Effects and Reliability
of Repetitive Transcranial Magnetic Stimulation

Effekte und Reliabilität
von repetitiver transkranieller Magnetstimulation

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Vollständiger Abdruck der von der Fakultät für Humanwissenschaften der Universität der Bundeswehr München zur Erlangung des akademischen Grades eines

Doktors der Philosophie

angenommenen Dissertation.

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Die Dissertation wurde am 29.09.2025 bei der Universität der Bundeswehr München eingereicht und durch die Fakultät für Humanwissenschaften am 27.02.2026 angenommen. Die mündliche Prüfung fand am 24.03.2026 statt.

Acknowledgements

Danksagung

Für meine Mama.
Und für meine Tochter.
Danke, dass ihr die zwei stärksten Frauen in meinem Leben seid, mein Halt und meine Inspiration!

Danke an alle, die mir in den letzten Jahren Beistand, Rat und Kraft gegeben haben:

Danke, Wolfgang, für deine allumfassende Unterstützung, deine vorausschauenden Ratschläge und deine tiefgründigen Kommentare!
Danke, Stefan, dass du unfassbar freundlich, enthusiastisch und unermüdlich mich durch das Getümmel der Wissenschaft(ler) gelotst hast!
Danke, Martin, für deinen unablässigen Einsatz (für uns, das Labor und die TMS), deine anleitenden Ermutigungen und ansteckende Freude!
Danke, Mirja, dass du ungefragt ein Girls-Girl bist, alle (Orga-)Sachen immer auf dem Schirm hast, und generell einfach die beste (Labor-)Partnerin bist, die es gibt!
Danke, MEXT-Team, für über drei Jahre grandiosen Austausch, grandiose Freundschaft und grandiose Wissenschaft!
Danke, TMS-Labor-Team, für die liebevolle Aufnahme, die Hilfe bei unzähligen Bestellvorgängen und das Beistehen in allen Lebenslagen!
Danke auch an alle Co-Autoren und Teilnehmenden der Experimente. Ohne euch stünde hier recht wenig!

Zu guter Letzt möchte ich meiner Familie danken: Meinem Papa mit seinen LaTeX-Tipps, Dirk mit seinen Promotions-Tipps und vor allem meinem Mann Stephan, der mich durch die schönsten, aufregendsten und angstvollsten Stunden begleitet hat und auch weiterhin zu Höchstform anspornt!

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique to induce longer lasting plasticity changes in the brain. Applied with lower frequency of about 1 Hz, it is considered to evoke inhibitory cortical effects, whereas with higher frequencies it can cause facilitatory effects. Other rTMS procedures with patterned and combined administration methods are also categorized according to their effects on cortical excitability. With single transcranial magnetic stimulation (TMS) pulses, derivations of cortical excitability, such as transcranial evoked potentials (TEPs), and of cortico-spinal excitability, such as motor evoked potentials (MEPs), can measure rTMS effects. Since high variability is associated with both TMS and rTMS measures, the present dissertation investigates rTMS effects and test-retest reliability along with influencing variables, such as the current direction induced in the brain during TMS pulse application. Three studies pursue the detailed examination of firstly, the effects and reliability of 1 and 20 Hz rTMS on MEPs, secondly, the effects and reliability of MEPs of previously published rTMS articles, and thirdly, the influence of current direction on TEPs and MEPs in a 1 Hz rTMS protocol. The first study revealed that neither inhibitory nor facilitatory effects were replicable, although there was descriptive tendency within the data. The reliability of both the 1 and 20 Hz rTMS protocol was low to moderate. The second study showed an overall low to moderate reliability of rTMS protocols with only two out of 15 articles showing high reliability, whereby no influences of factors inducing variability or publication bias was found. The third study further highlighted the lack of repeatability of rTMS effects by resulting in contrary effects for 1 Hz rTMS. Both MEP and TEP components were influenced by current direction. This dissertation emphasizes the variability in TMS and rTMS and calls upon improvement of application, data acquisition and preprocessing to increase both rTMS effects and reliability.

Zusammenfassung

Repetitive transkranielle Magnetstimulation (rTMS) ist eine nicht-invasive Technik, mit der zeitweilig andauernde Änderungen der Gehirnplastizität induziert werden können. Wenn rTMS mit niedriger Frequenz um circa 1 Hz angewendet wird, wird vermutet, dass es inhibitorische kortikale Effekte hervorruft, wohingegen höhere Frequenzen exzitatorische Effekte verursachen können. Andere rTMS Protokolle mit TMS Pulsen, die in einem bestimmten Muster abgegeben werden, oder solche mit verbundenen Stimulationsanwendungen, werden ebenso nach ihren Effekten auf kortikale Erregbarkeit eingeordnet. Mithilfe von transkranieller Magnetstimulation (TMS) mit Einzelpulsen können die Ableitungen von kortikaler Erregbarkeit, wie transkranielle evozierte Potentiale (TEPs), und kortiko-spinaler Erregbarkeit, wie motor-evozierte Potentiale, rTMS Effekte messen. Da hohe Variabilität in TMS und rTMS vorherrscht, untersucht diese Dissertation rTMS Effekte und Test-Retest-Reliabilität mit Einflussvariablen, wie der Stromrichtung, die während der Applikation eines TMS Pulses im Gehirn induziert wird. Drei Studien verfolgen die detaillierte Untersuchung von erstens, Effekten und Reliabilität von 1 und 20 Hz rTMS auf MEPs, zweitens, Effekten und Reliabilität auf MEPs von bereits veröffentlichten rTMS Artikeln, und von drittens, Einflüssen von Stromrichtung auf TEPs und MEPs in einem 1 Hz rTMS Protokoll. Die erste Studie zeigte, dass weder inhibitorische noch exzitatorische Effekte replizierbar waren, obwohl die Daten eine Tendenz dazu zeigten. Die Reliabilität von sowohl dem 1 als auch dem 20 Hz rTMS Protokoll war gering bis moderat. Die zweite Studie legte dar, dass rTMS Protokolle generell eine geringe bis moderate Reliabilität aufweisen, wobei nur zwei von 15 Artikeln hohe Reliabilitäten zeigten. Keine Einflüsse von variabilitätsinduzierenden Faktoren oder Publikationsbias wurden gefunden. Die dritte Studie betonte die mangelnde Wiederholbarkeit von rTMS Effekten durch Ergebnisse, die in die entgegengesetzte Richtung zu der erwarteten Inhibition von 1 Hz rTMS gingen. Sowohl MEPs als auch TEP Komponenten waren durch die Stromrichtung beeinflusst. Diese Dissertation hebt die Variabilität in TMS und rTMS hervor und ruft auf, sowohl Anwendung, als auch Datenerfassung und Vorverarbeitung zu verbessern, um rTMS Effekte und Reliabilität zu erhöhen.

Glossary of Terms

ADHD Attention deficit hyperactivity disorder

ADM Abductor digiti minimi

AEPs Auditory evoked potentials

AFz EEG electrode placed anterior frontal in the midline sagittal plane

AIC Akaike information criterion

ANOVA Analysis of variance

AP Anterior-posterior

APB Abductor pollicis brevis

AP-PA Anterior-posterior – posterior-anterior

ARTEMIS Annual Regensburg Transcranial Evoked Measures Interactive Symposium

AUC Area under the curve

|AUC| Rectified area under the curve

B-field Magnetic field

BIC Bayesian information criterion

BNDF Brain-derived neurotrophic factor

CD Current direction

CE Cortical excitability

CI Confidence interval

Cobot Collaborative robotic coil holder

CSE Cortico-spinal excitability

cTBS Continuous theta burst stimulation

C3 Central EEG electrode on the left

dlPFC Dorsolateral prefrontal cortex

D-wave Direct wave

EEG Electroencephalography

E-field Electrical field

EMG Electromyography

FCz Frontal central EEG electrode in the midline sagittal plane

FDI First dorsal interosseous

FDR False discovery rate

fMRI Functional magnetic resonance imaging

GABA Gamma-aminobutyric acid

GND Ground electrode

Hotspot Optimal individual position for TMS

ICA Independent component analysis

ICC Intraclass correlation coefficient

I-O curve Input-output curve

IPI Inter-pulse-interval

ISI Inter-stimulus-interval

iTBS Intermittent theta burst stimulation

iTEP Immediate transcranial evoked potential

ITI Inter-train-interval

I-waves Indirect waves

κ Cohens kappa

lofi-hife heuristic Low frequency inhibitory – high frequency excitatory heuristic

LTD Long-term depression

LTP Long-term potentiation

M Mean

Md Median

MEP Motor evoked potential

MEXT Modular extended transcranial magnetic stimulation

MDI Major depression inventory

MSO Maximum stimulator output

MWTB-Q Multiple-choice vocabulary intelligence test

M1 Primary motor cortex

n Number (of participants)

NIBS Non-invasive brain stimulation

NMDA N-methyl-D-aspartate

NN Use of neuonavigation

N15 Negative TEP peak at 15 ms

N45 Negative TEP peak at 45 ms

N100 Negative TEP peak at 100 ms

PA Posterior-anterior

PA-AP Posterior-anterior – anterior-posterior

PAS Paired associative stimulation

PAS$_{10}$ Paired associative stimulation with 10 ms ISI

PAS$_{25}$ Paired associative stimulation with 25 ms ISI

PFC Prefrontal cortex

PRISMA Preferred reporting items for systematic reviews and meta-analyses

p2p Peak-to-peak

P30 Positive TEP peak at 30 ms

P60 Positive TEP peak at 60 ms

QPS Quadripulse stimulation

Q1-4 Quarters 1 to 4

r Pearson correlation coefficient

RMT Resting motor threshold

rTMS Repetitive transcranial magnetic stimulation

SEPs Somatosensory evoked potentials

SD Standard deviation

SI1mV Stimulus intensity to evoke MEPs of 1 mV amplitude

SI50 MEP sizes halfway between minimal and maximal cortical excitability

SOUND Source-estimate-utilizing noise-discarding algorithm

spTMS Single pulse TMS

SSP-SIR Signal-space-projection-source-informed reconstruction

TAAC TMS adaptable auditory control

TBS Theta burst stimulation

TEP Transcranial evoked potential

tES Transcranial electric stimulation

TESA TMS-EEG signal analyser

TMS Transcranial magnetic stimulation

VAS Visual analogue scale

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1 Introduction

Transcranial magnetic stimulation (TMS) has been a tool for brain research, clinical diagnostics and in its application with higher frequencies (repetitive transcranial magnetic stimulation; rTMS) for therapeutic treatment of neuropsychiatric disorders for almost 50 years. Yet, underlying mechanisms are still poorly understood, not only because of its interaction with the highly variable human brain, but also because stimulation parameters and application procedures vary between laboratories and users and thus, experimental findings cannot be reproduced precisely. Some of the golden standards of application and interpretation are currently questioned, making it necessary to replicate previous findings and identify parameters that reduce variability and increase reliability of TMS and rTMS. This work aims to reproduce effects of rTMS and investigate their reliability in order to gain insights into the variability of TMS and rTMS and its sources.

1.1 Transcranial magnetic stimulation (TMS)

TMS is a non-invasive brain stimulation (NIBS) technique that can induce activity in underlying tissue by evoking an action potential through rapidly changing electrical fields. It is mainly used on the human brain (Hallett, 2000), but to identify mechanisms on a micro level, it can also be applied on cell cultures (Rotem & Moses, 2008), peripheral nerves and muscles (Okudera et al., 2015; Rossini et al., 2015) and animals (Mueller et al., 2014; Murphy et al., 2016).

1.1.1 History

TMS arose from the findings of transcranial electrical stimulation (tES). In animal experiments, descending activity within the cortico-spinal neurons after electrical single pulse stimulation were found (Patton & Amassian, 1954). Patrick A. Merton and H. Bert Morton evoked distal arm and foot twitches by anodal stimulation over the human cortex (Merton & Morton, 1980). The magnetic stimulation with a pulse source, which was previously only used on animals and peripheral nerve stimulation (Bickford R. G. & Fremming, 1965) was tested on the cortex by Anthony Barker with Merton in 1985 for the first time, where muscle contractions were derivable (Barker et al., 1985).

