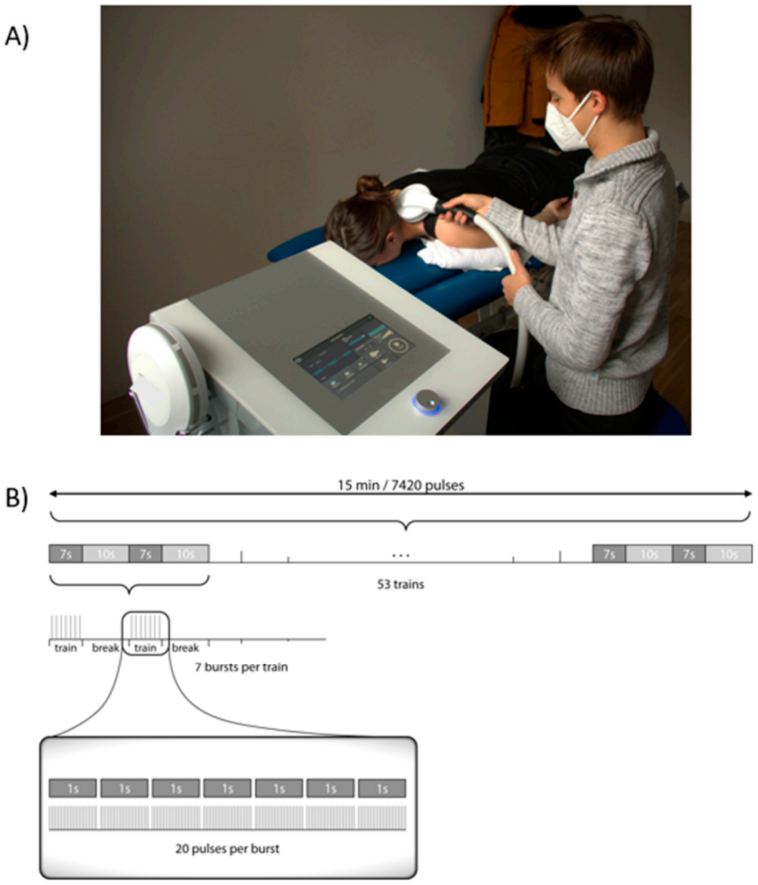

Figure 1. Clinical setup of rNMS treatment. (**A**) rNMS setting and coil positioning. (**B**) Stimulation protocol used for the rNMS treatments. Since 53 trains could not be visualized individually, which is why the repetition of trains is marked with [. . .]. Abbreviation: rNMS = repetitive neuromuscular magnetic stimulation.

2.4. Outcome Measures

This study used similar assessments as described in the study of Staisch et al. (2022) [36] and Börner et al. (2022) [37] and may partly reproduce the wording. Adherence: Adherence was defined as completing at least 5 of the 6 sessions of the rNMS intervention. If sessions were canceled, the reasons were asked for. Safety: A customized standardized questionnaire was used to assess any adverse events (AE) during or after stimulation. Satisfaction: After the intervention, patients and caregivers gave feedback on whether they would like to repeat or recommend rNMS using a customized standardized questionnaire. Clinical outcomes: During the whole course of the study, patients monitored headache symptoms using the headache calendar of the German Migraine and Headache Society [45]. Before the intervention and at FU 90 days after the intervention, headache-related impairment and quality of life were evaluated using the Pediatric Migraine Disability Assessment (PedMIDAS) [46] and a German generic quality of life instrument for patients and caregivers (KINDL questionnaire) [47]. Concurrently, subjects were asked to report life events having occurred during study participation. To identify mTrP in the UTM, a certified physiotherapist examined all participants using manual palpation at the time of screening, before and after the intervention, as well as during the FU exam 90 days after the intervention. In addition to mTrP assessments, reference points were defined as 1/3 and 2/3 of the distance from the vertebra C7 to the acromion above the left and right UTM to allow the investigation of changes in the whole musculature. Before and after each rNMS session as well as at FU examination 90 days after the intervention, PPT above each mTrP and all reference points were determined using algometry (Wagner Instrument, Greenwich, CT, USA). Measurements were performed three times per point.

2.5. Data Management

Data were pseudonymized and entered into Microsoft Excel data sheets (Microsoft Office Professional Plus 2016, Microsoft, Redmond, WA, USA). At least two independent analysts checked the data for plausibility. Based on the headache calendars covering 90 days, mean headache frequency, duration, and intensity were reported as headache days per month, hours, and with a 10-point visual analogue scale (VAS) (0 no pain, 10 extreme pain). A headache day was defined as a day with a headache lasting for at least two hours or shorter if headache specific medication was taken (according to the ICHD-3 [43]). Two patients documented the headache intensity on an alternative VAS scale (smaller range) and were therefore excluded from the headache intensity analysis. Two patients noted headache episodes consecutively without the use of the headache calendar template or exact dates, which is why they had to be excluded from the analysis separately comparing headache frequency in the first month, second months, and third months after rNMS treatment as well as from headache intensity and medication intake analyses due to missing information. PedMIDAS scores were available for 12 patients, since 1 patient was at preschool age and therefore not able to complete the PedMIDAS questionnaire as it is partly based on the child's participation in school. PedMIDAS scores can be categorized as follows: score of 0 to 10: little to none impairment, score of 11 to 30: mild impairment, score of 31 to 50: moderate impairment, and score >50: severe impairment [46]. The maximum pressure of the algometer was 10 kg/cm^2. If no pain was indicated when reaching 10 kg/cm^2, this pressure was defined as the PPT [48]. Based on the relative headache frequency reduction from baseline to FU, patients were assigned to one of four responder rate groups ($\geq$75%; $\geq$50%, $\geq$25%, <25%) [49]. The FU data regarding PPT were available for 12 patients as one FU examination was only possible via telephone.

2.6. Statistics

As this is the first prospective clinical study to deliver rNMS to a pediatric cohort affected by migraine, the study was primarily designed to assess its feasibility in this age group reflected by adherence to the intervention. As the primary endpoint, the adherence rate was calculated as the percentage of participants who did not discontinue the inter-

vention. A threshold of completing at least 5 of the 6 per protocol sessions was defined as fulfilling adherence to the intervention. Assuming that 90% of participants would adhere to the intervention, a sample size of $n = 12$ to $n = 15$ participants was intended to treat based on the expected confidence intervals. For the additional qualitative feasibility endpoints, a sample size estimation was not reasonable. By the time the study had been designed, not any pediatric data for the application of rNMS in migraine were available to base a power analysis with regard to the clinical endpoints on.

All statistical analyses were performed using SPSS (version 26/27; IBM SPSS Statistics for Windows, Armonk, NY, USA). The statistical significance level was set to $\alpha = 0.05$ for all tests. Adherence rate was defined as the percentage of completed rNMS sessions. Absolute/relative frequencies, means, standard deviations, medians, and ranges were calculated for characteristics, side effects, and the intervention feedback.

Normality of headache variables, questionnaire scores, and PPT were analyzed using Shapiro–Wilk tests. Differences in headache frequency, headache intensity, frequency of days with medication intake, and the KINDL scores of caregivers from baseline to FU were evaluated using paired *t*-tests. Differences in headache duration, PedMIDAS scores, and KINDL scores of participants from baseline to FU were investigated using Wilcoxon signed-rank tests. Differences in monthly headache frequency were compared at 4 time points (baseline, one month, two months, and three months after rNMS treatment, respectively) using a repeated-measures ANOVA. The mean PPT above the left and right UTM was calculated as the average of the PPT above the lateral and medial reference points and the mTrP. Differences in PPT above the left and right UTM were assessed using repeated-measures ANOVAs for the following time points: (1) before the first rNMS session (pre), (2) before the last rNMS session (post), and (3) at FU. For ANOVAs, the Bonferroni correction was used for post hoc comparisons. In the case of a significant Mauchley's test of sphericity, the Greenhaus–Geisser correction was applied.

3. Results

3.1. Screening

A total of 248 patients treated at the outpatient headache center during the enrollment period were screened for eligibility, of whom 20 patients fulfilled all inclusion criteria (8.1%) and completed the baseline period. A total of 6 patients (2.4%) were excluded after the 90-day baseline period due to (1) less than six headache days within the baseline period ($n = 3$), (2) absence of mTrP in the UTM during manual palpation at the end of baseline ($n = 2$), and denial to participate in the intervention period ($n = 1$). One patient was excluded from analysis due to incongruence of the clinical diagnosis and the headache symptoms recorded by the headache calendar ($n = 1$). (Figure 2 and Supplementary Table S1).

