Universitätsklinikum der LMU München, Klinik für Kinderheilkunde - Dr. von Haunersche Kinderklinik, Abteilung für Pädiatrische Neurologie und Entwicklungsmedizin & MUC - Munich University Center for Children with Medical and Developmental Complexity, iSPZ Hauner

Feasibility and clinical efficacy of repetitive neuromuscular magnetic stimulation in pediatric headache

Dissertation

zum Erwerb des Doktorgrades der Medizin

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität München

vorgelegt von

Jacob Staisch

aus

München

Jahr

2024

Mit Genehmigung der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

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List of abbreviations

rNMS	Repetitive neuromuscular magnetic stimulation
FU	Follow-up
PPT	Pressure pain threshold
UTM	Upper trapezius muscle
TTH	Tension-type headache
PTH	Post-traumatic headache
ICHD-3	International classification of headache diseases 3
TBI	Traumatic brain injury
mTrP	Myofascial trigger point
TVS	Trigeminovascular system
TCC	Trigemino-cervical complex
PMS	Peripheral magnetic stimulation
TES	Transcranial electrical stimulation
TMS	Transcranial magnetic stimulation
tDCS	Transcranial direct current stimulation
tONS	Transcutaneous occipital nerve stimulation
REN	Remote electrical neurostimulation
tVNS	Transcutaneous vagus nerve stimulation
tSNS	Transcutaneous supraorbital nerve stimulation
MRI	Magnetic resonance imaging

List of publications

A Articles (Part of the dissertation)
Corinna Börner†, **Jacob Staisch**†, Magdalena Lang, Ari Hauser, Iris Hannibal, Kristina Huß, Birgit Klose, Matthias F. Lechner, Nico Sollmann, Florian Heinen, Mirjam N. Landgraf and Michaela V. Bonfert †shared first author **Repetitive Neuromuscular Magnetic Stimulation for Pediatric Headache Disorders: Muscular Effects and Factors Affecting Level of Response** Brain sciences, 12, 932. https://doi.org/10.3390/brainsci12070932.
Jacob Staisch†, Corinna Börner†, Magdalena Lang, Ari Hauser, Iris Hannibal, Kristina Huß, Birgit Klose, Matthias F. Lechner, Nico Sollmann, Florian Heinen, Mirjam N. Landgraf and Michaela V. Bonfert †shared first author **Repetitive neuromuscular magnetic stimulation in children with headache** European Journal for Pediatric Neurology, 39, 40–48. https://doi.org/10.1016/j.ejpn.2022.04.010.
B Articles (other)
Corinna Börner-Schröder, Magdalena Lang, Giada Urban, Erik Zaidenstadt, **Jacob Staisch**, Ari Hauser, Iris Hannibal, Kristina Huß, Birgit Klose, Matthias F. Lechner, Nico Sollmann, Mirjam N. Landgraf, Florian Heinen and Michaela V. Bonfert **Neuromodulation in Pediatric Migraine using Repetitive Neuromuscular Magnetic Stimulation: A Feasibility Study** Children, 10, 1764. https://doi.org/10.3390/children10111764.
B Conference Abstracts
Magdalena Lang, Corinna Börner, Giada Urban, **Jacob Staisch**, Ari Hauser, Maximilian Frohnmüller, Iris Hannibal, Kristina Huß, Sigrid Kruse, Birgit Klose, Matthias F. Lechner, Nico Sollmann, Mirjam N. Landgraf, Florian Heinen and Michaela V. Bonfert **Effects of repetitive neuromuscular magnetic stimulation targeting the upper trapezius muscles in children and adolescents with episodic migraine** 32nd International Congress of Clinical Neurophysiology (ICCN) of the IFCN, September 2022
Magdalena Lang, Corinna Börner, Giada Urban, **Jacob Staisch**, Ari Hauser, Maximilian Frohnmüller, Iris Hannibal, Kristina Huß, Sigrid Kruse, Birgit Klose, Matthias F. Lechner, Nico Sollmann, Mirjam N. Landgraf, Florian Heinen and Michaela V. Bonfert