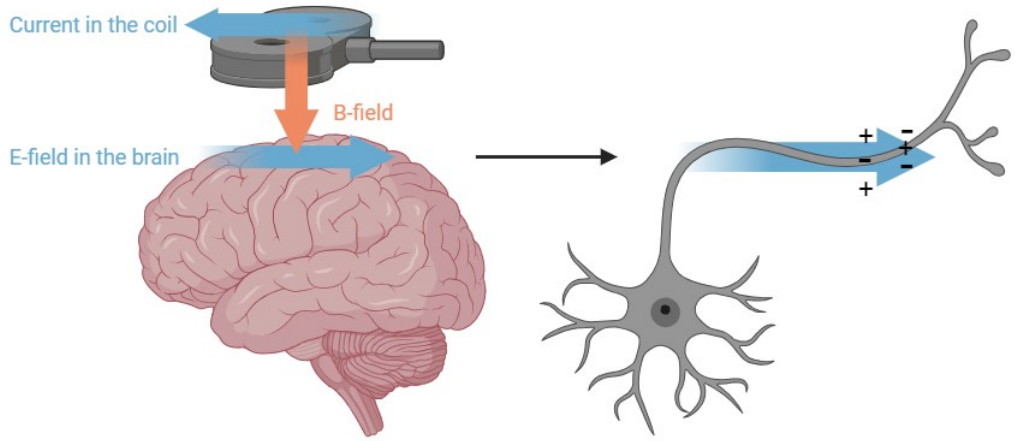
The technical aspects have not been changed essentially since the beginnings of TMS. The devices to produce the magnetic pulses used for stimulation comprise of a pulse source or stimulator that generates an electric current and a coil made of copper wire through which the current runs and thus a pulse is emitted (Gutiérrez-Muto et al., 2023). From using round coils in early administration of TMS pulses, nowadays, usually a figure-of-eight coil is used on the human cortex due to its focal stimulation

properties (Rösler et al., 1989). Yet, new TMS devices that are technically adapted to the areas of application are produced regularly (Gutiérrez-Muto et al., 2023). Thus, the electric properties of the pulse source, e.g. current voltage or circuits, and the coil design, e.g. diameter or number of windings, slightly vary within and between manufacturers (van Doren et al., 2015; Gutiérrez-Muto et al., 2023), which complicates the comparison of TMS effects. However, the basic mechanisms of inducing brain activity by evoking an action potential in underlying cortical neurons remain the same.

1.1.2 Mechanisms

When positioning the coil over the human head and applying a pulse, a brief electrical current passes through the coil and produces a rapidly changing magnetic field (**B**-field) where the lines of flux are perpendicular to the plane of the coil (Ilmoniemi et al., 1999; Wagner et al., 2009). This temporally changing magnetic field induces an electrical field (**E**-field) in the underlying cortical tissue according to Faraday's law that is perpendicular to the magnetic field, which is parallel to the plane of the coil (Ilmoniemi et al., 1999; Wagner et al., 2009). The electrical field in the tissue that usually spreads over a few square centimeters of cortical area generates a current flow that affects the transmembrane voltage of neuronal axons or dendrites and can lead to depolarization, eliciting action potentials that can be propagated (Ilmoniemi et al., 1999; Di Lazzaro et al., 2018). The magnetic field does not induce any currents. To sum up, a single TMS pulse can evoke and alter activity in the whole brain. This mechanism is depicted in Figure 1.

Figure 1
Current flow in the coil and brain



Notes. Schematic depiction of the current flow in the coil, the induced **B**- and **E**-field as well as the change of axonal membrane potential in a bent pyramidal neuron. This figure was created in https://BioRender.com (use of graphical templates).

Most important for the pulse to lead to a depolarization of cortical neurons and inducing action potentials are the field strength and field gradient (Roth & Basser, 1990; Ilmoniemi et al., 1999). The latter refers to the change of field strength along a spatial direction. In uniform electrical fields, such as those elicited directly under the middle of a figure-of-eight coil, the axonal membrane of the neuron needs to be curved or exhibit boundaries or running perpendicular to the electrical field lines to create a strong field gradient and enhance the probability of excitation (Maccabee et al., 1993). This phenomenon is shown schematically in Figure 1 on the right. Thus, pyramidal axons and axons that go parallel to the cortical surface but perpendicular to the electrical field seem to be suitable target structures of TMS (Di Lazzaro et al., 2001). By applying a TMS pulse over the primary motor cortex (M1), several responses in the pyramidal tract can be recorded via invasive bipolar electrodes. At high levels of stimulation intensity, 0.4 to 1.2 ms after the TMS pulse, a direct wave (D-wave) appear followed by up to seven volleys of indirect waves (I-waves) with intervals of about 1.5 ms in derivations of pyramidal neurons (Patton & Amassian, 1954; Rossini & Rossi, 1998; Di Lazzaro et al., 2018). Yet, the appearance of these volleys depends on the stimulation intensity and the orientation of the stimulation coil, indicating selective inputs to corticospinal neurons (Di Lazzaro et al., 2018).

These waves represent the propagation of the activity induced in the brain through the corticospinal pathway to the corresponding peripheral muscles and can link findings on direct cortical responses and the indirect peripheral measures.

Other neurons can also be activated as well as different circuits operated, for example via transsynaptic excitation propagation, but until now approaches to further investigate these activation patterns were shown to be very complex and have not been focused on scientifically (Spampinato et al., 2023).

1.2 Cortical and cortico-spinal excitability

Cortical excitability (CE) refers to neural activity and is the state of the brain that allows conclusions to be drawn about reactivity and thus the health and flexibility of neuronal transmission (Hallett, 2000; Freitas et al., 2013). It can be measured using TMS pulses over the cortex and derived via electroencephalography (EEG), functional near-infrared spectroscopy, functional magnetic resonance imaging (fMRI) or positron emission tomography (Pascual-Leone et al., 1999; Curtin et al., 2019). Cortico-spinal excitability (CSE) on the other hand denotes the activity of the combined pathway from brain to periphery, which can be derived via electromyography (EMG) from e.g. hand muscles (Spampinato et al., 2023). When assessing the effects of TMS on the human brain, usually the effects of TMS on CE or CSE are investigated. Historically, the CSE is the most common and investigated derived measure (Lefaucheur et al., 2014).

1.2.1 Motor evoked potential (MEP)

When emitting a TMS pulse over the motor cortex, the brief induction of an electrical field in the underlying tissue can result in depolarization of neurons and subsequently a propagation of action potentials through the cortico-spinal tract that cause a summation potential and twitch in the connected muscles, referred to as motor evoked potential (MEP) (Spampinato et al., 2023). This potential is typically measured via EMG in belly-tendon montage, i.e. with an active electrode (silver chloride) over the stimulated muscle belly, a reference electrode over the tendon of this specific muscle and a ground electrode over a bone more proximal to the stimulation site than the stimulated muscle (Rossini et al., 2015).

The MEP in hand muscles, such as the first dorsal interosseus (FDI), can be derived in a time window of circa 10 to 50 ms after the TMS pulse and typically consists of a biphasic wave (Day et al., 1989; van Doren et al., 2015). The parameters to derive from a MEP are the latency and the peak-to-peak (p2p) amplitude. To account for the total muscle sum potential, the area under the curve (AUC) from the rectified signal can also be investigated (Brown et al., 2017). Although showing variability, the MEP amplitude is considered a good indicator of CSE (Day et al., 1989; Bashir et al., 2017). An increase of CSE can thus be inferred from an increase of MEP peak-to-peak amplitude, whereas a decrease of CSE is manifested in a decrease of MEP amplitude. Additionally, the MEP amplitude is an indicator of stimulation sensitivity and the individual stimulation intensity for various protocols is derived from the resting motor threshold (RMT), as descripted below.

Resting motor threshold (RMT) The RMT is a measure of individual excitability of the cortico-spinal tract. With single TMS pulses over the individual hotspot (Rossini et al., 2015), i.e. the place over the motor cortex that elicits high and stable MEPs in the muscle of interest, MEPs are evoked and the intensity of these single pulses is adapted to the threshold, where 50 % of the MEPs have an amplitude of at least 50 µV (Rossini & Rossi, 1998).

With the help of the RMT, stimulation intensity personalized TMS protocols are possible. Hereby, the induced intensity is mainly linked to the desired effect. For example, suprathreshold protocols can enhance the activation probability of underlying cortical regions but on the other hand may result in the acquisition of peripheral muscle activity which can lead to unpleasant sensations on the head, affect safety and contaminate recordings (Rossi et al., 2021).

1.2.2 Transcranial evoked potential (TEP)

A measure of CE is the transcranial evoked potential (TEP). Hereby, the whole brain activity is measured via EEG directly after applying a TMS pulse over the

scalp (Komssi & Kähkönen, 2006; Tremblay et al., 2019). TEPs can be derived anywhere over the cortex and can be elicited even when applying TMS pulses with subthreshold intensity, i.e. stimulation below the RMT (Farzan & Bortoletto, 2022).

When applying TMS over the motor cortex, the typical TEP components N15, P30, N45, P60 and N100 are elicited within the first 150 ms (Bonato et al., 2006; Ahn & Fröhlich, 2021). These components are named after the respective brain activity amplitude deflection, i.e. negative (N) or positive (P) activity, and the respective latency of the deflection, i.e. 15 ms, 30 ms etc. Before the first 15 ms, immediate TEPs (iTEPs) can also be derived when the stimulation and recording parameters are adjusted accordingly and artifacts that overshadow the brain signal can be removed (Beck et al., 2024). Yet, within this work, we will omit iTEPs and focus on the components starting from circa 8 ms after the pulse, which is the time interval until the TMS artifact occurred in the data. Although initially the brain activity is expected directly over the stimulation site, i.e. the motor cortex, the signal propagation within the first 150 ms after the pulse also involves other brain regions (Tremblay et al., 2019). Thus, the topography of the TEP components differs and the cortico-cortical interaction makes it difficult to directly assign signals to respective functions (Kicić et al., 2008; Zazio et al., 2022).

Until now, the origin of the signal from the TEP components is not clearly identified. It has been found that the MEP amplitude correlates with the combined component amplitudes of N15 and P30 (Mäki & Ilmoniemi, 2010), as well as the cortico-cortical measure P15, which is derived contralateral to N15 (Guidali et al., 2023), revealing a relationship of the cortical and cortico-spinal activation. Since the MEP appears around 25 ms after the pulse, it also makes sense in physiological terms that the components N45 and P60 represent the reafferent motor signal (Mäki & Ilmoniemi, 2010; Petrichella et al., 2017; Ahn & Fröhlich, 2021). For TEP component N100, research has shown that it contributes to neuronal inhibition (Nikulin et al., 2003), also since its amplitude can be enhanced by gamma-aminobutyric acid (GABA)-B agonists, which is known to be an inhibitory neurotransmitter (Premoli et al., 2014).

Yet, these findings do not cover all influences to TEP components and the data is prone to a lot of noise and variability (Conde et al., 2019; Farzan & Bortoletto, 2022). Auditory evoked potentials (AEPs) that appear by the click sound of the TMS coil when a pulse is emitted, and somatosensory evoked potentials (SEPs) that occur when action potentials in the nerve fiber cells in the underlying skin are evoked, can confound cortical responses to TMS (Nikouline et al., 1999; Malcharek et al., 2011; Alhussaini et al., 2018; Conde et al., 2019; Rocchi et al., 2021). Also, since EEG also captures large signal of muscle and eye movement as well as electrode noise from ringing beneath the coil, the preprocessing of EEG signal is essential in reconstructing brain activity (Rogasch et al., 2022). With the TMS-EEG signal

analyser (TESA) pipeline, many identified sources of noise can be fairly isolated and subtracted from the data (Rogasch et al., 2017). Still, although TEPs yield the potential to serve as biomarker (Lioumis et al., 2009; Kerwin et al., 2018; Gogulski et al., 2024), due to high inter- and intra-individual variability of cortical activity, the effects of TMS on TEPs are not sufficiently investigated and for now lack reliability and validity across laboratories (Parmigiani et al., 2022).