3.2. Subject Characteristics

A total of 13 patients aged 12.2 ± 3.5 years (range: 6–17 years; 92.3% female) were enrolled in the study (Table 1 and Supplementary Table S2). A total of 3 patients were diagnosed with migraine with aura, of whom 2 patients additionally experienced tension type headache (TTH) characteristics. The remaining 10 patients were diagnosed with migraine without aura, with 5 patients also affected by TTH. The baseline mean headache frequency was 9.43 ± 5.86 headache days per month, with a median of 9.0 and an IQR 4.50–13.17 headache days per month. A total of 7 patients were experiencing neck pain at baseline; 6 patients received physiotherapy during baseline, 2 patients continued, and 1 patient started physiotherapy during the intervention period. All patients took acute medication: most patients used cyclooxygenase inhibitors ($n = 10$ ibuprofen, $n = 3$ naproxen, $n = 2$ acetylsalicylic acid); also triptans ($n = 4$) and paracetamol ($n = 2$) were prescribed. No patient took any preventive migraine medication, except magnesium ($n = 9$). Detailed subject and baseline characteristics are listed in Table 1.

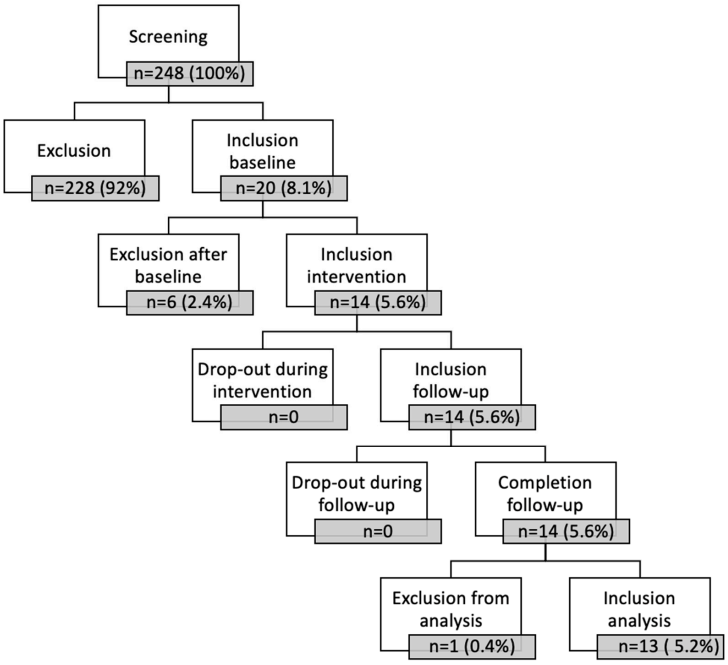

Figure 2. Screening scheme for study inclusion.

3.3. Treatment Characteristics

rNMS was performed with a mean stimulation intensity of 31.8 ± 12.3% of the maximum stimulator output on the left side and at 32.0 ± 11.6% of the maximum stimulator output on the right side.

3.4. Adherence

No dropouts were recorded. All participants completed all six rNMS sessions (adherence rate: 100%). Nine patients completed all sessions within a 3-week interval. For four patients, altogether eight sessions needed to be differently scheduled due to (1) acute illness of the patient (n = 2, 25%), (2) time constraints by the family (n = 1, 12.5%), (3) resource constraints by the outpatient clinic (n = 2, 25%), (4) absence without excuse (n = 2, 25%), and (5) accident due to weather conditions (n = 1, 12.5%) ending up in an intervention period of four to five weeks.

3.5. Safety

AEs were evaluated for 78 rNMS sessions. In 64 sessions (82.1%), no AEs were reported. A total of 16 side effects were reported for the remaining 14 rNMS sessions (17.9%) (Table 2). No AE led to discontinuation of the intervention.

Table 1. Characteristics of study participants (n = 13).

Characteristics		*n* (%)	Median (Range)
Age		-	12 (6–17)
Sex	Female	12 (92.3%)	-
Handedness	Right	10 (76.9%)	-
Headache Diagnosis			
Migraine with aura		1 (7.7%)	-
Migraine without aura		5 (38.5%)	-
Migraine with aura + TTH		2 (15.4%)	-
Migraine without aura + TTH		5 (38.5%)	-
Age at headache onset (years)		-	9 (2–15)
Time since headache onset (years)		-	3 (2–13)
Family history for migraine	Yes	3 (23.1%)	-
No		9 (69.2%)	-
Not known		1 (7.7%)	-
Neck pain at baseline	Yes	7 (53.8%)	-
No		6 (46.6%)	-
mTrP localization at baseline	Unilateral	5 (38.5%)	-
	Bilateral	8 (61.5%)	-
	Left	10 (45.5%)	-
Right		12 (54.5%)	-
mTrP entity at baseline	Latent	15 (68.2%)	-
Active		7 (31.8%)	-
Physiotherapy	During baseline	6 (46.2%)	-
During intervention		3 (23.1%)	-

Abbreviations: TTH = tension type headache, mTrP = myofascial trigger point.

Table 2. Adverse events (AEs) documented within n = 78 rNMS sessions.

AE (n = 91)	*n* (%)	Serious/Severe	Unexpected	Related
No side effects	64 (82.1%)			
Side effects	16 in 14 sessions (17.9%)			
During stimulation				
Trembling (arm/hand)	5 (6.4%)			X
Heaviness (at stimulation site)	2 (2.6%)			X
Tingling (at stimulation site)	1 (1.3%)			X
Arm pain	1 (1.3%)			X
Tension in shoulder-neck region (hand)	1 (1.3%)			X
In-between stimulations				
Headache	5 (6.4%)			X
Sore muscles	1 (1.3%)			X
Life events				
Suicide of school colleague	1 (7.7%)	X	X	
Health-related absence of caregiver [a]	1 (7.7%)			
Accident on ice	1 (7.7%)		X	

[a] For this variable, none of the criteria (serious/severe, unexpected, related) applied; they might have influenced the perception of headaches. Abbreviation: AE = adverse event.

3.6. Satisfaction

After the intervention, 13 subjects (100%) wanted to repeat rNMS and recommend it to other patients. A total of 13 caregivers (100%) would recommend rNMS to other children

with migraine, and 10 caregivers (76.9%) would repeat the intervention. The reason why 3 caregivers did not indicate to repeat the treatment was that they themselves did not perceive a sufficient improvement in their child's treated headache.

3.7. Headache Characteristics

Headache frequency numerically decreased from 9.43 ± 5.86 days per month during the baseline period by 2.53 days per month to 6.90 ± 4.53 days per month during the FU period. This reduction did not reach statistical significance (t = −1.848, $p = 0.089$, Table 3). Although the numerical drop of the mean monthly headache frequency was pronounced in the first (6.27 ± 4.52 days/month) and second month (6.45 ± 7.12 days/month) compared to the third month (9.00 ± 6.65 days/month) after the intervention, no statistically significant change was reached at any of these timepoints compared to the mean baseline headache frequency ($p = 0.204$, F = 1.76; Supplementary Table S3).

Table 3. Change in headache characteristics, PedMIDAS scores, and KINDL scores from baseline to FU.

Headache Characteristics	Pre		FU		Test Values		95% CI of Mean Difference
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	*t*/*Z*	*p*	
Headache frequency	9.43 (5.86)	9.00 (4.50–13.17)	6.90 (4.53)	5.60 (3.00–10.67)	$t = 1.848$	0.089	−0.45–5.52
Headache intensity	5.50 (0.97)	5.21 (4.75–6.73)	6.27 (1.47)	6.53 (4.24–7.09)	$t = -1.68$	0.142	−1.86–0.31
Headache duration	6.27 (4.82)	5.03 (3.56–7.35)	6.50 (4.70)	4.45 (2.59–9.41)	$Z = -0.89$	0.929	-
Medication frequency	4.42 (2.58)	4.33 (2.67–5.33)	2.73 (2.10)	2.00 (0.75–4.66)	$t = 1.94$	0.081	−0.25–3.65
PedMIDAS	35.00 (23.84)	24.00 (21.00–51.00)	20.67 (16.83)	16.00 (7.75–30.75)	$Z = -1.92$	0.055	-
KINDL Child	65.23 (19.02)	69.50 (46.13–82.75)	67.08 (18.04)	74.00 (58.38–79.25)	$Z = -0.420$	0.675	-
KINDL Caregiver	67.27 (11.99)	68.75 (58.38–77.63)	69.44 (9.64)	70.75 (61.50–78.75)	$t = -1.038$	0.320	−6.74–2.39

Comparisons were made using paired-samples *t*-tests or Wilcoxon signed-rank tests depending on normality. Abbreviations: pre = before the rNMS intervention, FU = follow-up, SD = standard deviation, IQR = interquartile range, CI = confidence interval, KINDL = Revidierter Fragebogen für KINDer und Jugendliche zur Erfassung der gesundheitsbezogenen Lebensqualität, PedMIDAS = Pediatric Migraine Disability Assessment.

Congruently, we registered a statistically non-significant reduction in medication frequency from 4.42 ± 2.58 days per month at baseline to 2.73 ± 2.10 days per month at FU (t = 1.94, $p = 0.081$) resulting in a mean reduction of 1.7 days per month. Headache intensity and duration did not relevantly change from baseline to FU.