Safety of, adherence to, and satisfaction with repetitive neuromuscular magnetic stimulation in children and adolescents with episodic migraine 32nd International Congress of Clinical Neurophysiology (ICCN) of the IFCN, September 2022
Corinna Börner, **Jacob Staisch**, Ari Hauser, Magdalena Lang, Maximilian Frohnmüller, Iris Hannibal, Kristina Huß, Sigrid Kruse, Birgit Klose, Matthias F. Lechner, Nico Sollmann, Mirjam N. Landgraf, Florian Heinen and Michaela V. Bonfert **Effects of repetitive neuromuscular magnetic stimulation targeting to the upper trapezius muscles in children with headache disorders** Deutsche Gesellschaft für klinische Neurophysiologie (DGKN) Jahreskongress 2022, April 2022
Corinna Börner, **Jacob Staisch**, Ari Hauser, Magdalena Lang, Maximilian Frohnmüller, Iris Hannibal, Kristina Huß, Sigrid Kruse, Birgit Klose, Matthias F. Lechner, Nico Sollmann, Mirjam N. Landgraf, Florian Heinen and Michaela V. Bonfert **Satisfaction with and safety of repetitive neuromuscular magnetic stimulation in children with headache disorders** Deutsche Gesellschaft für klinische Neurophysiologie (DGKN) Jahreskongress 2022, April 2022
Corinna Börner, Ari Hauser, **Jacob Staisch**, Magdalena Lang, Christina Göttler, J. Wagner, Florian Heinen, and Michaela V. Bonfert **Clinical Experiences with Repetitive Neuromuscular Magnetic Stimulation in Children with Posttraumatic Headache: A Retrospective Study** Abstracts of the 46th Annual Meeting of the Society for Neuropediatrics, November 2021

1. Contribution to the publications

1.1 Contribution to Paper I

Repetitive neuromuscular magnetic stimulation in children with headache

Via substantial involvement in project conception, execution, data curation and analysis, preparing and editing the manuscript draft I have contributed to this publication.

Conception of the project and submission of the study protocol were realized in collaboration with my supervisors (Florian Heinen, Mirjam Landgraf and Michaela Bonfert), a PhD student (Corinna Börner-Schröder) and myself. Michaela Bonfert and Corinna Börner-Schröder shared the responsibility for the project administration.

This publication is based on data collected during daily routine of the multimodal therapy setting in our pediatric headache clinic. Patients with a headache disorder and a muscular component diagnosed by a physician and physiotherapist were educated about the treatment together with their families after contraindications had been ruled out. If a patient and their family agreed to treatment, I scheduled treatment appointments together with Corinna Börner-Schröder, the medical doctoral student Magdalena Lang, and the neuroscience master student Ari Hauser.

Treatment of patients with repetitive neuromuscular magnetic stimulation (rNMS) and documentation of treatments were subject to shared responsibility within our team. My responsibility was to schedule and conduct the rNMS interventions consisting of 6 rNMS sessions spread over 2-3 weeks. A detailed description of the treatment process can be found in chapter 2.3. of the introductory summary. Three months after treatment, follow-up visits were scheduled (FU). During rNMS sessions and at FU, I did also measure pressure pain thresholds (PPT) above the upper trapezius muscle (UTM) via algometry. Regarding treatment documentation, I created form-sheets that helped tracking (1) headache characteristics (including frequency, intensity, and duration), (2) PPT above the UTM, (3) treatment characteristics (e.g., stimulation intensity), and (4) any side effects occurring during or in-between rNMS interventions.

Together with Corinna Börner-Schröder, I created a Microsoft Excel data mask to digitalize and analyze the paper-based rNMS treatment documentation. We curated the data collected and following this I conducted cross checks of the data, together with at least one member of our team. For the analysis of patient characteristics, feasibility, adverse events, stimulation characteristics, headache characteristics, and satisfaction, Excel and SPSS were used. The analysis was conducted by myself under the supervision of Corinna Börner-Schröder. I then interpreted the data together with my supervisors Florian Heinen, Michaela Bonfert and Mirjam Landgraf as well as physicians of our tertiary outpatient headache clinic Iris Hannibal, Kristina Huß and Corinna Börner-Schröder. Ari Hauser supported visualization of the data.

Together with Corinna Börner-Schröder I prepared the original manuscript draft for the publication of safety, feasibility, and acceptance of rNMS treatments targeting the UTM in pediatric headache disorders under supervision of Michaela Bonfert. Furthermore, I participated in the revision process until the manuscript was accepted.

As my contributions to the project and the publication were shared with Corinna Börner-Schröder, we decided to share the first authorship.

1.2 Contribution to Paper II

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

The data published in paper II was collected during the same intervention as for paper I. Accordingly, I contributed to various areas of the project, including project conceptualization, project execution, data curation, data analysis, and to the publication process of paper II. The initial project conception and submission of the study protocol were handled by my supervisors, Florian Heinen, Mirjam Landgraf, and Michaela Bonfert, supported by the PhD student Corinna Börner-Schröder and myself. Michaela Bonfert and Corinna Börner-Schröder jointly managed the project administration.

This publication is based on the analysis of routine data from our tertiary outpatient clinic. Assignment of responsibilities for patient management, treatment, and data management was the same as for paper I.