1.3 Repetitive transcranial magnetic stimulation (rTMS)

TMS cannot only be used to probe CE, but when delivered at an increased frequency ($\geq$ 0.9 Hz) or in repeated patterns (e.g. triplet pulses), it has been shown to alter CE and CSE (Pascual-Leone et al., 1994a; Wassermann et al., 1996; Klomjai et al., 2015). This so-called repetitive transcranial magnetic stimulation (rTMS) can also evoke sustained responses over several minutes (Ridding & Rothwell, 2007).

Typical investigated rTMS protocols involve frequencies of 1, 2, 5, 10 and 20 Hz as well as patterns of triplet pulses with a frequency of 50 Hz and inter-burst-intervals of 5 Hz, which is termed theta burst stimulation (TBS), and protocols that include a conditioning peripheral electrical pulse applied before the TMS pulse, termed paired associative stimulation (PAS) (Stefan et al., 2000; Huang et al., 2005; Klomjai et al., 2015). Other, more recently developed protocols include primed (Iyer et al., 2003) and accelerated protocols (Cole et al., 2020), as well as quadripulse stimulation (QPS) which consists of a pattern of four pulses that is applied with a frequency of 0.2 Hz for 30 min (Hamada et al., 2007), whereby the frequency of the four pulses within the pattern itself can vary from 10 to 666 Hz (Hamada & Ugawa, 2010). Usually, these protocols are developed to increase the effects of CE altering, i.e. cortical plasticity or neuromodulatory changes in the brain (Hamada et al., 2007), but the empirical evidence and thus validity is not yet as widespread as for more established protocols.

1.3.1 Effects

Since rTMS protocols can evoke a longer lasting modulation effect of synaptic plasticity and thus neuronal activity (Ridding & Rothwell, 2007), hereby, a distinction is made between two groups of rTMS protocols: One group includes protocols that cause an increase in cortical excitability and lead to excitation or facilitation. Typically, these include high-frequency rTMS ($\geq$ 5 Hz, sometimes even 2 Hz), intermittent theta burst stimulation (iTBS) and PAS with an inter-stimulus interval (ISI) between conditioning peripheral electrical pulse and TMS pulse of 25 ms (PAS_{25}) (Wolters et al., 2003; Fitzgerald et al., 2006; Klomjai et al., 2015). The other group includes protocols such as low-frequency rTMS (approximately 1 Hz), continuous theta burst stimulation (cTBS) and PAS with an ISI of 10 ms (PAS_{10}). These pro-

tocols tend to reduce cortical excitability and thus lead to inhibition (Wolters et al., 2003; Fitzgerald et al., 2006; Klomjai et al., 2015). This classification is merely a rule of thumb, that in the following will be referred to as lofi-hife heuristic (low frequency inhibitory – high frequency excitatory). It is mainly based on empirical research and underlying mechanisms on why these effects occur have not been fully understood yet.

One current explanation in the literature on these underlying mechanisms of excitation and inhibition are discussed as long-term potentiation (LTP), i.e. the increase of synaptic strength, and long-term depression (LTD), i.e. the decrease of synaptic strength, respectively (Matsuura et al., 1993; Bear & Malenka, 1994; Wassermann et al., 1996; Chen et al., 1997; Hoogendam et al., 2010). Hereby, it is considered that the timing of neuron stimulation is crucial, inducing LTP when first the presynaptic neuron and after that the postsynaptic neuron is stimulated within close temporal connection, and inducing LTD when first the postsynaptic neuron and then the presynaptic neuron is stimulated (Hoogendam et al., 2010), which can be modulated via N-methyl-D-aspartate (NMDA) receptor triggering and concurrent calcium ion release (Bear & Malenka, 1994). Also, both short (early; for 60 minutes) and long (late; up to weeks) lasting phases of LTP and LTD can occur, whereby the former is induced by the modifications of existing proteins, and the latter is expressed by gene expression and synthesis of proteins (Frey & Morris, 1998; Baltaci et al., 2019).

These bio-chemical reactions are also considered to found learning and memory mechanisms and contribute to neurological disease (Pfeiffer & Huber, 2006; Hoogendam et al., 2010). Therefore, evoking LTP and LTD – like effects by applying rTMS protocols to both healthy individuals and neuropsychiatric patients has been frequent subject of research (Mishra et al., 2011; Diana et al., 2017; Gefferie et al., 2023; Xu et al., 2023).

1.3.2 Applications

Since rTMS can be used to transiently alter brain activity towards both a reduced (inhibition; LTD) and enhanced (facilitation; LTP) state (Fitzgerald et al., 2006), protocols have been employed in basic (Fitzgerald et al., 2006), cognitive (Xu et al., 2023) and clinical (Mishra et al., 2011) areas of research.

Basic science research has been using rTMS protocols to investigate signal propagation, such as deriving LTP and LTD – like effects in CE and CSE (Pascual-Leone et al., 1994a; Chen et al., 1997; Esser et al., 2006; Casula et al., 2014). Additionally, cortico-cortical communication (Watanabe et al., 2014) and intrasubject dynamics (Crewther et al., 2021) have been frequent subject of research. Since the underlying mechanisms and intra- and interindividual responses to rTMS protocols have not

been fully understood, current literature is still investigating these aspects as well (Goldsworthy et al., 2021). In cognitive research, rTMS is used to evoke so called virtual lesions, so that neuro-cognitive processes can be actively interrupted (Pascual-Leone et al., 1999; Jahanshahi & Rothwell, 2000). With this tool, mechanisms of learning (Pascual-Leone et al., 1996) and memory (Mottaghy et al., 2000) can be investigated. Also an enhancement of cognitive capacity was shown after rTMS administration (Beynel et al., 2019), which is why current studies are trying to elaborate this effect.

Clinical applications comprise both diagnosis and therapy of neuropsychiatric disorders. For diagnostic research, typically TMS, also referred to as single pulse TMS (spTMS) to distinguish it from rTMS, is used for example to examine myelinization as well as deprivation of motor functions (Kobayashi & Pascual-Leone, 2003; Rossini & Rossi, 2007), yet also repetitive protocols of TMS are used to identify impairments (Di Lorenzo et al., 2020). Applications of rTMS can be employed in order to improve cortical plasticity and subsequent network dynamics ideally for a prolonged period of time for the treatment of Major Depression (Berlim et al., 2013; Cao et al., 2018; Cole et al., 2020), Attention deficit hyperactivity disorder (ADHD) (Chen et al., 2023), Schizophrenia (Brunelin et al., 2023; Jin et al., 2023), Parkinson's (Wagle Shukla et al., 2016), Alzheimer's (Chou et al., 2020) and other diseases (Diana et al., 2017; Schoisswohl et al., 2021).

In comparison to other therapeutic approaches such as psychopharmaceuticals, TMS and rTMS yield less and more harmless side effects. These side effects include sensations on the head, acoustic overstimulation by the click sound of the coil, risk for epileptic seizures, headaches and mood changes (Wassermann, 2000; Rossi et al., 2021). Thus, the clinical use can be beneficial to patients. Still, responder rates and heterogeneous findings indicate high variability and low reliability of rTMS effects (Goldsworthy et al., 2021).

1.4 Reliability

The reliability is, together with objectivity and validity, one of the main criteria of quality of experimental research. Originated from the Latin word "reliabilitas", it refers to the dependability or soundness of results. Hereby, the test-retest reliability, which is also called repeatability or reproducibility is a subcategory and denotes a measure of consistency of results in repeated testing. When a measured effect is reliable, the probability is high that the effect originates from the experimental manipulation and does not appear randomly or is influenced by other random factors. Thus, the manipulation would be dependable and sound.

Reliability is influenced by the variability of the measures, i.e. how different the observed outcome between examinations is, and by the proportion of systematic

and random measurement errors in the total measurement (Cohen, 1988; Aldridge et al., 2017). Therefore, test-retest reliability is higher when the variability between experimental repetitions is low. This can be measured via Pearson correlation coefficient (r), which requires linearity of the two measures to be correlated with. If no linearity can be assumed, the intraclass correlation coefficient (ICC) is a better parameter to be computed, because it does not require linearity and not only accounts for correlation, but also agreement between data points. Agreement means that values do not have to be equally spaced in order to have high agreement but can rather only be directed in the same direction. Both measures comprise ratios of variance.

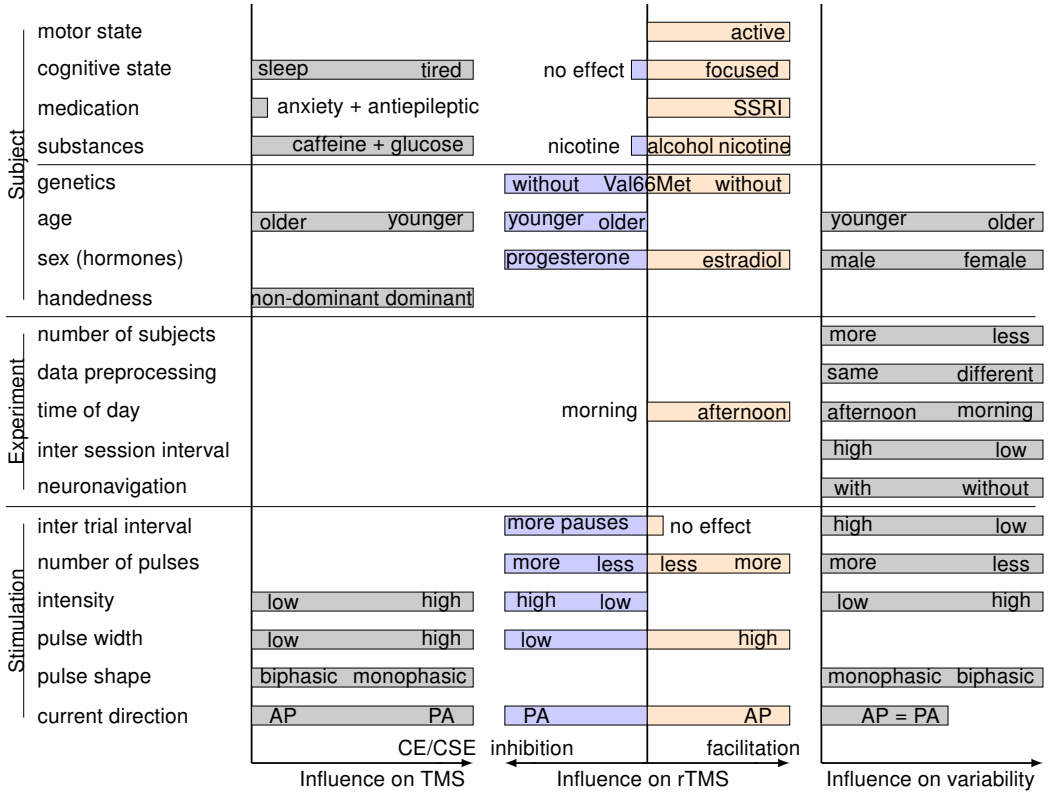
Test-retest reliability in TMS and rTMS effects has been shown to be insufficient (Héroux et al., 2015; Goldsworthy et al., 2021; Gaffney et al., 2023). In basic research, although within laboratories reliability of results occasionally seems to be fair (Lioumis et al., 2009; Hinder et al., 2014; Therrien-Blanchet et al., 2022), across laboratories 50 % of researchers are unable to reproduce published TMS effects (Héroux et al., 2015). Therefore, reliability of TMS and rTMS protocols should be increased in order to further establish magnetic stimulation procedures in both basic and clinical practice. To achieve this, the investigation of parameters that increase variability both within and between measurements might provide insight into the still insufficient reliability.

1.5 Variability in TMS and rTMS

Both TMS and rTMS are prone to variability (Pasley et al., 2009; Goldsworthy et al., 2021; Osnabruegge et al., 2023). A range of 19 to 79 % of healthy subjects show a response to rTMS protocols with the expected inhibition or facilitation (Guerra et al., 2020b). And despite being frequently used for the treatment of Major Depression, only about 25 % of Depression patients responded to treatment with rTMS and 19 % showed an improvement in their symptoms (Berlim et al., 2013). Thus, high variability in TMS and rTMS is a major topic in current research and subject to many improvement approaches (Matsumoto & Ugawa, 2020). To this date, three main groups of influences on variability have been identified: variability related to the stimulation parameters, variability related to the experimental setup and subject related variability (Ridding & Ziemann, 2010; Guerra et al., 2020b). Figure 2 summarizes the influence of the parameters on TMS, rTMS and variability, further described in the following sections.