Seven patients were classified as responders showing a relative reduction in headache frequency of ≥25%. Of these seven patients, headache frequency decreased ≥50% in three patients, of which two patients showed a reduction of ≥75%.

3.8. Headache-Related Disability

When comparing PedMIDAS scores at the group-level before intervention (35.00 ± 23.84) and at FU (20.67 ± 16.83), a transition from an average moderate to mild disability was observed (Z = −1.92, $p = 0.055$, Table 3). On the individual level, at baseline, "severe" disability was experienced by three patients, "moderate" disability by one patient, and "mild" disability by eight patients; no patient was categorized as "little to not" disabled (Figure 3). At FU, one patient was categorized as "severely", two patients as "moderately", six patients as "mildly", and three patients as "little to not" disabled. Two patients transitioned to a more severe category, whereas five patients turned to a less severe category, with one patient even dropping from "severe" to "little to none" disability. Five patients remained in their categories. Individual changes from baseline to FU in PedMIDAS scores, monthly headache frequency, intensity, and medication intake are depicted in Supplementary Table S4. No significant change in health-related quality of life was detected, neither in the total score of the KINDL questionnaire answered by the patient (baseline = 65.23 ± 19.02, FU = 67.08 ± 18.04, $p = 0.675$), nor in the questionnaire answered by the caregiver (baseline = 67.27 ± 11.99, FU = 69.44 ± 9.64, $p = 0.320$).

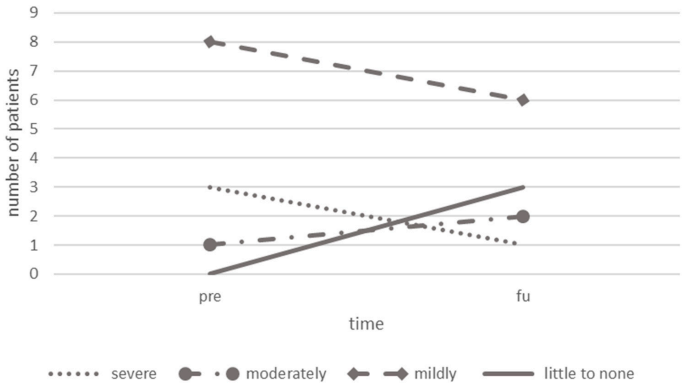

Figure 3. Comparison of PedMIDAS categories before and after rNMS treatment. Abbreviations: rNMS = repetitive neuromuscular magnetic stimulation, pre = before treatment, post = after treatment, PedMIDAS = Pediatric Migraine Disability Assessment.

3.9. Muscular Effects

Mean PPT measured above the left and right UTM significantly increased over time (left UTM: $p = 0.016$, right UTM: $p = 0.037$, Table 4 and Figure 4). Single comparisons of PPT above each assessed point (left lateral, left medial, left mTrP, right lateral, right medial, right mTrP) before and after the rNMS treatment are given in Supplementary Table S5.

Table 4. PPT comparison above the left and right UTM prior the first rNMS session (pre), prior the last rNMS session (post), and at the 3-month FU examination.

	Test Values			**Mean_Pre (SD)**	**Mean_Post (SD)**	**Mean_FU (SD)**	**Post Hoc Test**
	F	***p***	η^2				***p***
Left UTM	6.46	0.016 *	0.564	1.99 (0.77)	3.02 (1.61)	2.84 (1.13)	
Pre-post							0.097
Pre-FU							0.015 *
Post-FU							1.000
Right UTM	4.67	0.037 *	0.483	2.04 (0.67)	3.00 (1.55)	2.70 (1.00)	
Pre-post							0.126
Pre-FU							0.026 *
Post-FU							1.000

PPT comparisons above the left and right UTM using repeated-measures ANOVAs. Post hoc comparisons were performed with Bonferroni correction. Significant differences at $\alpha = 0.05$ are marked with an asterisk (*). Abbreviations: PPT = pressure pain threshold, UTM = upper trapezius muscle, FU = follow-up, pre = prior the first rNMS session, post = prior the last rNMS session, SD = standard deviation.

Of the seven patients with bilateral mTrP at baseline, one patient had only one unilateral mTrP at FU while the remaining six patients were still diagnosed with bilateral mTrP. Of five patients with unilateral mTrP at baseline (left n = one patient, right n = four patients), three patients had no mTrP at FU, while mTrP could be detected uni- and bilaterally in one patient, respectively.

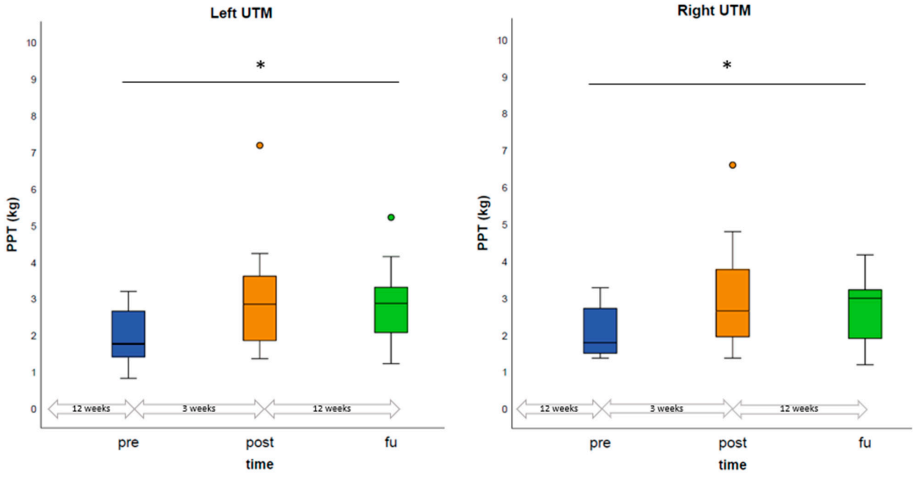

Figure 4. Comparison of PPT prior the first rNMS session, prior the last rNMS session, and at the 3-month FU examination. PPT above the left and right UTM were calculated based on the average of PPT above the lateral and medial reference points as well as the mTrP. Boxplots display the median PPT as well as the IQR. Significant differences are marked with an asterisk (*). Abbreviations: PPT = pressure pain threshold, mTrP = myofascial trigger point, pre = prior to the first rNMS session, post = prior to the last rNMS session, FU = follow-up, IQR = interquartile range.

4. Discussion

This study investigated the feasibility of the rNMS intervention as a non-pharmacological, non-invasive treatment option in a group of children affected by episodic migraine with involvement of the neck muscles. Feasibility measures were the adherence to, safety of, and satisfaction with the treatment. These measures were for the first time assessed in a prospective open-label design in this age group. In addition, preliminary clinical effects of the intervention were prospectively studied for the first time, not only focusing on changes in headache-related and muscular symptoms but on burden of migraine and in quality of life, too.

In this cohort, rNMS was feasible, safe, and well-accepted (adherence rate of 100%; no adverse events in 82.1% of rNMS sessions; 100% of patients would repeat and recommend rNMS). These results are in line with the findings from an observational report of rNMS as treatment in children and adolescents with different types of headache disorders, as well as to the results of studies involving adult participants [34–36].

Regarding the effects on headache-related symptoms, the monthly headache frequency and medication intake numerically decreased after the intervention, albeit without statistical significance. Importantly, seven patients (54%) were qualified as responders by experiencing a relief of their headache frequency by at least 25% and one additional participant reported a reduction close to the responder threshold (23%). This trend is comparable to findings in a cohort of children and adolescents with different types of headache disorders receiving rNMS, in that headache frequency and intensity were significantly reduced after rNMS (reduction from 17.1 ± 11.4 to 10.9 ± 10.9 headache days/month [mean ± SD]) [36] and comparable responder rates were observed for the group of participants affected by primary headaches, including nine patients with mixed-type headache and two with migraine only (43% responders in terms of ≥25% reduction, 14% responders in terms of ≥75% reduction) [36,37]. Similar findings have also been reported in previous studies investigating rNMS in young adults with episodic migraine (reduction

in headache frequency from 7.7 (5.7–12) to 5.3 (1.7–10.3) days/month [median (range)] and 7.7 ± 6.9 to 5.1 ± 4.8 days/month [mean ± SD]; reduction in medication intake from 4 (0–9.7) to 3 (0–9) days/month [median (range)] and 3.3 ± 2.8 to 2.8 ± 1.8 days/month [mean ± SD]) [33,35]. Moreover, a retrospective analysis of the pooled data of both studies showed similar developments, too (reduction in headache frequency from 8.17 ± 4.50 to 6.33 ± 4.38 days/month [mean ± SD], reduction in medication intake from 3.63 ± 2.58 to 3.10 ± 2.44 days/month [mean ± SD]) [50].