The same Microsoft Excel data template as applied for paper I was used to digitize and analyze the paper-based rNMS treatment records. We utilized Excel and SPSS for the analysis of PPT, responder rates, and potential factors influencing the response to rNMS treatment. The interpretation of the data was a joint effort involving myself, Corinna Börner-Schröder, my supervisors (Florian Heinen, Michaela Bonfert, and Mirjam Landgraf), physicians from our tertiary outpatient headache clinic (Iris Hannibal, Kristina Huß). Additionally, Ari Hauser assisted in visualizing the data.

Corinna Börner-Schröder and I worked together to prepare the initial draft of the manuscript for the publication focusing on the clinical and muscular effects together with possible response predictors of rNMS treatments targeting the UTM, under supervision of Michaela Bonfert. I did also participate in the revision process until the manuscript was accepted for publication.

Considering our shared contributions to the project and the publication, Corinna Börner-Schröder and I decided to share first author.

2. Introductory summary

2.1 Headache disorders

As patients enrolled in the analysis published in paper I and II were diagnosed either with migraine, tension-type headache (TTH), mixed-type headache or post-traumatic headache (PTH), the focus of this chapter will be kept on these headache disorders.

2.1.1 Epidemiology and clinical presentation

Primary headache disorders in childhood and adolescence are frequent and represent a major impairment [1-3]. For this age group, a prevalence for primary headaches of up to 62% is reported and in 2019 they were found to represent the second most disabling condition overall, with migraine and TTH being the most common types [4-6]. Notably, mixed-type headache including migraine and TTH are common among children and adolescents, and the risk of chronification is high as headache disorders are often underdiagnosed and consequently undertreated [7-11]. PTH is another prevalent headache disorder in the pediatric population, defined as the persistence of headache after a traumatic brain injury (TBI) [12, 13]. The prevalence of PTH in children and adolescents varies, ranging from 6.8% to 70% depending on the classification system applied and the time since injury [14].

According to the International Classification of Headache Diseases 3 (ICHD-3), TTH is characterized by mild to moderate pain, pressing or tightening quality, localized bilaterally and without autonomic symptoms [12]. Migraine, on the other hand, can be differentiated in migraine with and without aura, referring to the presence of transient neurological symptoms such as visual or sensory symptoms prior or concomitantly with the onset of the migraine headache [12]. Migraine headache is typically defined by moderate to severe pain lasting 4-72 hours in adults and possibly shorter in children [12]. Migraine headache has a pulsating pain quality, physical activity can increase headache and it can occur accompanied by autonomic symptoms like photophobia, phonophobia, nausea, and vomiting [12]. PTH is reported to have varying predominate phenotypes allowing the classification in migraine-like, TTH-like, daily headaches, and continuous headaches [12, 15-17].

One of the symptoms occurring concomitantly and commonly reported by patients affected from the outlined headache disorders is muscular impairment in the neck region [18-20]. In TTH, increased sensitivity of pericranial muscles has been found to be the most common concomitant symptom [21, 22]. In migraine, neck pain is more common than nausea – one of the defining characteristics of the disorder [23]. Also, in PTH patients, neck pain is frequent and may be associated with higher headache intensity [24]. Generally, muscular involvement in headache disorders can manifest as neck pain, tension, increased sensitivity to pain, and muscular imbalance [18, 25-27]. Hypersensitive spots within taut muscle bands triggering a referred sensation when palpated represent another form of muscular involvement also referred to as myofascial trigger points (mTrP) [28-33].

2.1.2 Pathophysiology

The pathophysiology of the three headache disorders is complex and not yet fully understood, especially in the case of TTH and PTH [34-36]. However, significant progress has been made in recent years [34]. Migraine, traditionally seen as a pain disorder primarily centered on headaches, is now understood to be a complex brain state with premonitory and postdromal symptoms [37, 38]. It involves bidirectional interactions between the central and peripheral nervous system, with central and peripheral sensitization, alterations in descending pain modulatory pathways, and neurogenic inflammation (mediated by e.g. calcitonin gene related peptide (CGRP)) playing key roles [35, 36, 39-41].

A central junction for the outlined interactions between the central and peripheral nervous system can be found in the trigeminal-cervical complex (TCC) as it contributes to the integration of information from both parts of the nervous system. [30, 42, 43]. Originating in the neck muscles, the upper cervical afferents (C1-C3/4) transmit both nociceptive and proprioceptive information to the caudal trigeminal nucleus and constitute peripheral input [37, 42, 44]. This input then converges with other peripheral information, especially sensory input from the head and face region conveyed by trigeminal branches [37, 42, 44]. Next, the trigemino-thalamic tract relays the information to higher pain processing centers in the brain [22, 45]. As a result, experiences of pain, tension, or manual palpation findings within the short neck muscles and the UTM can be comprehended as muscular contributions to different headache conditions [46, 47]. Therefore, the TCC can be understood as a key point in the multifaceted pathophysiology of migraine, TTH, and PTH by contributing to headache and muscular symptoms, particularly in the neck region [22, 36, 42, 44, 48, 49]. In PTH, muscular symptoms in the neck can be additionally explained by a whiplash-like trauma, causing a dysregulation of the muscle tone [36, 50].