Figure 2

Influences of stimulation, experimental and subject parameters on TMS, rTMS and variability



Notes. The graphs summarize, which parameters have influence on TMS and elicited CE and CSE (bar graph on the left), on rTMS and inhibition (blue) and facilitation (orange) of CE and CSE (bar graph in the middle), and on the variability of both TMS and rTMS measures (bar graph on the right). This figure was created with LaTeX (using the TikZ package).

A strong influencing factor seems to be the current direction that is induced in the cortex, because different neuronal networks can be activated with opposing flux directions (Spampinato, 2020) and thus, subsequent responses for TMS and rTMS on both micro and macro level differ (Pascual-Leone et al., 1994b; Kammer et al., 2001; Tings et al., 2005; Di Lazzaro & Ziemann, 2013; Spampinato, 2020). Therefore, this work will focus on the influence of current direction.

1.5.1 Stimulation parameter related variability

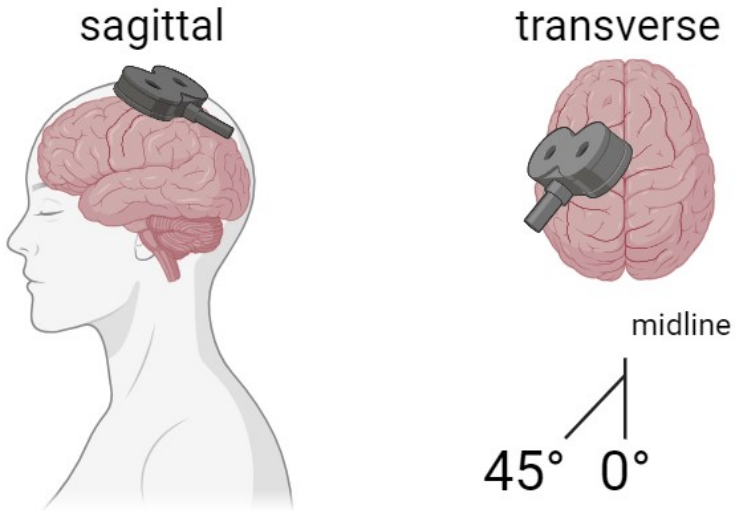
Currently, many different pulse sources are available on the market and in combination with different stimulation coils, the range of possible stimulation parameters is broad (van Doren et al., 2015; Gutiérrez-Muto et al., 2023). These parameters include pulse configurations such as the current direction, pulse shape, width and intensity, as well as the number of applied pulses, the inter-pulse-interval (frequency), inter-train-interval and jitter of pulses.

Current direction It has been found that CSE differs depending on the current direction induced in the brain (Day et al., 1989; Pascual-Leone et al., 1994b). Both, the winding of the coil in combination with the connected pulse source and the coil orientation affect which current direction is induced in the brain (Wagner et al., 2009; Davila-Pérez et al., 2018). The former is closely connected to the pulse shape: Depending on the emitted electrical current through the coil, the subsequent $\mathbf{E}$-field spreads in a certain direction for a fixed time period (Wagner et al., 2009). Thus, monophasic pulses always induce a current direction in the brain that goes spatially into one direction (e.g. posterior to anterior; P-A), whereas biphasic pulses induce a pattern of current direction that propagate into one direction and afterwards back into the opposite one (e.g. posterior to anterior and afterwards anterior to posterior; PA-AP) (Davila-Pérez et al., 2018). Monophasic pulses were often found to be more effective in TMS, which means that RMT was lower than with biphasic pulses (Casula et al., 2018) and MEPs were higher and more reliable (Davila-Pérez et al., 2018). Also rectangular pulses were more effective than sinusoidal pulses (Goetz et al., 2016). Since monophasic and biphasic pulses differ in the directionality of the pulse, also the main pulse phase that is responsible for the stimulation of underlying cortical tissue differs (Salvador et al., 2011). In monophasic pulses, this phase corresponds to the first slope of the pulse, which causes a high rate of change of the current and thus induces a high field gradient that can elicit action potentials in the cortical neurons (Kammer et al., 2001). In biphasic pulses, this high rate of change of the electric current occurs after the first slope of the current, from the first stationary point to the second, for example peak to trough of the phase (Sommer et al., 2006). Therefore, the second directionality of the pulse is more effective in stimulating than the first directionality (Maccabee et al., 1998). When comparing the current direction effects of monophasic to biphasic pulses, because of the different main phase that causes the stimulation, it is necessary to compare the directionality of the second phase of the biphasic pulse to the monophasic one (Corthout et al., 2001; Salvador et al., 2011; Di Lazzaro et al., 2018).

The factor coil orientation refers to external manipulation of the induced electric field by rotating the coil. Hereby, to effectively elicit MEPs, the optimal figure-of-eight coil orientation is perpendicular to the central sulcus (Brasil-Neto et al., 1992) or postcentral gyrus (Richter et al., 2013), which in most subjects is $45°$ or $225°$ to the midline (Balslev et al., 2007). Figure 3 depicts this application and coil orientation. The current flow within this orientation also influences measures of CE and CSE: The hotspot for anteriorly directed pulses was located more anteriorly than for pulses in posterior direction, both monophasic and biphasic (Stephani et al., 2016). The RMT for pulses inducing a current direction from posterior to anterior (PA) was found to be lower than for anterior to posterior (AP) directed pulses (Kammer et al., 2001; D'Ostilio et al., 2016; Stephani et al., 2016; Casula et al., 2018; Davila-Pérez

et al., 2018) and MEP latency shorter (D'Ostilio et al., 2016; Davila-Pérez et al., 2018). For TEPs, a difference in amplitude depending on the directionality was found, whereby monophasic PA pulses induced higher amplitudes in positive peaks than AP pulses, whereas monophasic AP pulses induced larger negative peaks than the PA ones (Casula et al., 2018). PA-directed pulses also induced higher inhibition after 1 Hz rTMS (Goetz et al., 2016), whereas AP-directed pulses (biphasic PA-AP pulses) induced higher excitatory changes after 5 Hz rTMS (Sommer et al., 2013a) and correlated stronger with MEP excitation (Halawa et al., 2021). Both current directions seem to induce equal reliable RMT, MEP amplitude and latency (Davila-Pérez et al., 2018).

Figure 3
TMS application and coil rotation at $45°$ *rotation to the midline*



Notes. This TMS coil rotation, depicted in both sagittal and transverse plane, is common in most subjects to effectively evoke cortical excitability. This figure was created in https://BioRender.com.

Other stimulation parameters Another factor to influence outcome measures of TMS and rTMS is the width of the applied pulse. Pulse width mainly has an impact on the overall energy that is emitted into the brain. When the stimulation intensity is kept constant, increasing the pulse width results in a decreased motor threshold (Peterchev et al., 2013; Halawa et al., 2019). Also, narrower pulses resulted in longer MEP latencies (Halawa et al., 2019). For a facilitatory 5 Hz rTMS protocol, wider pulses evoke significant effects in comparison to narrower ones (Halawa et al., 2021). In an inhibitory 1 Hz rTMS protocol, narrower pulse widths resulted in inhibition, whereas wider ones resulted in excitation of MEPs (Halawa et al., 2019).

When increasing the stimulation intensity, usually the amplitude of MEPs increases along with increased reliability values and the variability decreases (Ngomo

et al., 2012; Cueva et al., 2016; Brown et al., 2017; Pellegrini et al., 2018), although some experiments report otherwise (Kamen, 2004; Christie et al., 2007). Also TEP amplitudes in stimulations over M1 and the prefrontal cortex (PFC) showed intensity dependency, revealing higher TEP amplitudes for higher intensities (Komssi et al., 2004; Kähkönen et al., 2005a; Kähkönen et al., 2005b; Lioumis et al., 2009; Rogasch et al., 2013) and overall significant reliability of TEP amplitudes and latencies (Lioumis et al., 2009). With increased intensity, especially in the direction of subthreshold to suprathreshold, also the inhibitory effects of 1 Hz rTMS were more pronounced (Fitzgerald, 2002; Lang et al., 2006). Yet, with varying suprathreshold intensities, high variability in MEPs was also found with outcomes differing from the lofi-hife heuristic (Pascual-Leone et al., 1994a).

The duration of a measurement, which is defined by the number of pulses and inter-pulse-intervals (IPI) as well as inter-train-intervals (ITI) is another factor that influences variability in cortical excitability measures (Osnabruegge et al., 2023). In general, increasing the number of applied pulses both within and between sessions leads to higher reliability and thus reduces variability in the measures (Christie et al., 2007; Bastani & Jaberzadeh, 2012; Goldsworthy et al., 2016; Hashemirad et al., 2017; Biabani et al., 2018). For TEPs assessed with TMS over the medial dorsolateral prefrontal cortex (dlPFC), the minimal number of pulses needed to get reliable results was found to be 25 with increasing number of pulses also revealing reliable values in adjacent target areas (Gogulski et al., 2024). Between sessions of TMS on the same day, 60-100 pulses were found to reveal good reliability (Kerwin et al., 2018). In rTMS, an increased number of pulses was found to produce variable patterns dependent on the subject (Schoisswohl et al., 2024) and sometimes led to no differences in effects, indicating a ceiling effect (Tang et al., 2019). Good to excellent reliability was also found for minimal IPIs of 4 s (Vaseghi et al., 2015; Hassanzahraee et al., 2019). All IPIs above 1 s should not modulate cortical excitability, which therefore represents the border between TMS and rTMS. Yet, MEP amplitude reductions at TMS with 2 s IPI in comparison to 5 and 10 s IPI (Matilainen et al., 2022) reveal that IPIs of at least 4 s are optimal for assessing cortical excitability without modulating effects. But also rTMS protocols can be modulated and evoke different effects when adjusting the pauses between pulses, i.e. the stimulation frequency (Fitzgerald et al., 2006), as well as the ITI, i.e. pauses between stimulation segments. For example in a segmented 1 Hz protocol, longer ITIs resulted in enhanced inhibition of MEP amplitude (Pitkänen et al., 2017) and more pulses applied in a 1 Hz and 10 Hz rTMS protocol resulted in enhanced inhibition and facilitation, respectively (Maeda et al., 2000a). But in a 20 Hz protocol, duration of ITI had no effect on the increase in cortical excitability after stimulation (Cash et al., 2017).

In general, single TMS pulses are optimally applied with a jittered IPI, because when the stimulation is predictable, MEPs were found to be additionally affected

by internal predictive coding mechanisms of the motor system and amplitudes are suppressed in comparison to unpredictable MEPs (Tran et al., 2021).

1.5.2 Experimental setup related variability

All over the world, experimental TMS setups differ with respect to the devices and their manufacturers (Gutiérrez-Muto et al., 2023) as well as the general sophistication of the technical equipment, such as implementing a neuronavigation tracking system or robotic devices to adjust the stimulation position frequently, mainly due to financial issues (Fleming et al., 2012). While it is known that some equipment strongly increases the objectivity and precision of a stimulation procedure and thus can enhance reliability (Ahdab et al., 2010), the benefits of other gadgets and optimization procedures is not yet fully proven (Herwig, 2002; Kallioniemi et al., 2022). Additionally, methodological choices in the experimental procedure can contribute to increased variability of outcome measures, such as the interval between sessions, the time of day at which the examination is carried out, the data preprocessing choices and the sample characteristics (Ridding & Ziemann, 2010; Guerra et al., 2020b).