With regard to headache-related disability, a significant reduction in MIDAS scores was reported after rNMS in adults with episodic migraine in previous studies (MIDAS Score reduction from 26.33 ± 13.89 to 15.37 ± 12.30 [mean ± SD]) [50]. In congruence, in the current first ever report on the impact of rNMS to the burden of migraine, PedMIDAS scores decreased on average by 14.33 units from baseline to FU, which corresponds to a reduction of 40.9%. These results are clinically meaningful, considering the highly problematic consequences of school absenteeism, and avoidance of physical and everyday activities in childhood due to migraine symptoms. Thus, a decreased PedMIDAS score likely reflects increased participation after rNMS, representing an important criterion regarding the treatment of pediatric migraine. In our pediatric cohort, more patients were classified as being mildly to not at all disabled after the rNMS intervention. With regard to the KINDL scores, no changes in health-related quality of life were reported after rNMS, neither by patients nor by their caregivers. However, it should be noted that baseline KINDL scores (65.23 ± 19.02) were already almost at the same level as reference values of healthy children in the KIGGS study ("Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland", performed by the Robert Koch-Institute; mean: 76.90; 95% confidence interval 76.70–77.10) [51] and BELLA study ("BEfragung zum seeLischen WohLbefinden und VerhAlten", submodule of the KIGGS study; 76.30 ± 10.10) [52]. Hence, ceiling effects may have hampered the detection of further improvement.

Regarding muscular effects, the current analysis demonstrated an increase in PPT from pre- to post-assessments above the UTM, reflecting a relief of muscular hypersensitivity. This effect lasted until the 3-month FU, implicating that a decrease in local muscular hypersensitivity induced by rNMS can be sustained for a certain period of time. Of importance, in contrast to the long-term muscular effects of rNMS portrayed in this study, the majority of studies evaluating the effects of neuromodulation methods only included acute short-time FU (e.g., FU period of 10 min) [53–60]. Our findings are congruent with previous investigations of rNMS in children [37] as well as in adults affected by headaches. Our results show an increase in PPT from pre- to post-assessment of 0.96 ± 0.42 kg/cm^2 for the right and 1.03 ± 0.42 kg/cm^2 for the left UTM, which is comparable to PPT increases reported in the adult studies (right UTM: 0.4 (−1.1–2.5) kg/cm^2 [median (range)] and 0.8 kg/cm^2 [mean, SD for difference not given]; left UTM: 0.6 (−0.5–2.6) kg/cm^2 [median (range)] and 0.6 kg/cm^2 [mean, SD for difference not given]) [34,35]. PPT after rNMS measured above the UTM increased to a level of PPT measured in pediatric patients with chronic pain above the non-pain control sites and in a healthy reference population [61]. In addition, PPT above the UTM prior to rNMS were comparable or lower than PPT measured in adult migraine patients. PPT after rNMS were similar or even higher than PPT of healthy controls [62,63]. Together, this suggests an even more pronounced muscular hypersensitivity in pediatric patients than in healthy adults, which can potentially be reset to a level of healthy controls by rNMS targeting the UTM as a muscle considered part of the TCC. This may be interpreted as a sign of network reorganization via the TTC, eventually including the desensitization of the hypersensitive trigeminal nucleus caudalis [64].

Regarding the aspect of neuroinflammation in migraine pathogenesis, magnetic resonance imaging (MRI) studies suggest neuroinflammatory mechanisms on the muscular level [65,66], in addition to the well-described CGRP-related (Calcitonin Gene-Related Peptide) alterations on the leptomeningeal vascular level [67,68]. The relief of muscular symptoms (e.g., increased PPT, decreased number of mTrP) by rNMS points at a possible relief from muscular neuroinflammation. In addition to the beneficial clinical effects, the

important interplay of the peripheral and central networks is emphasized, once more. This context might call for further in-depth investigations of alterations of muscles involved in migraine pathogenesis via the TCC, i.e., by advanced imaging on behalf of T2 mapping and other advances MRI-based techniques [65,66].

Neurostimulation as acute or prophylactic migraine treatment is quite a novel approach; thus, the number of studies is still limited to date and no data exist for the pediatric population for the majority of modalities [7,69]. For the acute migraine treatment and migraine prophylaxis, the following approaches have been investigated: transcranial magnetic stimulation [70], transcranial direct current stimulation [71], transcutaneous occipital nerve stimulation [53,72], transcutaneous supraorbital nerve stimulation [54,73], transcutaneous vagus nerve stimulation [74,75], and remote electrical neuromodulation [60]. In comparison to the abovementioned techniques, rNMS specifically targets the muscle and could treat the muscular level in addition to central effectors—including in children and adolescents. Specifically, it has several aspects that might facilitate its use in the pediatric setting, including in particular a painless application. Therefore, rNMS may be better accepted by patients, which is an important factor in the pediatric field [36,69,76]. Regarding the association of migraine, neck pain, and muscular hypersensitivity, rNMS is unique in targeting both the muscular and the central pathophysiological mechanisms conceptualized within the framework of the TCC [17,19], which is achieved via a single "from bottom-up" approach [69]. Thus, rNMS may represent a valuable non-invasive, non-pharmacological component within the future treatment concepts for pediatric migraine. Against the background of these promising results in children, data from large-scale randomized controlled trials in adults are expected to pave the way for a widespread application of rNMS across all age groups (https://drks.de/search/de/trial/DRKS00024470 accessed on 20 October 2023).

As this study included a rather small cohort of 13 patients with migraine, findings are not generalizable to the whole population of pediatric patients affected by migraine. Despite the small cohort, the assumption that 90% of participants would adhere to the intervention led to a sample size calculation of $n = 12$ to $n = 15$ participants needing to be treated to reach reasonable confidence intervals (CI $\pm$ 15.2 to $\pm$ 16.9), which enhances the reliability of the effects despite the sample size limitation. Yet, given the strict in- and exclusion criteria, the data represent the feasibility and preliminary effects in a cohort of pediatric patients affected by migraine as clinically homogenously as possible. In particular, assuring a relatively high baseline frequency of headaches and the presence of muscular involvement through an expert manual palpation, together with the rule out of comorbidities like somatoform or psychiatric disorders, represent important quality criteria of the study. Another reason for limitations in the sample size had been the ongoing COVID-19 pandemic, that restricted outpatient contacts to a minimum. Given the age range of the study population, no conclusions regarding when to start a neurostimulation during the trajectory of migraine can be drawn. Headache documentation is especially challenging in children and adolescents, which should be considered when interpreting the reported results. Novel, digitalized kids-friendly applications are urgently needed to ensure a more feasible headache documentation in clinical practice and research. Regarding muscular effects, only one FU examination took place 90 days after the intervention. While numerically decreased headache frequency was pronounced during the first and second month after the intervention, no conclusions regarding trajectory or wear-off effects regarding the muscular symptoms can be made to date. Future studies should therefore consider implementing physiotherapeutic assessment at several time points during FU and may additionally implement objective point-of-care imaging measures to assess muscular changes (e.g., muscular ultrasound or infrared thermography). Furthermore, the lack of objective neurophysiological outcome measures (e.g., fMRI) limits the interpretability of the here-reported rNMS effects, and further studies including neurophysiological outcome measures are needed to underpin the pathophysiological hypothesis of the distinct mechanisms of action of rNMS in migraine. Concerning algometry, it should be noticed that measurements in young children (6–8 years) may not be as reliable as in adults or older children, which is due to

difficulties in describing perceptions and a higher sensitivity to pain stimuli [63]. A setting effect may have affected the here-presented outcomes, especially since this effect might be higher in the pediatric population in general [5,11,77]. Furthermore, there may be an increased placebo response to interventions using a medical device compared to pharmacologic treatment modalities [77]. In addition, three psychosocial AEs were reported by three patients during the study period, which may have interfered with the effects reported here. Since the study was carried out during the COVID-19 pandemic, the closure of schools, sports clubs, and recreational facilities, social distancing, and the rapid change in legal restrictions may have affected the patients' daily routine, as well as overall quality of life and burden of headache. Since migraine is a very common disorder in pediatric age but nevertheless characterized as one of the most underfunded diseases [78,79], more sham-controlled studies investigating non-pharmacological, non-invasive treatment options for pediatric patients are urgently needed.

5. Conclusions

rNMS interventions were safe, feasible, and well-accepted by children and adolescents with migraine. Although statistically non-significant, the monthly headache frequency, medication intake, and—particularly important and reported for the first time in this context—PedMIDAS scores demonstrated a relevant decrease from baseline to FU on an individual basis. Together with the potential to reduce the symptoms on the muscular level, rNMS might become a valuable option introducing neuromodulation from bottom up to the multimodal armentarium for children with episodic migraine. Therefore, future controlled studies are highly needed to further assess the current beneficial findings and to elucidate the specific neurophysiological mechanisms of rNMS in peripheral and central processes of pain processing.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/children10111764/s1; Table S1: Screening. Screening and reasons of exclusion; Table S2: Participants' characteristics. More detailed characteristics of the study participants; Table S3: Changes in monthly headache frequency of $n = 11$ patients for the first month, second month, and third month after rNMS intervention compared to baseline; Table S4: Individual changes from baseline to FU in PedMIDAS scores, monthly headache frequency, headache intensity, and medication intake; Table S5: (A) Comparison of PPT before the first (pre1) and before the last treatment sessions (pre6). (B) Comparison of PPT after the first (post1) and after the last treatment sessions (post6).