2.1.3 Treatment

In the treatment of headache disorders, a general distinction is made between acute and prophylactic measures. In children and adolescents with acute migraine, TTH, or PTH, pharmacotherapy is often the first line of treatment while data and clinical guidelines are scarce [51-53]. In terms of prophylaxis, on the other side, burdensome migraine, TTH, and PTH are typically addressed through a multi-modal, interdisciplinary therapeutic approach that involves education, lifestyle management, physiotherapy, relaxation techniques and behavioral therapy [36, 54-56]. Prophylactic pharmacotherapy may be a convenient option but is often inadequate for children and adolescents due to its potential side effects and uncertain benefits [57, 58]. Therefore, non-pharmacological and non-invasive treatment modalities should be implemented prior to considering pharmacological approaches [54, 56, 57]. To date, there is a paucity of non-pharmacological, non-invasive, safe and feasible treatments for headache disorders, highlighting the pressing need for innovations [8, 54, 56, 59]. For children and adolescents who suffer from headache disorders this need is even more urgent as shortcomings of pharmacological interventions tend to be even more pronounced [8, 60]. Non-invasive neuromodulation can combine these properties and has lately emerged as a promising, non-pharmacological approach in the treatment of headache disorders [59].

2.2 Neurostimulation

Neurostimulation is a non-pharmacological concept in headache treatment. It is an approach aiming to modulate information processing of cerebral or neuromuscular structures through electrical or magnetic stimulation [59, 61].

Peripheral magnetic stimulation (PMS) was first investigated in the 1980s and represents the first form of neuromodulation through magnetic stimulation [62, 63]. The physical mechanism behind PMS is electromagnetic induction [64-67]. PMS is performed by placing a coil designed of copper windings with an electric current running through it over a peripheral nerve [65, 66]. The electric current in the coil creates a radial magnetic field that generates an electric field in the underlying tissue through changes in magnetic flux density [64, 66, 68]. This physiologically sized electric current can trigger action potentials in nerve fibers [68]. Direct and indirect stimulation of afferent nerves can affect the neuronal plasticity of the brain by modulating sensorimotor networks and initiating network reorganization [69-73]. Compared to electrical stimulation, PMS offers the advantages of being painless, easy, flexible, and patient-adaptive to use, and does not require direct skin contact [59, 66, 74]. As our research group developed PMS protocols that did not target to a peripheral nerve itself, but to the region with high density of terminal efferent nerve branches to evoke a distinct contraction of the target muscle, we introduced the wording of repetitive neuromuscular magnetic stimulation (rNMS) to characterize this form of peripheral magnetic stimulation.

For the acute and prophylactic treatment of headache disorders, several neurostimulation techniques have been investigated, including both central and peripheral modalities, usually focusing on migraine. Among central approaches, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have received considerable attention [75-77]. In parallel, a range of peripheral stimulation methods targeting neuromuscular structures have been investigated. Empirical evidence supports the efficacy of peripheral modalities for the acute relief of migraine attacks [59, 78]. These include transcutaneous vagus nerve stimulation (tVNS), which involves stimulation of either cervical or auricular segments of the vagus nerve; transcutaneous supraorbital nerve stimulation (tSNS), which targets bilateral supratrochlear and supraorbital nerves; and remote electrical neurostimulation (REN), which targets cutaneous afferents of the upper arm [79-83]. For migraine prophylaxis, transcutaneous occipital nerve stimulation (tONS), which focuses on the bilateral occipital nerves, and tSNS have shown efficacy [81, 84-86]. However, it is important to note that scientific literature available focusing on neuromodulation in TTH and PTH remains particularly sparse. Specific neuromodulatory interventions have not yet been established [22, 36].

Given this background, a protocol using repetitive neuromuscular magnetic stimulation (rNMS) targeting the UTM as a novel, non-invasive neuromodulating treatment for headache disorders was developed by our research group. Two previous studies investigated the approach in adults with frequent episodic migraine demonstrating encouraging results [87-89]. Given the possibility of myofascial mechanisms affecting the neck muscles working as a cofactor or trigger of migraine, a reduction of muscular hyperalgesia and headache symptoms has been reported, while being safe, well-tolerated, feasible, and well-accepted [87-89]. 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 [90, 91]. The rNMS interventions were thoroughly documented and analyzed retrospectively with regards to safety, clinical efficacy, local muscular effects, and potential factors predicting response to rNMS. These findings were then published in two papers building the foundation of this dissertation.