To improve the accuracy of coil placement over the scalp throughout an experiment and thus increase objectivity and stimulation efficacy, the use of neuronavigation with individual magnetic resonance imaging (MRI) brain images is considered as superior to placements with standard metrics as often used in a clinical application (Julkunen et al., 2009; Sack et al., 2009; Ahdab et al., 2010). Hereby, there are different contributors to be considered: Firstly, the stimulation hotspot can be evaluated visually due to exact depictions of cortical structures, for example the hand knob (Dubbioso et al., 2021). Secondly, a systematic investigation of different stimulation positions can be undertaken, since several targets can be saved within a neuronavigation software that can be repeatedly aimed at, also in random order to enhance independence between different targets and thus reliability of measurements (Littmann et al., 2013; Agboada et al., 2023). Thirdly, an exact targeting at further investigations, even at other days of session is possible and thus, variability of coil position is reduced (Jung et al., 2010). Yet, reliability measures of the neuronavigation method not always differs from hand-held applications (Jung et al., 2010; Fleming et al., 2012). By including a collaborative robotic coil holder (cobot) into the setup, an even further objective investigation of cortical excitability is possible (Rossi et al., 2021; Agboada et al., 2023). In doing so, the coil position throughout the experiment is not only monitored, but also adjusted within seconds, so that the optimal stimulation position can be maintained within a radius of 2 mm (Agboada et al., 2023).

Since rTMS especially is known for its longer lasting modulation of brain activity and excitability (Ridding & Rothwell, 2007), the time between stimulations or intersession interval is an important factor to consider when interpreting experimental

results. The ongoing effect of rTMS has been reported to last up to 60 minutes (Ridding & Rothwell, 2007), yet, trajectory effects may last longer, as reported by the occurrence of cumulative plastic changes after 24 hours of 1 Hz rTMS stimulation (Bäumer et al., 2003). Thus, variability can increase through cumulative effects.

Comparable to hormonal oscillations during the menstrual cycle, the circadian rhythm influences the hormonal status, which also affects CE and CSE (Smith et al., 2002; Ly et al., 2016). Thus, time of day has been reported a mediating factor when it comes to cortical excitability (Sale et al., 2008; Ly et al., 2016). For example, facilitatory effects were greater and more reliable in the afternoon than in the morning (Sale et al., 2007; 2008). Yet, others have found no relevant significant changes during the day (ter Braack et al., 2019).

Additionally, also differences between laboratories in preprocessing and choice of statistical methods can bias outcome parameters like TEPs and MEPs. Within TEP preprocessing, Rogasch et al. (2022) showed that even small changes in a pipeline can lead to differences in TEP amplitude and topography. Especially different filter options can cause significant changes in the results (de Cheveigné & Nelken, 2019). Also the selected time windows influence reliability of TEPs, indicating that longer and later windows showed higher reliability values than shorter and earlier ones (Gogulski et al., 2024). Within one preprocessing method, TEPs seem to be reliable (Lioumis et al., 2009; Kerwin et al., 2018). When it comes to MEP preprocessing and analysis, the use of peak-to-peak (p2p) amplitude values in comparison to the AUC reveals potential reason for variability (Brown et al., 2017). Also, MEP latencies are differently postulated and vary in reliability (Bigoni et al., 2022).

The sample characteristics, especially the number of subjects to investigate in both basic and clinical research should be matched to the power of the respective stimulation procedure and its effect (Thomas & Juanes, 1996). Often, the estimated power is based upon previous research and only about 20 % of researchers use power calculations (Héroux et al., 2015). Biases, such as the publication bias and differences in research populations, can influence the experimental outcomes and thus lead to overestimation of effect power (Easterbrook et al., 1991). In general, examining a higher number of subjects and thus reach more power within the analyses is a goal throughout NIBS research with some big data attempts on the way (Corp et al., 2020). Since for experimental research within one laboratory the investigation of a large group of subjects is difficult due to time and money limitations, with appropriate experimental designs and analysis methods that account for individual differences researchers can counteract this limitation (Harrison et al., 2018).

Other influences on the variability of TMS and rTMS that can be derived from subject characteristics are examined in the next section in detail.

1.5.3 Subject related variability

TMS and rTMS measures are known to vary between subjects and depend on intra-subject states (Ridding & Ziemann, 2010; Guerra et al., 2020b; Pellegrini et al., 2020). As in every neuroscientific field investigating humans, the neuronal structure and function differ between participants and deductions from average findings over a heterogenous group of subjects may be representative for a population but often fail to account for individual deviations. Since experimental results are often based on averaging individual results, it is necessary to investigate both inter-subject and intra-subject influences to TMS and rTMS outcomes or to account for individual differences within the analysis, e.g. by linear mixed effect models.

Inter-subject factors Factors to influence TMS and rTMS measures that are different across subjects are for example handedness, sex and associated hormones, age, genetics and health (Ridding & Ziemann, 2010; Guerra et al., 2020b), but concerning each factor, not all results picture similar influences, strengthening the importance of investigating individual parameters and their combinations to gain detailed insights into the mechanisms of TMS and rTMS.

Handedness is especially important to investigate when MEPs are derived as dependent measure or RMT as reference for adjusting the stimulation intensity, since both derivations involve the motor system and cortico-spinal nerve propagation. Although Triggs et al. (1994) and Chagas et al. (2018) found significant different thresholds between subjects' hemispheres to evoke MEPs, whereby the dominant hand and contralateral hemisphere needed less stimulation intensity, others revealed no differences between hemispheres (Livingston et al., 2010; Cueva et al., 2016).

The main contributing parameter in combination with the subjects' sex is the status of hormones, especially ovarian steroid levels, that influence cortical excitability, whereby, progesterone has an inhibitory and estradiol an excitatory function (Smith et al., 2002). The late follicular phase of the menstrual cycle seems to enhance facilitation (Smith et al., 2002) and in facilitatory rTMS protocols, motor plasticity was reduced in the early days of the cycle (Inghilleri et al., 2004). In many studies, females and males do not differ between TMS derived measures, like RMT or MEP amplitude (Livingston et al., 2010; Cueva et al., 2016), but the variability of MEPs seems to be increased in females (Pitcher et al., 2003). Additionally, hormones are prone to influences of circadian, ultradian and infradian cycles.

When it comes to the factor age, the current literature mainly focuses on the distinction between younger and older subjects. Mainly, the cutoff for subjects to be considered as old was around 50 years (Rossini et al., 1992; Cueva et al., 2016). Older subjects tend to have a higher RMT (Rossini et al., 1992; Chagas et al., 2018; Corp et al., 2020), lower MEP amplitudes (Cueva et al., 2016), as well as higher

variability in MEPs than younger ones (Pitcher et al., 2003). Also motor inhibition with rTMS was reduced in older individuals (Todd et al., 2010).

Within the subjects' genetic code, the brain-derived neurotrophic factor (BNDF) polymorphism Val66Met seems to influence CE the most (Cheeran et al., 2008; Di Lazzaro et al., 2015). Hereby, subjects with the BNDF polymorphism reveal reduced motor plasticity and thus showed no inhibition effect of cTBS and facilitation effect of iTBS than the subjects without the polymorphism (Cheeran et al., 2008).

Overall, the subjects' health has an impact on CE and CSE derivations, largely depending on the kind of disease: Since TMS can be used to diagnose and rTMS to treat neuropsychiatric diseases, the measures on patients show deviations from healthy subjects (Vucic et al., 2013; Di Lorenzo et al., 2020; Li et al., 2023; Tecchio et al., 2023). Thus, to reduce variability within the sample to be examined, participants should be either healthy or fulfil similar disease criteria.

Intra-subject factors Parameters that influence TMS and rTMS outcomes and can vary within subjects are mainly substance and medication intake, but also the cognitive and motor system state of a subject can bias individual responses to magnetic stimulation (Ridding & Ziemann, 2010; Guerra et al., 2020b).

Substances such as nicotine were found to reduce inhibition and increase facilitatory effects of rTMS procedures (Swayne et al., 2009; Thirugnanasambandam et al., 2011). Yet, reproducing these effects was not entirely possible (Grundey et al., 2012). Also, caffeine in combination with glucose was found to induce excitation of CSE (Specterman et al., 2005), whereas alcohol (ethanol) reduces LTP-like plasticity (Lücke et al., 2014).

Medications like the benzodiazepine lorazepam, which is used as a pharmaceutic against anxiety, or antiepileptic drugs reduce CSE (Ziemann et al., 1996; Boroojerdi et al., 2001), whereas antidepressant serotonin reuptake blockers such as citalopram increase facilitatory effects (Nitsche et al., 2009).

Within the cognitive state, mainly the subjects' attention during magnetic stimulation influences derived measures (Ridding & Ziemann, 2010). When focusing the attention towards the stimulated target, increased facilitation was found (Stefan et al., 2004; Conte et al., 2008), yet no increased inhibition in an 1 Hz rTMS protocol (Conte et al., 2008). Additionally, during sleep CSE was found to be reduced (Avesani et al., 2008), whereas in brief time intervals of reduced alertness towards sleep, MEPs were increased (Noreika et al., 2020). Similarly, the hormonal status is affected by other circadian, ultradian and infradian cycles, such as cortisol levels over the day. Hereby, also sleep behavior can confound cortisol levels (O'Byrne et al., 2021) and can affect the cognitive state in addition.

Also the motor system state, i.e. regular exercise or activity can modify rTMS outcomes (Ridding & Ziemann, 2010). For example, more higher activity levels in

subjects showed increased facilitation (Cirillo et al., 2009).

1.6 Research questions

Although TMS and rTMS have been frequently used in basic science experiments and clinical investigations for almost half a century, there are still uncertainties as to which exact mechanisms lead to the research results and which parameters and their interaction contribute to cortical excitability and neuromodulatory changes (Klomjai et al., 2015; Spampinato et al., 2023). The high variability of outcomes and low number of repetition of results contribute to these uncertainties (Héroux et al., 2015; Goldsworthy et al., 2021). Besides the core mechanisms of TMS of **E**-field induction and action potential propagation as well as rTMS of LTD- and LTP-like neuromodulation, there are several parameters that are known to influence TMS and rTMS effects, but their interaction and degree of influence as well as other potential unknown parameters are still to be investigated in detail (Ridding & Ziemann, 2010; Guerra et al., 2020b).

Thus, the present thesis aims to replicate previous findings and to validate the common assumptions of the lofi-hife heuristic, takes on the task of creating an overview over effects and reliabilities of rTMS procedures, as well as investigates the influence of current direction on rTMS effects. Two experimental studies and one review study have been conducted in order to pursue these goals. The studies have been published in peer-reviewed journals: The first study in Brain Research with open access under the CC BY NC ND licence (Prei et al., 2023), the second study in Frontiers in Human Neuroscience with open access under the CC BY license (Kanig et al., 2023), and the third study in Brain Research Bulletin with open access under the CC BY license (Kanig et al., 2025). Figures and tables are numbered sectionwise within this thesis to ensure comparability to the published versions.

All studies were carried out at the Center of Neuromodulation at the University of Regensburg, which is a cooperation partner of the University of the Bundeswehr Munich as part of the dtec.bw funded project MEXT (Modular Extended Transcranial Magnetic Stimulation). The project MEXT aims to conceptualize, manufacture and validate a new TMS pulse source that is able to generate arbitrary pulses with adjustable pulse width and shape and thus may combine these stimulation parameters to an optimal, i.e. action potential eliciting (TMS) and neuromodulating (rTMS), stimulation. The present studies contribute to this project by validating the effects of common rTMS protocols to generate requirements for the application of the new pulse source, as well as investigating the parameter current direction to further investigate in which direction the pulse shape should be directed to enable efficient stimulation.

The first study to be included, “Limited evidence for reliability of low and high

frequency rTMS over the motor cortex" (Prei et al., 2023), investigates the CSE effects of 1 Hz and 20 Hz rTMS and their reliability in a standard clinical setting. Hereby, we did not use technology like neuronavigation or cobot-guided coil adjustment, since it is uncommon in a clinical routine. Both MEP amplitude mean and median were computed as dependent variables to account for outlier bias. Reliability measures included both r and ICC to enhance comparability with other studies. Additionally, analyses on single-subject level were carried out to further gain insights into individual responses to 1 and 20 Hz rTMS and the accordance to the lofi-hife heuristic.