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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.

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6. Paper II

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Repetitive neuromuscular magnetic stimulation in children with headache

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ABSTRACT

Introduction: Repetitive neuromuscular magnetic stimulation (rNMS) was previously applied in adult patients with episodic migraine, showing beneficial effects on headache characteristics, high safety, and convincing satisfaction. This study aims to assess rNMS as a personalized intervention in pediatric headache.
Methods: Retrospective chart review including patients with migraine, TTH, mixed type headache, or PTH, who had received at least one test rNMS session targeting the upper trapezius muscles (UTM).
Results: 33 patients (13.9 ± 2.5 years; 61% females) were included in the primary analysis, resulting in a total of 182 rNMS sessions. 43 adverse events were documented for 40 of those sessions (22%). Most common side effects were tingling (32.6%), muscle sore (25.5%), shoulder (9.3%) and back pain (9.3%). Secondly, in patients (n = 20) undergoing the intervention, headache frequency ($p = 0.017$) and minimum and maximum intensities ($p = 0.017$; $p = 0.023$) significantly decreased from baseline to 3-month after intervention. 11 patients (44%) were classified as ≥25% responders, with 7 patients (28%) experiencing a ≥75% reduction of headache days. After 73% of interventions, patients reported rNMS helped very well or well. A majority of patients would repeat (88.5%) and recommend rNMS (96.2%) to other patients.
Conclusion: rNMS seems to meet the criteria of safety, feasibility, and acceptance among children and adolescents with three age-typical headache disorders. A significant reduction in headache frequency and intensity during a 3 months follow-up was documented. Larger, prospective, randomized, sham-controlled studies are urgently needed to confirm if rNMS may become a new valuable non-invasive, non-pharmacological treatment option for pediatric headache disorders.

1. Introduction

According to the Global Burden of Disease Study, headache disorders are common in childhood and adolescence [1,2]. The most frequent but often underreported and underdiagnosed headache disorder in school age children and adolescents is tension-type headache (TTH), followed by migraine, which is attributed to a risk of chronification and a high burden of disease [3–8]. Frequently, a mixed type headache comprising episodes of migraine and TTH is present in this age group [9]. In addition, post-traumatic headache (PTH), defined as the persistence of headache after traumatic brain injury (TBI), occurs in about 7.8–13.7% of pediatric TBI patients [10–12]. PTH is classified into migraine-like, TTH-like, or continuous daily headaches based on their predominating phenotypes with mixed-types being very frequently diagnosed [10,13,14].

Within the complex pathophysiology of migraine, TTH, and PTH, the trigemino-cervical complex (TCC) represents the cornerstone of the interplay of peripheral and central mechanisms within the nervous

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system for pain perception, processing, perpetuation, and sensitization [15–19]. Nociceptive and proprioceptive information of the neck muscles is delivered to the caudal trigeminal nucleus via the upper cervical afferents (C1–C3) and processed together with the sensory information of the head and face region delivered by the trigeminal branches [17, 20]. From the trigeminal nucleus, information is delivered to the higher pain processing centers via the trigemino-thalamic tract [16,21]. Therefore, pain, tension, and manual palpation findings in the neck and upper trapezius muscles (UTM) can be understood as muscular involvements in patients with different headache entities [20–36]. In this context, taut bands, hypersensitive spots, and referred pain during palpation serve together as diagnostic criteria for myofascial trigger points (mTrP) [28,37].

Burdensome TTH, migraine, and PTH are usually approached using a multi-modal, interdisciplinary therapeutic approach including education, lifestyle management, physiotherapy, and behavioral therapy, alongside with pharmacotherapy [19,38–40]. While effective drugs are available for acute migraine and migraine-like attacks, the evidence for pharmaco-prophylaxis in pediatric patients with migraine or TTH is limited and side effects have to be respected [6,41,42]. Since there are no evidence-based guidelines for pharmacotherapy of pediatric PTH, the treatment is usually adapted from recommendations for primary headaches types [19,43–45]. The lack of evidence as well as the low benefit-risk ratio of the available drugs stress the importance of non-pharmacological, non-invasive, safe, and well-tolerated treatment options to complement the armentarium of such multi-modal approach to pediatric headache disorders [38].

Neuromodulation by electrical stimulation of cranial or peripheral nerves represents a novel approach for the treatment of headache disorders [46]. Given frequent muscular involvement in pediatric headache disorders, a protocol for repetitive neuromuscular magnetic stimulation (rNMS) targeting the UTM was developed. By electromagnetic induction, rNMS induces a physiologically sized electric current in the respective body region leading to a depolarization of motor and afferent nerves [47]. Hereby a muscular contraction via the stimulation of the terminal branches of 2nd-order motoneurons is directly induced; the muscular contraction itself triggers the activation of muscle spindles and mechanoreceptors of the muscular-tendon unit and the skin. Concurrently, terminal sensory nerve fibers in joint capsules, ligaments, and the skin are directly activated [48,49]. It is hypothesized that this increase in proprioceptive inflow modulates sensorimotor integration and pain processing pathways – in the case of stimulation of the UTM via the TCC [47,48,50,51].

Against this background, rNMS has demonstrated encouraging results in adults with frequent episodic migraine with respect to a decrease of muscular hyperalgesia as well as headache symptoms, while being reported to be safe, well-tolerated, feasible, and well-accepted [52–54]. Based on these findings, our outpatient pediatric headache clinic implemented a rNMS regimen for children and adolescents with headache disorders including TTH, migraine, mixed-type headache, and PTH. The aim of this study was to evaluate the safety and clinical efficacy of rNMS targeting the UTM in children and adolescents with headache disorders.

2. Materials and methods

2.1. Ethics

The institutional review board of the medical faculty of the University of Munich (LMU) approved the study (vote 21–0574).

2.2. Observational retrospective study design

We identified patients who had been offered rNMS intervention in the outpatient pediatric headache clinic by chart review. Patients were included in the study if the indication for rNMS was based on a diagnosis of (1) episodic migraine, (2) episodic TTH, (3) mixed type headache (episodic migraine PLUS TTH), or (4) subacute (>3 weeks post-injury) or persistent (>8 weeks post-injury) PTH [55,56]. The review period covered files of patients presenting to the headache clinic between August 2020 and May 2021 (including first presentations and clinical follow-up visits).

2.3. Setup and rNMS intervention

Within the multi-modal treatment regimen of the outpatient pediatric headache clinic, rNMS is considered for patients with the following inclusion criteria: (1) continuous, daily, or frequent headache episodes and (2) involvement of the neck muscles. Muscular involvement is defined by the presence of restricted range of motion, muscular imbalance, pain with muscle stretching, pain with muscle contraction, generalized hypertonia, generalized or focal hyperalgesia, taut bands, hypersensitive spots, and referred sensation/pain during palpation – with the last three symptoms clustered together for defining a mTrP [28, 37]. Exclusion criteria comprise the following contraindications for magnetic stimulation: (1) diagnosis of epilepsy, (2) metallic implants, implanted shunt systems or other biomedical devices, and (3) pregnancy.

The patients and their caregivers are thoroughly educated about neurostimulation by rNMS. If they are interested in the intervention, a trial session is offered. If patients opt for an intervention by rNMS afterwards, six consecutive treatment sessions are scheduled during two to three weeks. However, adjustments of intervals in-between sessions are possible according to the family's needs and resources. All patients are followed up after the intervention on a regular basis within the multimodal treatment regimen comprising appointments with child neurologists, physiotherapists, and psychologists depending on the individual needs.

An eMFieldPro system (Zimmer MedizinSysteme GmbH, Neu-Ulm, Germany; CE Nr 0123) specifically designed for the point of care treatment is used for stimulation. The stimulator is equipped with a round coil (diameter of the copper winding of 7.6 cm) and a maximum output of a 2.5 T magnetic field is used for stimulation. During stimulation, the patient is in a comfortable prone position on a physical-examination couch. At the beginning of every rNMS session, the stimulation intensity is adjusted on an individual basis (slow increase until a muscle contraction is observed, but the patient is still feeling comfortable, using a 7-point smiley scale rating the stimulation from "very comfortable" to "not comfortable at all"). The coil is handheld by the therapist in the position assuring a contraction. The optimal coil positioning above the UTM is repeatedly sought for each subject, session, and body side (Fig. 1A). The right- and left-sided UTM are consecutively stimulated in each session, with the starting side alternating from session to session. Stimulation is delivered as single pulses with rectangular pulse shape and a pulse duration of 250 μs. The direction of induced current is from outside to inside of the coil. 15 min stimulation of each side consists of a total of 7420 pulses with a 20-Hz frequency, 7 s ON-time, and 10 s OFF-time, resulting in 53 trains including 7 bursts per train and 20 pulses per burst (140 pulses per train; Fig. 1B). These stimulation parameters are used for all subjects and sessions. Stimulations are always carried out by the same operators. A break of approximately 2 min takes place between the stimulation of both sides, during which the operator changes the coil position to the contralateral side.