2.3 Repetitive neuromuscular magnetic stimulation

2.3.1 Stimulation parameters

The characteristics of magnetic fields created by rNMS or TMS respectively is determined by multiple parameters. Fixed parameters are the number of turns of copper windings within the coil and the geometry of the coil in use. The more windings a coil has, the stronger the output, as the magnetic fields of each turn are added up [68]. Coils are usually eight-shaped or round, which have different maximum effects and penetration depths. The eight-shaped coil produces a stronger and more concentrated electric field compared to the round coil because the currents intersect in the center of the coil [68]. The round coil is more suitable when deeper and larger structures need to be stimulated, as its stimulates a deeper tissue in a wider area [68]. The choice of coil depends on the specific aim of the stimulation. Adjustable parameters are the strength of the electric current running through the coil, frequency of stimulation, pattern of stimulation and duration of intervention. The strength of the current running though the coil depends on the adjustable discharge voltage, which is expressed as a percentage (0-100%). The frequency for repetitive stimulation usually lies between 20 and 25 Hz [70]. Stimulation protocols are applied either continuously or intermittently, with ON (active stimulation) and OFF phases (no stimulation). The total number of stimuli applied depends on the frequency chosen, the ON and OFF phases, and the total duration of the treatment. Treatment frequency was also analyzed in our publications.

2.3.2 Stimulation setup

The point-of-care rNMS treatment in our project was performed with an eMFieldPro system (manufactured by Zimmer MedizinSysteme GmbH, Neu-Ulm, Germany; CE No. 0123). The system utilizes a round coil with a copper winding diameter of 7.6 cm and has the power to generate a maximum magnetic field output of 2.5 Tesla for stimulation. During the stimulation process, the patient is positioned comfortably in a prone position on an examination couch. At the start of each rNMS session, the stimulation intensity is individually tailored to each patient. The intensity is gradually increased until a muscle contraction of the UTM is observed while ensuring that the patient remains comfortable. This adjustment is made using a 7-point smiley rating scale, ranging from “very comfortable” to “not comfortable at all”. The therapist holds the coil in a position that ensures muscle contraction, and the optimal coil placement above the UTM is determined individually for each subject, session, and body side. Both the right and left sides of the UTM are stimulated consecutively in each session, with the starting side alternating between sessions. Stimulation is delivered as single rectangular pulses lasting 250 µs. The induction current flows from the outside to the inside of the coil. Each 15-minute stimulation session for each side consists of a total of 7420 pulses delivered at a frequency of 20 Hz. The session follows a pattern of 7-second ON-time followed by 10-second OFF-time, resulting in 53 trains, each comprising 7 bursts with 20 pulses per burst (a total of 140 pulses per train) [90, 91]. The outlined stimulation parameters and approach are consistent for all subjects and sessions, and the stimulations are consistently administered by the same operators. There is an approximate 2-minute break between stimulating each side, during which the operator repositions the coil for stimulation on the contralateral side [90, 91]. The stimulation protocol applied is similar to the protocol used for young adults, which is detailed in Renner et al. (2019) [88-90].

The population in our outpatient clinic was treated with an average stimulation intensity for the left UTM of 25.0% relative to the maximum stimulator output with a standard deviation of 11.3%, while for the right UTM, it was 25.8% with a standard deviation of 11.6%. In terms of treatment frequency, 8 interventions (32%) were conducted less than twice a week, 11 interventions (44%) occurred twice a week, and 6 interventions (24%) took place more than twice a week [90, 91].

2.3.3 Feasibility, adverse events, and acceptance

As no findings on feasibility and acceptance of rNMS in children and adolescents with headache disorders were available, this was the main objective of our analysis published in paper I. After each rNMS session and before the next session, patients were asked to report any discomfort or adverse events (AE) experienced during or after rNMS. Upon completion of the final rNMS session, both, patients and caregivers were provided with a customized questionnaire to evaluate their overall experience with the stimulation, encompassing AE, alterations in headache and muscular symptoms, as well as their level of readiness to repeat the treatment and further recommend it to others [90, 91].