The second study, "Retest reliability of repetitive transcranial magnetic stimulation over the healthy human motor cortex: a systematic review and meta-analysis" (Kanig et al., 2023), focused on giving an overview of, systematically reviewing and analyzing rTMS test-retest reliability studies concerning the rTMS effects and reliability. Additionally, possible predictors of reliability values were examined such as the methodological quality of these studies, which was assessed via ratings of a standardized checklist on TMS experiments (Chipchase et al., 2012), year of publication, repetition interval between rTMS sessions, sex ratio of the investigated sample, the use of neuronavigation and excitability of the rTMS protocol. The publication bias within the set of publications was investigated via Rosenthal fail-safe N (Rosenthal, 1979), funnel plot and asymmetry test (Egger et al., 1997).

The third study, "Influences of current direction on 1 Hz motor cortex rTMS" (Kanig et al., 2025), comprised of an experiment to investigate the effects of 1 Hz rTMS on CE and CSE and compare these for two induced current directions in the brain, namely anterior-posterior – posterior-anterior (AP-PA; default setting in the pulse source) and posterior-anterior – anterior-posterior (PA-AP; reversed setting in the pulse source). Within this experimental procedure we implemented a standardized and technological advanced setup by using neuronavigation and a cobot to increase objectivity during application. Also, variables that might have possibly confounded rTMS effects, such as differences in RMT, TMS masking loudness, perceived loudness of the coil click and attention, excitement and tiredness, were investigated. Lastly, we were interested in the correlation between the CE and CSE measures.

2 First study: Limited evidence for reliability of low and high frequency rTMS over the motor cortex

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The following texts, figures and tables are pre-edited versions of the final article:

Prei, K., Kanig, C., Osnabruegge, M., Langguth, B., Mack, W., Abdelnaim, M., Schecklmann, M., & Schoisswohl, S. (2023). Limited evidence for reliability of low and high frequency rTMS over the motor cortex. *Brain Research, 1820,* 148534. https://doi.org/10.1016/j.brainres.2023.148534

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2.1 Abstract

Objective. The aim of this study was to investigate the reliability of low-frequency and high-frequency repetitive transcranial magnetic stimulation (rTMS) on healthy individuals over the motor cortex. A secondary outcome was the assessment if low-frequency rTMS results in inhibition and high-frequency rTMS results in facilitation.
Methods. In this experiment, 30 healthy participants received on four consecutive days one session each with application of 1 Hz or 20 Hz rTMS over the left motor cortex. 1 Hz and 20 Hz were applied in alternating order, whereby the starting frequency was randomized. Motor evoked potentials (MEPs) were measured before and after each session. Reliability measures were intraclass and Pearson's correlation coefficient (ICC and r).
Results. ICCs and r values were low to moderate. Notably, within subgroups of less confounded measures, we found good r values for 20 Hz rTMS. The group-level analysis did not demonstrate a clear low-frequency inhibition and high-frequency facilitation pattern. At the single-subject level, only one participant exhibited significant changes consistent with the expected pattern, with concurrent decreases in MEPs following 1 Hz sessions and increases following 20 Hz sessions.
Conclusion. The investigated neuromodulatory protocols show low to moderate reliability. Results are questioning the low-frequency inhibition and high-frequency facilitation pattern.
Significance. Methodological improvements for the usage of rTMS are necessary to increase validity and reliability of non-invasive brain stimulation.

2.2 Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique whereby electromagnetic pulses are administered to the scalp. The change of magnetic flux can lead to the depolarization of underlying cortical neurons (Barker et al., 1985; Allen et al., 2007). Single TMS pulses applied over the primary motor cortex (M1) can elicit contralateral peripheral motor responses termed motor evoked potentials (MEPs), which are measured by electromyography (EMG) (Rossini et al., 2015). MEPs are typically used as a parameter of cortical excitability (Paulus et al., 2008). The application of TMS pulses in a rhythmic manner with specific frequencies is referred to as repetitive transcranial magnetic stimulation (rTMS) (Pascual-Leone et al., 1994a) and is capable to induce changes in cortical excitability, that can persist beyond stimulation offset (Hallett, 2000; Siebner & Rothwell, 2003). It is assumed that the local changes in cortical excitability (i.e. neuroplasticity) are frequency dependent: low frequency rTMS (about 1 Hz) induces inhibitory effects whereas high frequency rTMS ($\geq$ 5 Hz) evokes excitatory effects (Maeda et al., 2000b; Fitzgerald et al., 2006; Cohen et al., 2010; Thut & Pascual-Leone, 2010; Beynel et al., 2020), hereinafter referred to as lofi-hife heuristic (low frequency inhibitory - high frequency excitatory). Not only were such frequency dependent effects observable for the measurement of MEPs, but also for EEG-derived measures (Thut & Pascual-Leone, 2010 for overview). Possible mechanisms of inhibition are disputed to be the recruitment of later I waves, which have been shown to be modulated by inhibitory protocols (Di Lazzaro et al., 2004) and resemble effects of gamma aminobutyric acid in a way that its agent lorazepam can reduce the inhibitory effects (Fitzgerald et al., 2005). Facilitatory effects might occur due to summation of poly-synaptic effects in motor neurons (Pascual-Leone et al., 1994a). Additionally, it has been found that the inhibitory effects of 1 Hz rTMS were enhanced with a dopamine receptor agonist (Lang et al., 2008) while with an N-methyl-D-aspartate receptor antagonist both inhibitory and excitatory effects were blocked (Huang et al., 2007). Yet, there is still discussion on which parameters are influencing these longer lasting cortical excitability effects.

Several study results were incompatible to the lofi-hife heuristic questioning its validity. Various researchers did neither realize inhibiting effects with low frequency protocols (e.g., 1 Hz) (Berardelli et al., 1999; Modugno et al., 2003; Brighina et al., 2005; Daskalakis et al., 2006) nor facilitatory effects with high frequency protocols (e.g., 20 Hz) (Wassermann et al., 1998; Maeda et al., 2000b; Daskalakis et al., 2006).

In line with limited evidence for the validity of lofi-hife heuristic, examinations of reliability of rTMS are scarce. Until now, the reproducibility of commonly used 1 and 20 Hz rTMS protocols has been investigated in only 6 studies (Maeda et al., 2000b; Sommer et al., 2002a; Bäumer et al., 2003; Modugno et al., 2003; Cohen et al., 2010;

Magnuson et al., 2023). Four of them only compared MEP amplitudes or MEP area under the curve between sessions using rather small sample sizes ($n = 4 - 10$) and did not report any measure of reliability (Sommer et al., 2002a; Bäumer et al., 2003; Modugno et al., 2003; Cohen et al., 2010). The experiments which calculated Pearson's correlation coefficients (*r*) and intraclass correlation coefficients (ICC) were conducted by Maeda et al. (2000b) and Magnuson et al. (2023). Maeda and colleagues demonstrated in 20 participants correlations between low ($r = 0.266$ for 1 Hz and $r = 0.260$ for 10 Hz; $p > .050$) and moderate ($r = 0.543$ for 20 Hz; $p = .013$) effect size. Reliability values from 28 participants for 1 Hz rTMS including sham correction by Magnuson et al. did not exceed $ICC = 0.216$. The reliability of other TMS-based neuromodulatory methods like intermittent and continuous theta-burst stimulation (TBS) is classified as low to moderate as well (Jannati et al., 2019; Boucher et al., 2021). Yet, reliability of rTMS procedures that stay close to common clinical practice, i.e., an intervention of 20 minutes (George et al., 1995; Garcia-Toro et al., 2006) without neuronavigation have not been investigated.

Given that there is high within- and between-subject variability (Ridding & Ziemann, 2010; Pell et al., 2011; Guerra et al., 2020b) and that there is a limited number of studies on the reliability of rTMS, the aim of the present work is to investigate the day-to-day retest reliability of a low and a high frequency rTMS protocol (1 Hz, 20 Hz) on group and single-subject level as it is commonly used in experimental and clinical environments. We therefore aimed to keep our experimental setup as close to clinical application as possible. Additionally, we tested whether we could reproduce lofi-hife heuristic-conform effects.

2.3 Methods

2.3.1 Sample characteristics

The analyzed sample consisted of 30 healthy volunteers (22 female; age range: 19 – 29 years, $M = 22.90, SD = 2.75$). The included participants had an estimated average intelligence quotient of 110.2 ($SD = 8.8$) according to the Multiple Selection Vocabulary Test (Merz et al., 1975), scores higher than 33.3 in the Edinburgh Handedness Inventory ($M = 85.0, SD = 16.8$; only left-handed: -100, only right-handed: +100) (Oldfield, 1971) and < 20 points (cut-off for clinic relevant depression) in the Major Depression Inventory (MDI; $M = 5.3, SD = 3.3$) (Bech et al., 2001). Starting with a sample of 41 participants, two were excluded due to indications of depression via MDI and Structured Clinical Interview for DSM-IV Axis I Disorders (Münster, 1999), assessed by a trained clinical professional. Moreover, nine people with a resting motor threshold (RMT) above 55 % maximum stimulator output were excluded in order to prevent overheating of the passively cooled TMS coil and increase the stimulation tolerability for the volunteers. The included participants had

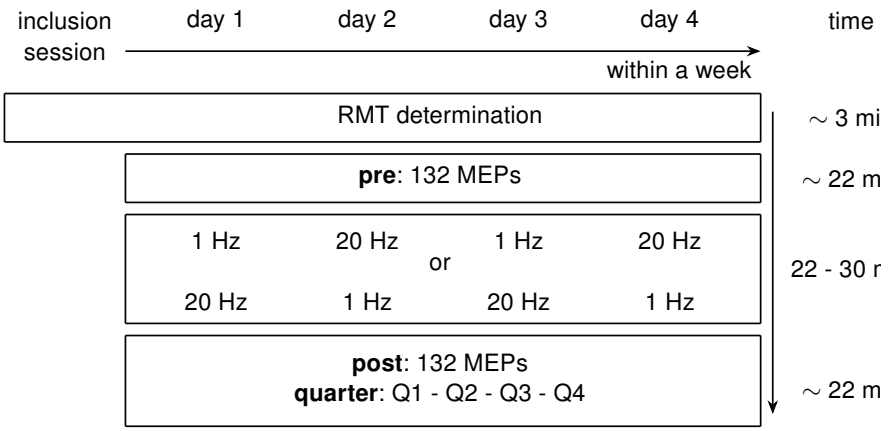
no regular intake of medications apart from contraceptives.

The study protocol, which is according to the Declaration of Helsinki, was reviewed and approved by the local ethics committee of the University of Regensburg (ethical approval number: 16-101-0305). All participants gave their informed consent before the start of the experiment.

2.3.2 Study procedure

The entire experiment consisted of an inclusion session in which the motor hotspot and RMT of the participants were determined as well as the questionnaires completed, which was followed by the main crossover experiment with four consecutive rTMS sessions (Figure 1). All experiments were conducted by the same investigator at the Centre for Neuromodulation at the University of Regensburg, Germany.

Figure 1
Study procedure



Notes. The inclusion session comprised only a resting motor threshold (RMT) determination. Each day of the main experiment included a RMT determination, a pre-measurement of cortical excitability with 132 motor evoked potentials (MEPs), a protocol of repetitive transcranial magnetic stimulation (rTMS) (1800 pulses, 1 Hz or 20 Hz) and a post-measurement identical to the pre-measurement. The participants in our study alternated between 1 Hz and 20 Hz sessions, with half of the 30 participants starting with a 1 Hz session and the other half starting with a 20 Hz session. To analyze the time-course after rTMS, the 132 MEPs post-measurement were divided up into quarters of 33 MEPs (Q1-Q4).

In the inclusion session, we searched the hotspot where TMS pulses elicited the highest and most stable MEPs in the FDI muscle, with relatively lowest stimulation intensity. To do this, we started from the C3 electrode position (10-20 electroencephalography system) with an orientation at about $45°$ of the TMS coil in

posterior-anterior direction to the sagittal midline of the head and the handle pointing backwards. The hotspot and landmarks for placing were marked on a blank cap to ensure a coil positioning as constant as possible in subsequent stimulation sessions. RMT was defined as five out of ten TMS pulses inducing a MEP with a peak-to-peak amplitude of at least 50 µV (Rossini et al., 1994; Rothwell et al., 1999).