2.4. Assessment of adverse events and satisfaction

Directly after each rNMS session as well as at the beginning of the next session, the patients are asked for any unpleasant sensations or adverse events (AE) that appeared during or after rNMS. After the last rNMS session, the patients and one caregiver are asked to fill in a customized questionnaire to assess the overall experience of the stimulation including AE, changes in headache and muscular symptoms, and

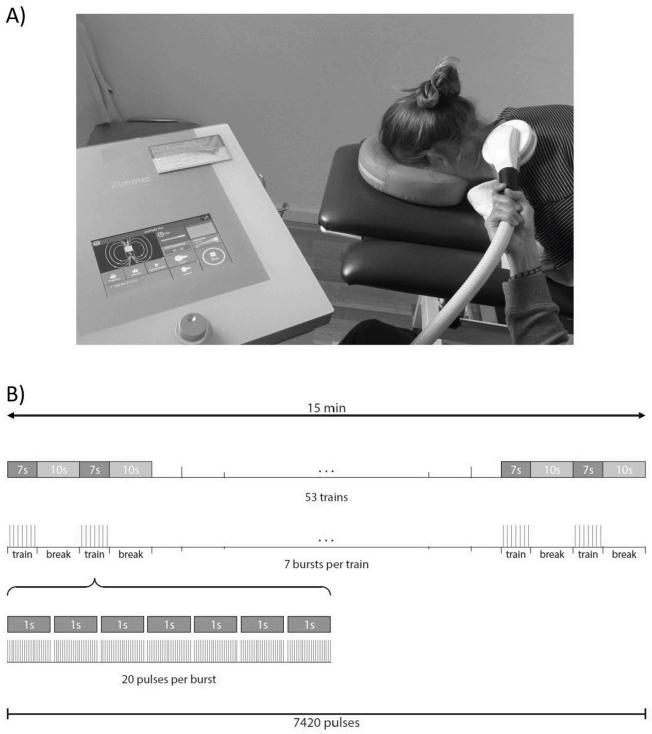

Fig. 1. Clinical set-up of rNMS intervention for headache disorders. A: rNMS setting and coil positioning. B: Stimulation protocol used for the rNMS treatments: 15 min of stimulation consist of 53 trains of 7 s and 10 s break in-between trains. Each train includes 7 bursts of 20 Hz - 20 pulses per second. In total, 15 min of stimulation consist of 7420 pulses.

the motivation to repeat and recommend the treatment. During a follow-up examination (FU) at about three months after the intervention, patients are asked to retrospectively evaluate the satisfaction with rNMS.

2.5. Headache characteristics

Before rNMS and at FU, patients are asked to report about their headache characteristics within the last three months in order to retrieve mean headache frequency, mean headache duration, and mean headache intensity (minimum and maximum). Before the rNMS intervention, patients are asked about headache triggers, premonitory symptoms, headache localization, headache characteristics, accompanying symptoms, medication, and other therapies.

2.6. Data management

Details of rNMS sessions and results from FU examinations are documented using paper-based clinical report forms. Data of patients identified during the chart review were anonymized and entered into Microsoft Excel data sheets (Microsoft Office Professional Plus 2016, Microsoft, Redmond, Washington, USA). Cross-checking of data entry was done by at least two independent analysts. With a majority of patients being adolescents, most of them were not accompanied by their legal guardian throughout the treatment. This explains the differing numbers of caregivers being specifically asked about their satisfaction. Satisfaction questionnaire was not offered to all patients who underwent the intervention as it was only introduced to the clinical work up in October 2020. Headache frequency was reported as headache days per month. Headache duration was assessed in hours. In addition, subjects rated their minimal and maximal headache intensities on a 10-point visual analogue scale (VAS), with 0 indicating no pain and 10 indicating extreme pain.

2.7. Statistical analysis

All statistical analyses were performed using Microsoft Excel (Microsoft Office Professional Plus 2016, Microsoft, Redmond, Washington, USA) and SPSS (version 26/27; IBM SPSS Statistics for Windows, Armonk, NY, USA). The significance level for all tests was set to $\alpha = 0.05$. Absolute and relative frequencies, means, standard deviations (SDs), medians, and ranges were calculated for subject and intervention characteristics, AE, and reports of satisfaction. One patient was identified as an outlier based on a late FU (210 days after last session), translating to $>$ 3 SDs above the mean FU time of the sample (91.7 ± 26.7 days). Adherence rate was calculated as percentage of patients having started and completed the intervention. Completion was defined as having undergone at least 5 of the a priori scheduled sessions. AE were analyzed based on their absolute and relative frequencies.

Satisfaction was assessed based on the absolute and relative frequencies regarding the motivation to repeat and recommend rNMS as well as the classification of the overall evaluation of the intervention.

Headache variables (headache frequency, minimal headache intensity, maximal headache intensity, and headache duration) were checked for normality using Shapiro-Wilk tests. Headache frequency, headache duration, and the maximum headache intensity were not normally distributed and thus differences from baseline to FU status were calculated using Wilcoxon signed-rank tests. The minimum headache intensity was normally distributed and differences from baseline to FU status were assessed using paired t-tests. Pearson correlation coefficients between time since headache onset to rNMS intervention and time from trauma to rNMS intervention, respectively, and changes in headache frequency were calculated.

3. Results

3.1. Chart review

During the chart review, 36 patients were identified, who were offered rNMS treatment between August 1st' 2020 and May 15th' 2021 (Suppl. Figure 1). Since 3 patients were not interested in treatment, 33 patients completed at least one trial session. Data of these 33 patients were analyzed regarding AE. 6 patients did not opt for rNMS treatment after the trial session due to start of an inpatient rehabilitation period (n = 1, 16.7%), start of a different treatment (n = 1, 16.7%), non-compliance (n = 1, 16.7%), no interest in the treatment (n = 1, 16.7%), the loss of contact to the patient (n = 1, 16.7%), and having experienced back pain during stimulation (n = 1, 16.7%). Thus, 27 patients started the rNMS intervention, of whom 4 patients discontinued the intervention. Reasons for discontinuation were non-compliance (n = 1, 25%), time intensity of the treatment (n = 2, 50%), and shoulder pain (n = 1, 25%). The remaining 23 patients (adherence rate of 85.2%) completed the rNMS intervention with at least 5 out of 6 sessions, 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. 2 patients were lost to FU and data of 1 patient was classified as outlier based on a late FU (>3 SDs above mean FU time) and excluded from analysis. Therefore, data from 20 patients receiving 25 rNMS interventions were finally available for analysis of headache characteristics. FU took place 4–20 weeks after the last treatment session, with 20 (80%) of FU taking place after 8–16 weeks. As stated in the methods section, patient/caregiver reported outcome was not available for all of the interventions (patient-reported treatment evaluation: n = 24 interventions; repetition [patients]: n = 25 interventions; repetition [caregivers] n = 11 interventions; recommendation [patients] n = 19 interventions; recommendation [caregivers] n = 9 interventions).

3.2. Adverse events

AE were analyzed for 182 rNMS sessions of 33 patients, who received at least one treatment session (Table 1 and Fig. 2). In 142 (78%) of rNMS sessions, no AE were reported. 43 AE were reported for 40 sessions (22%). Side effects during treatment included tingling at the stimulation site, in the arm or hand (n = 14, 32.6%), shoulder pain (n = 4, 9.3%), back pain (n = 4, 9.3%), feeling of heaviness (n = 2, 4.7%), trembling (n = 1, 2.3%), and unpleasant tension at the stimulation site (n = 1, 2.3%). Side effects in-between interventions included muscle sore (n = 11, 25.5%), headache (n = 2, 4.7%), and a short-lasting muscle cramp in the upper arm (n = 1, 2.3%). AE categorized as unlikely related to the intervention were described in 3 sessions by 2 patients and included shoulder pain (n = 2, 4.7%) and an electrifying feeling radiating to the right hip (n = 1, 2.3%).