In a comprehensive analysis of 182 rNMS sessions involving 33 patients, all of whom underwent at least one rNMS session, it was observed that for 78% of these sessions (n=142 sessions), no adverse events (AE) were reported. Conversely, adverse events were reported in 22% of the sessions (n=40 sessions), yielding a total of 43 reported AE. Side effects experienced during rNMS treatment encompassed sensations of 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%), a feeling of heaviness (n=2, 4.7%), trembling (n=1, 2.3%), and an unpleasant tension at the site of stimulation (n=1, 2.3%). Additionally, side effects manifesting between interventions included muscle soreness (n=11, 25.5%), headaches (n=2, 4.7%), and a brief muscle cramp in the upper arm (n=1, 2.3%). Furthermore, AE categorized as unlikely to be directly related to the intervention were described in 3 sessions by 2 patients, incorporating shoulder pain (n=2, 4.7%) and a sensation of electrification radiating to the right hip (n=1, 2.3%). There were no serious adverse events reported in neither of the two previous studies in young adults or in the present analysis. Also, patterns and frequencies of adverse events were very similar in both of the studies [90]. In the pediatric cohort, 4 dropouts were documented due to the time intensity of the treatment, non-appearance and an orthopedic comorbidity; they were therefore not related to the treatment itself [90]. In young adults, no dropouts were reported, which may be due to a higher morbidity in the analyzed population [90].

At a subsequent follow-up examination (FU), conducted approximately three months post-intervention, patients were asked to retrospectively assess their satisfaction with rNMS. Following 13 interventions (54.2%), the therapy was rated as highly effective ("the therapy helped very well"). In 5 cases (20.8%), it was considered beneficial ("the therapy helped well"). Only 1 intervention (4.2%) yielded an indecisive rating, while 3 (12.5%) were viewed as rather unsuccessful (“the therapy was rather not successful”), and 2 (8.3%) as ineffective (“the therapy did not help at all”). Remarkably, after 88.5% of interventions (n=23) patients expressed their willingness to undergo rNMS again and all caregivers interviewed were in favor of repeating the intervention. 95% of patients (n=19) were inclined to recommend the treatment to other affected minors, consistent with recommendations of all caregivers interviewed (n=9) [90]. Similar numbers were reported in young adults (treatment rated effective by 73.7% of patients, treatment would be repeated by 94,7% of patients, treatment recommended by 89.5% of patients) [88, 89].

2.3.4 Central and muscular effects

To investigate central effects of rNMS, headache frequency, headache intensity (minimum and maximum), and headache duration regarding headaches over the last 3 months were documented prior to treatment and at FU. A statistically significant reduction was observed in headache frequency, maximum and minimum headache intensity. Notably, almost half of the patients (n=11, 44%) were classified as responders, with a relative reduction in headache frequency from pre-treatment to FU of at least 25% indicating a significant reduction in the number of headache days. In cases where patients responded positively to rNMS intervention, response was particularly strong, with the majority (n= 7, 28%) achieving a 75% or greater reduction in headache frequency [90]. Central effects were observed irrespective of individual headache diagnosis [91].

Muscular effects were assessed through PPT before and after each treatment, as well as during FU examination. Muscular hypersensitivity showed a significant reduction from pre-treatment to post-treatment assessment. This decline was maintained until FU, with levels consistently lower than those observed at baseline. This effect was especially pronounced in PTH patients [91].

2.3.5 Factors affecting level of response

Patients with a reduction in headache frequency of at least 25% compared from pre-treatment to FU were defined as responders. Presence of neck pain, type of headache disorder, and treatment time frame were investigated as possible factors affecting level of response. Neck pain was found to be a factor contributing to a pronounced response to rNMS with 60% of patients with neck pain classified as responders and 20% of patients without neck pain. For headache disorders, no differences were found. rNMS being administered twice per week showed the highest reduction in headache frequency compared to rNMS being administered less or more often than twice per week [91].

2.4 Limitations and future directions

Our project demonstrated rNMS to be feasible, safe and well-accepted in a pediatric cohort with different headache disorders. Moreover, rNMS was found to have a positive impact on headache symptoms and muscular hyperalgesia, irrespective of the specific diagnosis, and proved highly effective in patients with neck pain.

Findings of this analysis are subject to limitations. The cohort was small, analyzed retrospectively and without control group, so the extent of the placebo effect cannot be determined – a phenomenon particularly common in children and adolescents [60, 92]. The intervention was embedded in a multimodal treatment. Therefore, patients were seen by other specialists like physiotherapists or psychotherapists making it difficult to attribute the results solely to rNMS. In addition, the analysis was conducted during the COVID-19 pandemic period, which brought significant lifestyle changes for children and adolescents in Germany. These changes included school closures, digital distance learning, increased screen time, and social distancing. Given the known influence of lifestyle on headache, it is difficult to quantify the specific impact of the pandemic on our sample. Data from Italy suggest that school closures reduced headache intensity and frequency in schoolchildren with different headache disorders during the first wave of the pandemic [93]. However, a significant increase in the frequency of migraine attacks and in the use of prophylactic medication was reported during the second wave of the pandemic, when most of the data for this analysis were collected [94]. Furthermore, scheduling and implementation of treatments became more complex due to quarantine of patients in contact with individuals infected with SARS-CoV-2 or being infected themselves.