The main experiment took place over four days from Monday through Friday. In four participants one session was postponed to a later appointment due to scheduling conflicts. On each day one study session was conducted. The four sessions consisted of two identical stimulation sessions for 1 Hz and 20 Hz rTMS with both frequencies in alternating order (cf. Figure 1). Participants were divided into two groups via balanced randomization method to either getting applied the 1 Hz or 20 Hz rTMS protocol in the first session. Each session was conducted at the same time of day (either always 8 am, 10 am, 12 noon or 2 pm) to prevent intrasubject effects due to the circadian rhythm (Sale et al., 2007). The participants were required to abstain from caffeine, alcohol or medication excluding contraceptives, and to maintain their current sleep rhythm throughout the experiment.

At the beginning of each session, the caps were put on based on the landmarks followed by motor hotspot and RMT determination, which started from the position marked in the inclusion session. Potential changes in hotspot position were marked on the cap. The participants were asked to lie as still and relaxed as possible with no explicit attention focus, but to keep their head and right hand in a steady position, which was monitored visually. We also used a vacuum cushion and coil holder to ensure that the position of the participant's head relative to the coil remained as unchanged as possible. Coil position and EMG data were observed during the experiment and in case of coil-slipping from the marked hotspot or the absence of EMG responses on TMS pulses for more than a minute the coil position was corrected and documented as "coil correction" within a session.

2.3.3 Repetitive transcranial magnetic stimulation (rTMS)

For TMS and the subsequent rTMS sessions we used a MAGPro X100 stimulator as well as a figure-of-eight coils of the model MCF-B65 (all Medtronics Plc, Ireland). For each participant, the same coil was used throughout the entire experiment.

Each rTMS protocol consisted of a total of 1800 stimuli, which were administered at 110 % of the individual RMT. The stimulation target for each participant was the left motor hotspot. During the low frequency sessions, the stimulation was performed at 1 Hz for 30 min continuously. During the high frequency sessions, 45 trains of 40 stimuli were given at 20 Hz with inter-train intervals of 28 s, resulting in a total rTMS time of 22 min. We used biphasic pulses producing an initial current direction in anterior-posterior direction in the brain. The procedures matched those of a former

experiment (Eldaief et al., 2011).

2.3.4 Motor evoked potentials (MEPs)

Before and directly after rTMS, we performed MEP measurements consisting of 132 TMS pulses applied at 110 % RMT in the same manner on all four days. The stimuli were presented with a jittered interstimulus interval of 10 ± 2 s via Presentation (Version 20.1, Neurobehavioral Systems Inc., United States). This resulted in a mean duration of 22 min per MEP measurement.

MEPs were recorded via surface electrodes (Ag/AgCl) from the right first dorsal interosseus muscle (FDI) in belly-tendon montage. The ground and reference electrodes were fixed on both styloid processes. The signal was amplified by a 16-channel amplifier (V-Amp, Brain Products GmbH, Germany), processed with Brain Vision Recorder V-Amp Edition (Version 1.10, Brain Products GmbH, Germany) and analyzed offline with Brain Vision Analyzer (Version 1.05.0005, Brain Products GmbH, Germany). The sampling rate was 500 Hz for the first four and 2000 Hz for the remaining 26 participants. A zero phase Butterworth filter was applied (1 Hz cutoff, notch filter at 50 Hz). The stimulus interval was defined from 10 ms before to 60 ms after the stimulus. MEP amplitudes were calculated peak-to-peak. At 110 % RMT, a small proportion of trials may not elicit MEPs with high or noticeable amplitudes. While some researchers have chosen to exclude all MEPs below a certain threshold, such as 50 µV (Nguyen et al., 2019) or outside a certain range, such as 2.5 *SDs* from average amplitude (Jannati et al., 2019; Boucher et al., 2021), our aim was to maximize the inclusion of MEPs to capture potential changes before and after rTMS. Consequently, we excluded only segments that did not exhibit a distinct MEP pattern, characterized by a biphasic signal with a clear minimum followed by a maximum and visually distinguishable from the baseline activity. We referred to these excluded segments as "invalid MEPs" in our subsequent analyses.

2.3.5 Statistical analysis

Preprocessing We used SPSS Version 25.0 (IBM Corp., USA) for statistical analyses. The significance level was 5 % for all computations. We calculated the mean (M) and, to include a more resistant measure against outliers, the median (Md) of the entire MEP measurement, i.e., 132 segments, and the quarters per measurement (Q1-Q4; 33 consecutive measures each).

To ensure comparability of MEP responses across measurements, we were interested in the amount of coil corrections and invalid trials per measure. Overall, 17.5 % of the segments needed to be excluded according to the above-mentioned criteria and in 19.17 % of the pre and post measurements, the coil needed to be adjusted. With three subsamples of participants (n = 11 participants without coil correction; $n = 9$

participants with at least 75 % valid MEPs in every condition; $n = 7$ participants with no coil correction and greater than 75 % valid MEPs) we repeated the analyses on a group level to see if this preselection leads to more prominent effects or improved reliability.

Effects of rTMS: lofi-hife heuristic 2 ("frequency"; 1 Hz vs 20 Hz) × 2 ("session"; first vs second) × 2 ("within-session time"; pre vs. post rTMS) × 4 ("quarter"; Q1-Q4) repeated measurement ANOVAs were performed for M and Md. These analyses aimed to assess the validity of the lofi-hife heuristic by looking for frequency-specific rTMS-induced changes ("frequency" × "within-session time") and whether these interactions were stable during the follow-up periods and between the sessions (influence of the factors "quarter" and "session"). Post-hoc paired *t*-tests were conducted in case of main or interaction effects with *p*-values adjusted by false discovery rate (FDR) due to multiple testing (Benjamini & Hochberg, 1995; Kim & van de Wiel, 2008).

At single-subject level, we calculated the number of participants whose MEP amplitudes were either significantly (*t*-test) or descriptively higher, lower or unchanged after the respective rTMS (post) intervention in comparison to before (pre). To further elaborate these descriptive and significant individual day-to-day changes of MEP response to the different frequencies, we conducted Chi-squared tests with the contingency tables of both sessions for 1 Hz and 20 Hz stimulation. Thus, we were able to derive information about the stability of rTMS effects and hints to reliability at single-subject level.

Reliability Reliability group measures were the intraclass correlation coefficient (ICC) and Pearson's correlation coefficient (*r*). Since we were interested in rTMS induced effects, we used the differences from post (for the whole measurement and the four quarters) to pre (for the whole measurement) of M and Md to adjust for the baseline activity in each session. We calculated two-way mixed effect ICCs with general agreement and *r* for each dependent variable (M and Md) for the whole measurement as well as the separate quarters between the 2 sessions of both 1 Hz and 20 Hz rTMS protocols. ICC and *r* results were compared to zero, the *p*-values were FDR adjusted within the group of five values (whole measurement and four quarters).

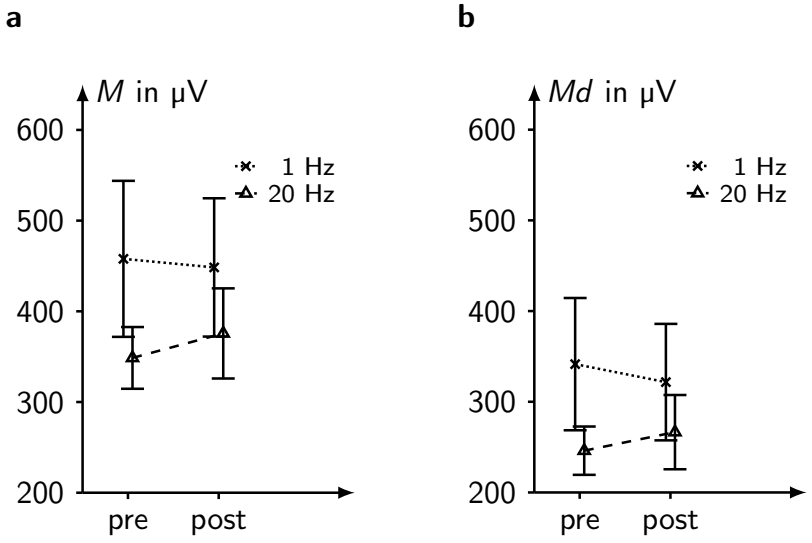
2.4 Results

Subjects had a mean RMT of 43.83 ($SD = 5.79, min = 33, max = 54$). Overall mean MEP amplitude was 409.33 µV across subjects ($SD = 296.26$).

2.4.1 Effects of rTMS: lofi-hife heuristic

According to the lofi-hife heuristic, we expected an interaction effect of "within-session time" and "frequency" in the $2 \times 2 \times 2 \times 4$ ANOVAs for M and Md (increase of MEPs from pre to post for 20 Hz and decrease for 1 Hz), but this interaction remained non-significant (M: $F(1, 29) < 1$, $p = .533$, $\eta_p^2 = .014$; Md: $F(1, 29) < 1$, $p = .453$, $\eta_p^2 = .020$) (cf. Figure 2). Yet, descriptive values reveal an overall increase of mean and median MEP amplitude after 20 Hz rTMS and a decrease after 1 Hz rTMS. Interactions of "within-session time" and "frequency" with "quarters" or "session" were not found as well (M: $F(2.16, 62.66) < 1$, $p = .407$, $\eta_p^2 = .031$ and $F(1, 29) = 1.458$, $p = .237$, $\eta_p^2 = .048$; Md: $F(1.66, 48.13) < 1$, $p = .614$, $\eta_p^2 = .022$ and $F(1, 29) = 1.846$, $p = .185$, partial $\eta_p^2 = .060$). The Greenhouse–Geisser adjustment was used for the "within-session time" $\times$ "frequency" $\times$ "quarters" interaction of M and Md to correct for violations of sphericity. Within ANOVAs of the three subsamples (at least 75 % valid MEPs, no coil correction and both), none of the expected interactions was evident.

Figure 2
„Frequency" × „within-session time" interaction of mean MEP amplitudes (a) and median MEP amplitudes (b)



Notes. Depicted values were averaged over both sessions of one frequency and represent the total sample of 132 applied TMS pulses, i.e., all four quarters. Error bars represent standard error. M = Mean. Md = Median.

In the analyses of single-subject level, we expected an individual decrease for 1 Hz and an increase for 20 Hz, based on the heuristic. Significant decreases of MEP

amplitudes after 1 Hz were observed in 2 out of 30 participants from pre to post. One of them was at the same time the only participant who had significant MEP increases after both 20 Hz sessions, making him the only person in the sample to consistently respond according to the lofi-hife heuristic. According to descriptive inspection of data, 14 out of 30 participants exhibited a decrease of MEP amplitudes from pre to post in both 1 Hz sessions. Likewise, post 20 Hz rTMS, 9 out of 30 participants had higher MEP amplitudes than pre 20 Hz rTMS in both sessions. Four participants showed decreases in MEPs due to 1 Hz and increases due to 20 Hz concomitantly.

For the contingency tables of significant changes of MEP amplitudes within participants, Chi-square tests of independence showed no association between session 1 and 2 for 1 Hz ($\chi^2(4) = 8.914$, $p = .062$) and 20 Hz ($\chi^2(4) = 2.066$, $p = .755$) (see Table 1). We found significant associations for descriptive changes after 1 Hz rTMS on single-subject level between both sessions ($\chi^2(1) = 6.696$, $p = .019$), based on Chi-squared tests of independence (see Table 2). There was no association between session 1 and 2 for descriptive changes after 20 Hz ($\chi^2(1) < 1$, $p = .713$).

Table 1
*Contingency tables for **significant** changes of the amplitudes of motor evoked potentials (MEPs) from pre to post for the individual participants*

1 Hz					
		Session 2			
		Decrease	No change	Increase	Total
Session 1	Decrease	2	4	4	10
	No change	3	10	2	15
	Increase	1	0	4	5
	Total	6	14	10	30
20 Hz					
		Session 2			
		Decrease	No change	Increase	Total
Session 1	Decrease	2	3	4	9
	No change	7	9	2	18
	Increase	1	5	1	7
	Total	6	14	10	30

Notes. Values refer to the number of people who show a significant difference in the MEP amplitudes per session from pre to post rTMS application in a paired *t*-test.