3.3. Characteristics of patients who underwent a complete rNMS intervention

The 20 patients, who underwent a full rNMS intervention and were eligible for further analysis, had a mean age of 14.1 ± 2.7 years (range: 8–17 years), and 12 patients were females (60%) (Table 2). 8 patients were diagnosed with migraine without aura and TTH (40%), 7 patients with PTH (35%), 2 patients with migraine with aura (10%), 2 patients with migraine without aura (10%), and 1 patient with migraine with aura and TTH (5%). The family history for migraine was positive for 12 patients (60%). Patients had a mean age of 11.8 ± 2.8 years at headache onset (range: 6–16 years). For PTH patients, the mean time since trauma was 715.4 ± 665.8 days (range: 24–1609 days). 12 patients (60%) used acute pain medication including ibuprofen (n = 10, 40%), naproxen (n = 4, 16%), triptans (n = 6, 24%), and paracetamol (n = 3, 12%). 11 patients (44%) were taking magnesium on a regular basis. Neck pain was indicated by 15 subjects (60%) prior to the beginning of the intervention block. 12 patients (48%) had physiotherapy in the 3 months before the intervention. 5 patients (20%) continued physiotherapy during the intervention interval. During the 3-months FU period, 4 patients (16%) continued physiotherapy and 5 patients (20%) started physiotherapy.

3.4. Stimulation characteristics

The mean stimulation intensity was 25.0 ± 11.3% of the maximum stimulator output for the left and 25.8 ± 11.6% of the maximum stimulator output for the right UTM (Table 2). Treatment frequency was less than 2 sessions per week for 8 (32%), 2 sessions per week for 11 (44%),

Table 1
Adverse events for n = 182 rNMS sessions.

Adverse events (N = 185)	N (%)	Serious/Severe	Unexpected	Related	Causal for treatment discontinuation
No adverse events	142 (76.8%)				
Adverse events	43 (23.2%)				
During stimulation					
Tingling (arm/hand)	11 (25.6%)			X	
Shoulder pain	4 (9.3%)			X	
Back pain	4 (9.3%)			X	X (n = 1)
Tingling (at stimulation site)	3 (6.9%)			X	
Heaviness (at stimulation site)	2 (4.7%)			X	
Shoulder pain	2 (4.7%)		X		X (n = 1, 2x pain)
Trembling (hand)	1 (2.3%)			X	
Electrifying feeling, radiating to the right hip	1 (2.3%)		X		
Unpleasant tension	1 (2.3%)			X	
In-between stimulations					
Muscle sore	11 (25.6%)			X	
Headache	2 (4.7%)			X	
Cramp in the upper arm	1 (2.3%)			X	

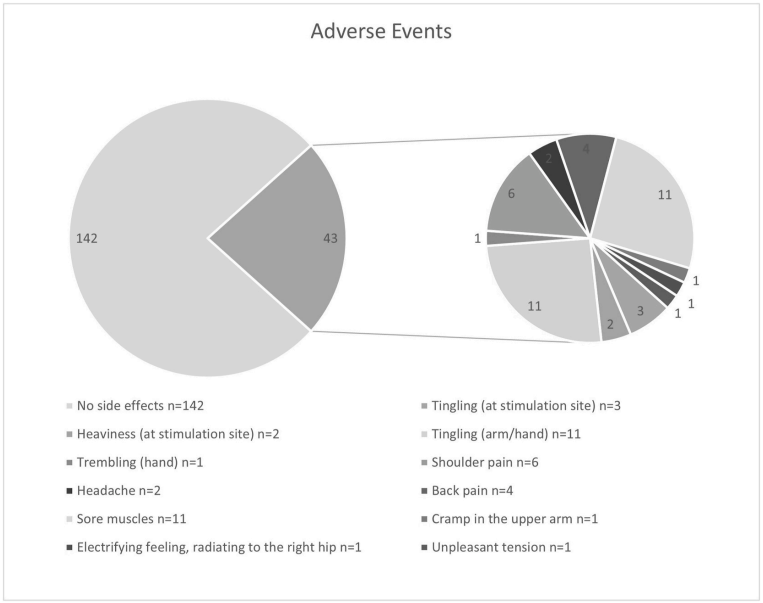

Fig. 2. Adverse events (AE) reported in n = 182 rNMS sessions. The numbers in the figure describe the absolute number of appearances of a certain AE.

Table 2
Characteristics of n = 20 patients and n = 25 rNMS interventions included in the analysis.

N = 20 patients				N = 25 interventions			
Characteristics		N (%)	Median (range)	Characteristics		N (%)	Median (range)
Age		–	15 (8–17)	**Mean stimulation intensity**	Left	–	25 (9–59)
Sex	Female	12 (60%)	–		Right	–	26 (8–63)
Handedness	Right	18 (90%)	–	**Mean contraction-generating intensity (n = 19)**	Left	–	15 (2–23)
					Right		14 (2–26)
Migraine without aura		2 (10%)	–	**rNMS frequency**	1x/week	5 (20%)	
Migraine with aura + TTH		1 (5%)	–		2x/week	11 (44%)	–
Migraine without aura + TTH		8 (40%)	–		3x/week	4 (16%)	–
PTH		7 (35%)	–		6x/week	2 (8%)	–
Age of headache onset		–	12 (6–16)		1–2x/week over 4 weeks	3 (12%)	–
Time since headache onset (years)		–	2 (0–8)	**Follow-up time (days)**			87 (35–154)
Age at trauma (n = 7)		–	12 (10–16)		After <2 months	1 (4%)	–
Time since trauma (days) (n = 7)		–	747 (24–1609)		After 2–3 months	15 (60%)	–
Treatment repetitions					After 3–4 months	5 (20%)	–
One block		15 (75%)	–		After 4–5 months	4 (16%)	–
Two blocks		5 (25%)	–				

Table 3
Change in headache characteristics from baseline to follow-up (FU).

Headache characteristics	Mean pre (SD)	Mean FU (SD)	Relative mean difference	Test values		95% Confidence interval	
				t/*Z*	*p*	Lower value	Upper value
Headache frequency	17.08 (11.44)	10.88 (10.94)	-.36	$Z = -2.39$	.017*	–	–
Headache intensity (min)	4.88 (2.17)	3.54 (2.36)	-.27	$t = 2.58$	.017*	.27	2.40
Headache intensity (max)	7.92 (1.61)	6.33 (2.48)	-.20	$Z = -2.28$	.023*	–	–
Headache duration	15.74 (19.19)	11.89 (9.23)	-.24	$Z = -.53$	.600	–	–

Frequency as headache days per month; intensity on a 10-point scale VAS, duration in hours. Analyses were done using paired t-tests or Wilcoxon tests. Asterisks (*) mark significant differences at α = 0.05. Abbreviations: SD standard deviation, FU follow-up.

and more than 2 sessions per week for 6 interventions (24%).

3.5. Change in headache characteristics

Changes in headache characteristics are summarized in Table 3 (Table 3). Headache frequency statistically significantly decreased from 17.1 ± 11.4 days per month at baseline to 10.9 ± 10.9 days per month at FU (Z = −2.39, p = 0.017) (Fig. 3A). The mean reduction of headache frequency was 7.8 days per month, translating to a relative mean reduction of 36%. The minimal and maximal headache intensities statistically significantly decreased from 4.9 ± 2.2 and 7.9 ± 1.6 at baseline to 3.5 ± 2.4 and 6.3 ± 2.5 on the VAS at FU, respectively (t = 2.58, p = 0.017; Z = −2.28, p = 0.023) (Fig. 3B and C). This reduction corresponds to a relative decrease of 27% in minimum and 20% in maximum headache intensity. Headache duration did not statistically significantly change from baseline to FU (p = 0.60) (Fig. 3D). When comparing patients with and without physiotherapy during intervention and/or FU, no significant difference in the relative change of headache characteristics from baseline to FU were found (Supplemental Table 2).

When categorizing patients by responder rates based on the relative reduction in headache frequency, 14 out of 25 patients were non-responders (<25% reduction, 56%) and 11 patients were 25% responders (≥25% reduction, 44%), of which 10 patients were 50% responders (≥50% reduction, 40%) and 7 patients were 75% responders (≥75% reduction, 28%).

There was no linear relationship between time from headache onset to start of rNMS intervention and the relative mean change in headache frequency (Pearson's r = 0.09, p = 0.663). Regarding the 7 PTH patients, a weak positive correlation was found between time from trauma to start of rNMS intervention and the relative mean change in headache frequency (Pearson's r = 0.21, p = 0.534). The shorter the time between trauma and treatment, the higher the relative reduction in headache frequency. The relative change in headache frequency ranged from −1 to 1, with negative values indicating a reduction and positive values an increase in headache frequency.

3.6. Satisfaction with rNMS

After 13 interventions (54.2%), the treatment was rated as "the therapy helped very well", after 5 interventions (20.8%) as "the therapy helped well", after 1 intervention (4.2%) as "indecisive", after 3 interventions (12.5%) as "the therapy was rather not successful", and after 2 interventions (8.3%) as "the therapy did not help at all". After 23 (88.5%) interventions, patients stated that they would repeat the intervention with rNMS. All of the asked caregivers (n = 11) would like their child to repeat the intervention. 18 (96.2%) of the asked patients (n = 19) would recommend the treatment to other affected minors, as would all of the asked caregivers (n = 9).