In the context of pediatric headache disorders, rNMS emerged as a promising, point-of-care neuromodulation approach. It has been demonstrated to be safe, feasible, and highly accepted among children and adolescents. Three age-typical headache disorders (migraine, TTH, and PTH) experienced a significant reduction in headache frequency and intensity during the three-month follow-up. However, to assess the potential of rNMS as a valuable, noninvasive, and personalized treatment complementing the multimodal regimen for pediatric headache disorders, larger controlled studies are essential [90, 91].

To address such shortcomings, our research group is currently conducting a prospective, randomized, sham controlled, multiparametric diagnostic study (MagMig study, DRKS00024470) including young adults with high-frequent episodic migraine to further investigate the efficacy of rNMS and to identify its mechanisms of action. During my research time, I contributed to the study set-up including rNMS treatments and study assessments comprising a physiotherapeutic diagnostic of the UTM, sonography of the UTM, magnetic resonance imaging (MRI) of the UTM, and cranial MRI. As I was particularly involved in the planning phase of the study, I helped with drafting the documentation sheets and created an overview of existing migraine applications for mobile devices to be potentially used by study participants.

3. Abstract (Deutsch):

Einleitung: Primäre Kopfschmerzerkrankungen wie Migräne, Kopfschmerz vom Spannungstyp (TTH) und deren Mischtyp stellen auch im Kindes- und Jugendalter hoch relevante Erkrankungsbilder dar. Als sekundäre Kopfschmerzerkrankung ist auch der posttraumatische Kopfschmerz (PTH) wegen seiner Häufigkeit herauszustellen. Alle diese Kopfschmerzerkrankungen können in Abhängigkeit von der Frequenz und Ausprägung der einzelnen Attacke eine erhebliche Belastung darstellen. Nachdem wir die repetitive neuromuskuläre Magnetstimulation (rNMS) bei jungen Erwachsenen als sicher, gut durchführbar und gut akzeptiert belegt haben, werden in dieser retrospektiven Analyse die Sicherheit, Durchführbarkeit und Akzeptanz sowie die klinischen Auswirkungen in einer pädiatrischen Kohorte („first-in-child“) untersucht.

Methodik: Eine Kohorte von n=33 Kindern und Jugendlichen, die n=182 rNMS Behandlungen in einem klinischen Umfeld erhielten, werden retrospektiv hinsichtlich der Durchführbarkeit und Wirksamkeit von rNMS am oberen Trapezius Muskel analysiert. Verschiedene Parameter, darunter die Intensität und Häufigkeit der Behandlung, die Sicherheit, die zentralen und muskulären Effekte und Faktoren, die das Ausmaß des Ansprechens beeinflussen können, werden untersucht.

Ergebnisse: Die Ergebnisse deuten darauf hin, dass die rNMS ein vielversprechender, nicht-pharmakologischer, neuromodulatorischer Ansatz bei pädiatrischen Kopfschmerzerkrankungen sein kann. Sie zeigen, dass rNMS praktikabel durchführbar, sicher und gut akzeptiert ist: keine unerwünschten Nebenwirkungen bei 76,8% der Behandlungseinheiten; nach 88.5% der Behandlungsblocks würden Patienten die Behandlung wiederholen; 95% der Patienten würden die Behandlung weiterempfehlen. Therapeutisch wegweisend geht sie mit einer signifikanten Verringerung der Häufigkeit und Intensität von Kopfschmerzen einher. Insbesondere bei PTH-Patienten konnte die muskuläre Hypersensibilität reduziert und diese Reduktion bis zur Nachuntersuchung nach 3 Monaten aufrechterhalten werden. Nackenschmerzen erwiesen sich dann auch als ein Faktor, der das Ansprechen auf die rNMS positiv anzunehmen lässt.

Schlussfolgerung: rNMS bietet eine neue, nicht-pharmakologische, personalisierte Behandlungsoption für Kinder und Jugendliche mit Kopfschmerzerkrankungen, die sie sich als sicher, durchführbar, hoch akzeptiert und wirksam gezeigt hat. Grundsätzlich scheint sich die Intervention – unabhängig von der spezifischen ICHD-3 Diagnose – positiv auf die Kopfschmerzsymptome auszuwirken. Patienten mit Nackenschmerzen scheinen biologisch plausibel besonders responsiv zu sein, was konzeptuell auf eine Neuromodulation der zentralen nozizeptiven Verarbeitung im trigemino-zervikalen Komplex bezogen werden kann. Trotz klarer Einschränkungen bietet diese Analyse eine

Grundlage für künftige Forschung und die mögliche Integration von rNMS in eine multimodale Behandlung von pädiatrischen Kopfschmerzerkrankungen. Größere, kontrollierte Studien sind erforderlich, um die Wirksamkeit und den Nutzen der rNMS in dieser Bevölkerungsgruppe zu bestätigen und möglicherweise weiterzuentwickeln.

4. Abstract (English):

Introduction: Pediatric primary headache disorders, including migraine, tension-type headache (TTH) and their mixed-type pose a significant burden on young individuals. Post-traumatic headache (PTH) is also to be emphasized as a secondary headache disorder due to its prevalence. Depending on frequency and severity of individual attacks, these headache disorders can represent a considerable burden. After we found repetitive neuromuscular magnetic stimulation (rNMS) to be safe, feasible and well accepted in young adults, in this analysis safety, feasibility, acceptance as well as clinical impact in the pediatric age group („first-in-child“) are retrospectively assessed.

Materials and Methods: A cohort of n=33 children and adolescents who received n=182 rNMS sessions in a clinical setting are retrospectively analyzed regarding feasibility and effectiveness of rNMS targeting the upper trapezius muscle (UTM). Various parameters, including intensity and frequency of treatment, safety, central and muscular effects, and factors affecting the level of response are evaluated.

Results: The project findings suggest that rNMS holds promise as a point-of-care non-pharmacological neuromodulation approach for pediatric headache disorders. It demonstrates that rNMS is practically feasible, safe, well-accepted (No adverse events in 76.8% of sessions, 94.7% of patients would undergo the treatment again, 85.3% would recommend the treatment). Therapeutically groundbreaking, the treatment seems to be associated with a significant reduction in headache frequency and intensity. Especially in PTH patients muscular hypersensitivity was reduced, and the reduction sustained until the follow-up assessment 3 months later. Neck pain then also emerged as a factor positively influencing the response to rNMS.

Conclusion: Repetitive neuromuscular magnetic stimulation (rNMS) offers a new, non-pharmacological and personalized treatment option for children and adolescents with headache disorders as it was found to be safe, feasible, and highly accepted. In principle, rNMS appears to have a positive impact on headache symptoms - irrespective of the specific ICHD-3 diagnosis. Patients with neck pain seem biologically plausible to be particularly responsive which can be conceptually related to neuromodulation of central nociceptive processing within the trigemino-cervical complex. Despite clear limitations, this analysis provides a foundation for future research and the potential integration of rNMS into a multimodal regimen for pediatric headache disorders. Larger controlled studies are warranted to confirm and potentially develop the efficacy and utility of rNMS in this population further.

5. Paper I

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Repetitive neuromuscular magnetic stimulation in children with headache

European Journal for Pediatric Neurology, 39, 40–48.
https://doi.org/10.1016/j.ejpn.2022.04.010.

6. Paper II

Corinna Börner†, **Jacob Staisch**†, Magdalena Lang, Ari Hauser, Iris Hannibal, Kristina Huß, Birgit Klose, Matthias F. Lechner, Nico Sollmann, Florian Heinen, Mirjam N. Landgraf and Michaela V. Bonfert †shared first author

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

Brain sciences, 12, 932. https://doi.org/10.3390/brainsci12070932.

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Acknowledgements

I am deeply grateful to Florian Heinen, Michaela V. Bonfert, and Mirjam Landgraf for giving me the opportunity to join their research group, for sharing their expertise, and for their patient guidance throughout the entire process of this thesis. I want to thank Stephan Thorban for his scholarly advice from afar. My supervisors’ support, encouragement, and constructive feedback have been instrumental in shaping this work.

I extend my sincere gratitude to Corinna Börner-Schröder for her guidance, collaboration, insightful discussions, and shared dedication to advancing our research endeavors. Her contributions have greatly enriched this project and her scientific approach has been truly inspiring.

In addition, I wish to thank our whole research team, especially Magdalena Lang, Ari Hauser, and Matthias Lechner, for all the countless opportunities to learn from one another.

Also, the team of our clinic’s outpatient headache clinic built the framework of this thesis through their cooperation, assistance, and valuable insights. Their commitment to excellence in patient care and research has been inspiring and enlightening. Thank you!

Finally, I wish to acknowledge the unwavering support and understanding of my family and friends. I am profoundly grateful for their love, encouragement, and sacrifices that enabled me to pursue my academic aspirations.