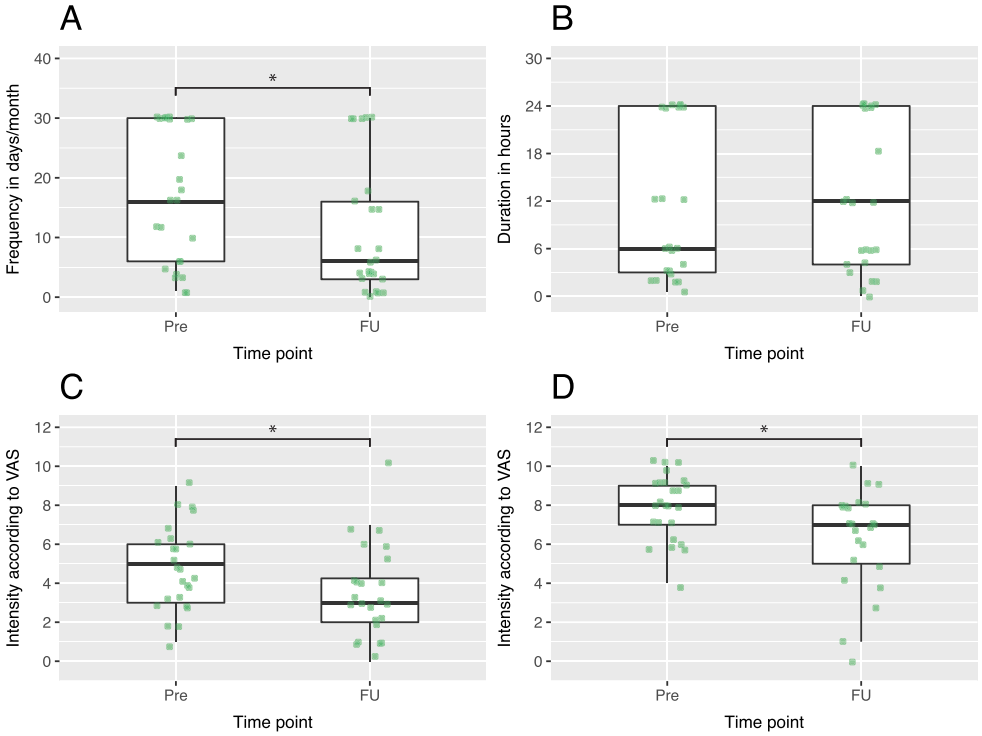

Fig. 3. Change in headache characteristics from baseline to follow-up. A: headache frequency in days per month, B: headache duration in hours, C: minimum headache intensity on a 10-point visual analogue scale, D: maximum headache intensity on a 10-point visual analogue scale. Significant differences at α = 0.05 are marked with an asterisk (*). Abbreviations: pre: before rNMS treatment, post: after rNMS treatment, VAS: visual analogue scale.

4. Discussion

This study evaluated the safety, feasibility, and clinical efficacy of as well as satisfaction with rNMS targeting the UTM in children and adolescents with headache disorders. In the majority of rNMS sessions (78%), no AE were reported. Adherence rate in patients that opted for rNMS intervention after the trial session was 85.2%. Concerning headache characteristics, a statistically significant reduction of the headache frequency and the maximal and minimal headache intensity was achieved. Specifically, almost half of the patients could be classified as responders with regard to the individual reduction of headache days. Interestingly, if patients responded to the rNMS intervention, the response was very good to excellent as the majority of responders achieved a ≥75% reduction of headache frequency. 75% of patients rated the intervention as successful. Most patients (88.5%) would repeat the treatment as confirmed by all asked caregivers. Similarly, almost all patients (96.2%) would recommend rNMS to other affected children and adolescents as confirmed by all asked caregivers.

To date, only two previous studies explored the feasibility and effects of rNMS as a novel intervention for migraine [52–54]. In these studies, young adults with frequent episodic migraine were enrolled and received a rNMS intervention including 6 sessions (stimulation protocol: 15 min/side, 20-Hz frequency, 15 s ON-time, and 30 s OFF-time). Compared to 4 patients who discontinued the treatment in the pediatric sample, no dropouts were reported by the two previous studies in adults [53,54]. However, the reasons for discontinuation in the pediatric cohort were not related to the treatment itself but included the time intensity of treatment including travel to the outpatient clinic, non-compliance, and an orthopedic comorbidity (impingement-like shoulder pain). Furthermore, in the two studies and the present analysis, no serious AE occurred, and very similar patterns and frequencies of side effects were reported.

Similar to the numbers observed in our analysis, 90% and 89.5% of participants of the two studies would have recommended the treatment to other patients, respectively [53,54]. In one of the studies, 84.2% of participants reported at the 3-month FU that they were satisfied with the treatment [53], and 75% of pediatric patients rated the intervention as successful for the present study. Moreover, a high acceptance rate was observed among the young patients with 88.5% being motivated to repeat the intervention. However, this rate was a bit lower than in the two previous studies [53,54]. The reason may be that the pediatric cohort included patients with episodic migraine, TTH, and PTH with mixed levels of disease burden, for whom the stimulation protocol was partly experienced as very time-consuming. In comparison, the adults in previous studies had a high burden of disease and therefore the motivation to repeat the rNMS sessions might have been higher [52–54].

Multimodal treatment regimen for pediatric headaches call for innovative, safe, and feasible personalized approaches to modulate pain origin, processing, and perception [46]. As rNMS, other approaches of peripheral neurostimulation have only been investigated in adult patients, so far [46]. Based on the available low number of sham-controlled studies, transcutaneous occipital nerve stimulation (tONS) [57] and transcutaneous supraorbital nerve stimulation (tSNS) [58] demonstrated efficacy in the prevention of episodic migraine with 50% response rates of 36–41% at different stimulation frequencies and 38%, respectively. Reduction in monthly headaches days was reported with a mean of 4 and 2 days for tONS and tSNS, respectively [46,59]. Safety is excellent in both treatments, and satisfaction rate yielded 65–77% for tONS and 70% in tSNS [57,58].

Compared to tONS and tSNS, rNMS uniquely represents a *neurostimulation from bottom-up not directly addressing a cranial nerve itself*. Headache symptoms are addressed via modulation of the proprioseNsory input stemming from the UTM, that is processed via the TCC [46]. The choice of the UTM as target is reasonable and easy to explain to the patients, as they often are well aware of the interplay of muscular and headache symptoms. During personalized rNMS, the effector organ "muscle" is directly addressed, and patients are able to control the treatment by deciding about the stimulation intensity. The patient experiences self-efficacy but is still embedded within *a close to a physiotherapist setting*.

This analysis is the first to assess rNMS as a novel, personalized, non-pharmacological, non-invasive option in pediatric patients with headache disorders. As the current study reports data collected during daily clinical routine in a multi-modal interdisciplinary setting, a heterogeneous group of patients with different headache disorders was studied – including the so far in clinical research underrepresented mixed-type headache and PTH. To investigate predictors of treatment response (i.e. specific headache type), studies with higher sample sizes are needed. In addition, patients were allowed to receive other therapies like physiotherapy during rNMS treatment. Even though no difference in rNMS efficacy was found between patients with and without therapy, this point needs to be considered when interpreting the results of this study and should be controlled for in future studies. Moreover, this analysis only included one FU time point approximately 3 months after treatment. Thus, randomized, sham-controlled, longitudinal studies with several FU points are urgently warranted to further investigate the trajectory of the effects rNMS exerts on muscular and headache symptoms. Furthermore, a magnetic stimulator designed for the point of care setting was used. This technical progress allows for a kids-friendly treatment atmosphere and overcomes restriction of exclusive availability in neurophysiological research environments. A setting/placebo effect might have influenced the analysis, which might generally be higher in children and adolescents and for treatments using a medical device [3,42,60]. Thus, future studies with a prospective and controlled design investigating larger patient samples are needed. Also, these studies should investigate, which patient's or headache's characteristics may predict an excellent response to rNMS.

The analysis covers a period during the Covid-19 pandemic. During these times, life of children and adolescents in Germany drastically changed – regarding intermittent closure of schools, distance learning via digital tools, strong increase of screen time, and social distancing from peers, friends, and family members not living in the same household. Since lifestyle factors are known to influence headache symptoms [61], the possible impact of Covid-19-related lifestyle changes on headache in our sample cannot be estimated. Data from Italy show that the closure of schools had been beneficial in terms of a reduction in headache intensity and frequency for school children suffering from different headache disorders [62]. Future studies could consider such influences in a controlled setting.

5. Conclusion

As a novel, point of care neuromodulation, rNMS seems to meet the criteria of safety, feasibility, and acceptance among children and adolescents with three age-typical headache disorders. In this first-line report, a significant reduction in headache frequency and intensity during a 3 months FU was documented. Larger controlled studies are needed to assess the potential of rNMS to become a valuable non-invasive, non-pharmacological, personalized treatment option complementing the armentarium of a multimodal regimen for pediatric headache disorders.

Competing interests

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). 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2022.04.010.

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