Table 2
*Contingency tables for **descriptive** changes of the amplitudes of motor evoked potentials (MEPs) from pre to post for the individual participants*

1 Hz				
		Session 2		
		Decrease	Increase	Total
Session 1	Decrease	14	6	20
	Increase	2	8	10
	Total	16	14	30
20 Hz				
		Session 2		
		Decrease	Increase	Total
Session 1	Decrease	7	8	15
	Increase	6	9	15
	Total	13	17	30

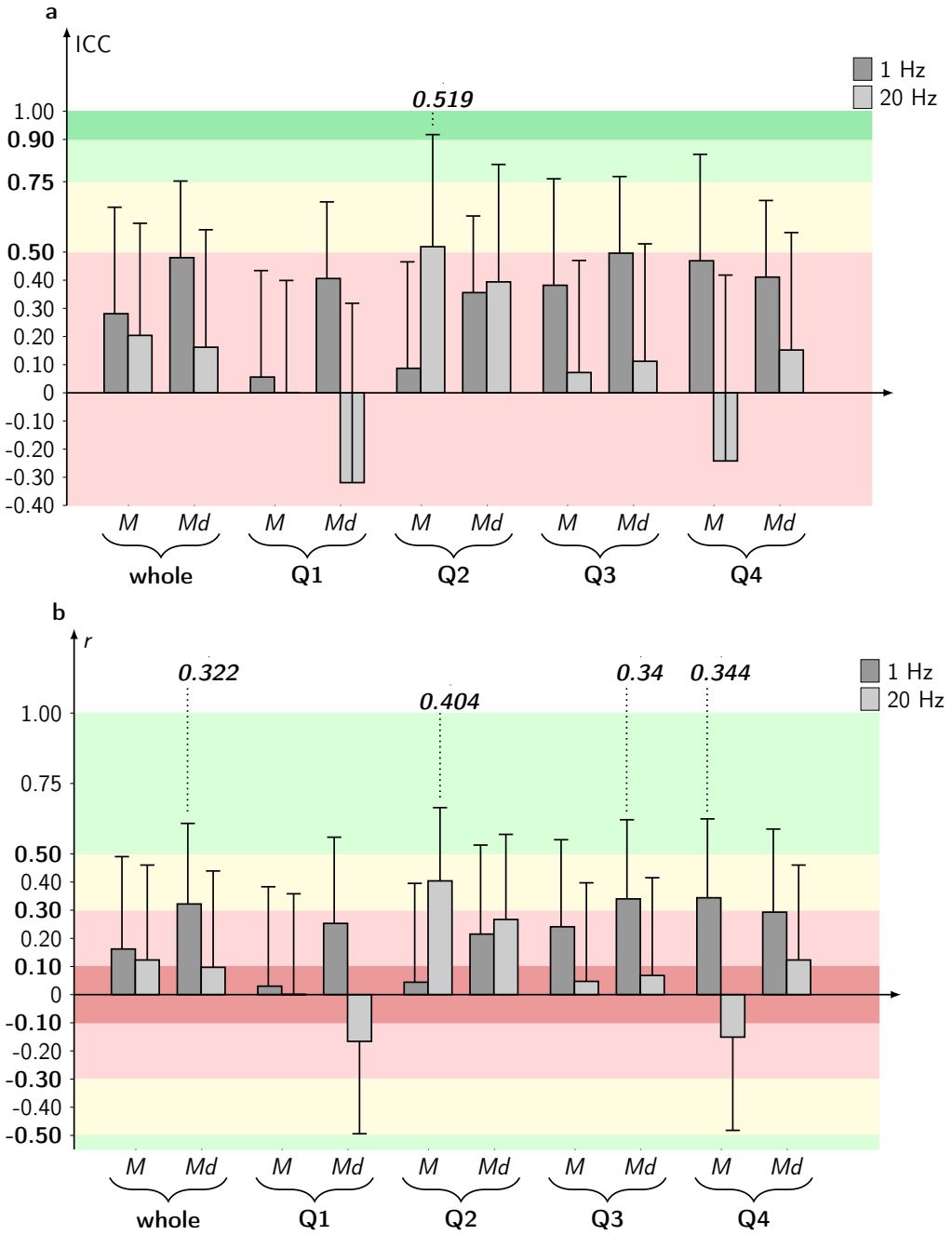
Notes. Values refer to the number of people who show a numerical difference in the MEP amplitudes per session from pre to post rTMS application. The changes of sessions 1 and 2 of 1 Hz rTMS are significantly associated.

2.4.2 Test-retest reliability

ICC and *r* for M and Md classified the test-retest reliability of rTMS effects for low and high frequency protocols mostly as poor ($ICC < 0.5; r < 0.3$). After FDR adjustment, no correlations (ICC and *r*) were identified, that are significantly divergent of zero, neither for the whole measurement nor for the quarters. There were no significant reliability differences over time (i.e., over the course of the 132 pulses after the rTMS), but descriptively the lowest reliability values occurred for both 1 and 20 Hz. ICC and *r* for the whole sample are depicted in Figure 3.

Figure 3

Intraclass correlation coefficient (ICC) (a) and Pearson's correlation coefficient (r) (b) of 1 Hz and 20 Hz rTMS between session 1 and 2



Notes. Calculations were made for the whole measurement as well as for the quarters: quarter 1 (Q1), quarter 2 (Q2), quarter 3 (Q3), quarter 4 (Q4). Error bars represent the upper/lower bound of the 95 % confidence interval. Colors represent the reliability/effect size areas as trivial (darker red), poor/low (lighter red), medium/moderate (yellow), good/large (lighter green) or excellent (darker green). ICC and *r* values significantly different from zero are depicted as values over the respective bar. All numerical values of ICC and *r* are listed in Supplementary Table S1. M = mean; Md = median.

For the three subsamples (at least 75 % valid MEPs, no coil correction and both), in the 20 Hz sessions, ICCs ranged up to 0.67 and *r* up to 0.77 and in the 1 Hz sessions up to .22 and .12, respectively. We found significant ICC measures after FDR correction in the ICCs of the subsample with at least 75 % valid MEPs for M in the fourth quarter of 20 Hz stimulation ($ICC = 0.667$, $p_{\mathrm{FDR}} = 0.049$) and for Md in the second quarter of 20 Hz stimulation ($ICC = 0.619$, $p_{\mathrm{FDR}} = 0.042$). No other significant correlations were detected for the three subsamples.

2.5 Discussion

The present paper studies the validity of the lofi-hife heuristic and the day-to-day reliability of rTMS effects in a non-neuronavigated setup on group and single-subject level. In sum, we found no evidence for the lofi-hife heuristic. Reliability measures stayed within a low to medium range.

2.5.1 Validity of the lofi-hife heuristic

We could not reproduce the statements of the lofi-hife heuristic. At group level, the expected interaction of “frequency” and “within-session time” in M and Md where 1 Hz rTMS leads to inhibition and 20 Hz to facilitation of cortical excitability did not occur. Although, at group level a numeric tendency was apparent. An influence of the factor "quarter" on this interaction which might hint to a fading of the effects (Gilio et al., 2007) also failed significance. Stronger rTMS effects on repeated measures have been reported before (Maeda et al., 2000a; Cohen et al., 2010), but in our case no corresponding interaction with the "session" factor was shown.

The analyses of subsamples with no coil corrections, at least 75 % valid MEPs or both yielded no heuristic-conform effects as well. Still, the statistical power of these analyses with fewer participants is lower compared to the whole sample, which is why present effects might be undetected yet. In general, experiments with higher sample size are needed to identify the validity of the lofi-hife heuristic.

At single-subject level, 27 % of all 1 Hz measurements and 28 % of all 20 Hz measurements showed significant heuristic-conform neuroplastic changes (for descriptive differences 60 % and 53 %, respectively). Therefore, it was found that almost three quarters of the measurements were not in line with the heuristic and showed either no changes or even changes opposite to the heuristic. Only one participant (for descriptive differences four participants) reacted according to the heuristic in all four measurements.

Overall, our study found no evidence for the lofi-hife heuristic at group and single subject level. The literature reveals ambiguous results about the effect of rTMS over the motor cortex on cortical excitability (Fitzgerald et al., 2006), which is unsurprising considering the impact of variability (Ridding & Ziemann, 2010; Pell

et al., 2011; Polanía et al., 2018). Many factors such as the participants' intrinsic state (Stefan et al., 2004), age (Bashir et al., 2014) or medication (Ziemann et al., 2015) can influence the effects of rTMS and not all factors may have been identified yet (Guerra et al., 2020b). Therefore, variability of outcome measures is a common challenge in the interpretation of dependent variables.

Closely related to the question of the validity of the heuristic and the challenge due to variability is the question of the reliability of the rTMS effects. Solely looking at the direction of the descriptive MEP changes from pre to post, a significant relation between the 2 sessions of 1 Hz rTMS emerged. Notably, this effect was caused not only by the 47 % of participants who responded in conformity with the lofi-hife heuristic, but also by the 27 % of participants who responded excitatory. Stable effects which are independent of the heuristic can therefore still occur.

2.5.2 Test-retest reliability

In our setting, test-retest reliability at group level was low to moderate for M and Md for both ICC (Koo & Li, 2016) and *r* (Cohen, 1992). Reliability measures for Md were descriptively slightly larger than for M. Therefore, the inclusion of outliers in the analyses may lower the correlation coefficients. While a standardized method of dealing with outliers is missing (Guerra et al., 2020a), methods such as using the Md or excluding amplitudes outside of 2.5 SD ± M could lead to more stable results. However, it remains unclear whether these methods are truly suited for representing cortical excitation better than evaluations that include the outliers.

The magnitude of reliability measured by *r* for 1 Hz rTMS is similar to Maeda et al. (2000b) and Magnuson et al. (2023). For 20 Hz higher values ($r = .543$) were demonstrated by Maeda et al. (2000b). Stimulation parameters differed from our setup, thus hampering comparability: Although Maeda et al. also investigated healthy right-handed participants over the left motor cortex twice per rTMS frequency, they stimulated with all rTMS protocols throughout a session on one day with different equipment, i.e., a Magstim Super Rapid with a 70 mm figure-of-eight coil. Also, the authors used a subthreshold stimulation intensity (90 % RMT), a shorter protocol (4 min and 240 stimuli vs. 22 – 30 min and 1800 stimuli in the present experiment) and pre- and post-measurements were based on fewer MEPs (10 vs. 132 trials) derived from the abductor pollicis brevis muscle. Previous research suggests that our setting with a higher stimulation intensity and protocols with more pulses would result in more reliable effects (Nojima et al., 2013). Nevertheless, we did not achieve better reliability than Maeda et al. (2000b). Ten MEPs cover only the first 3 min after rTMS, comparable to Q1 (0 - 5.5 min) of our study, where we achieved descriptively the lowest reliability measures. Looking at TBS protocols, the lowest reliability was observed directly after the intervention at 5 and 10 min as well. Better reliability was

achieved in the second half of the recording (between 30 and 60 min post continuous TBS) (Jannati et al., 2019). In comparison to Magnuson et al. (2023) who also investigated healthy individuals and elicited MEPs with 110 % RMT in the right FDI with a MagPro X100 and cooled B65 coil stimulating M1, reliability values are in the same range. Although, we applied twice the number of pulses within the rTMS protocol, neither inhibition effects nor higher reliability values were present in our analyses.

In the subgroups, we expected better reliability measures due to the exclusion of the possible confounding factors coil corrections and (high number of) invalid MEPs. Whereas no such tendency was seen for 1 Hz, 20 Hz showed improved values for ICC and *r*. For the group with at least 75 % valid MEPs, two ICCs differed significantly from zero. Thus, the role of controlling the coil position and achieving valid MEPs may be more important for 20 Hz protocols than for 1 Hz protocols. Discomfort, pain and muscle twitching caused by high frequency rTMS is more often reported than in case of low frequency stimulation (Kaur et al., 2019) and make arousal and movements more likely. This can lead to coil slipping and invalid MEPs and thus needs to be controlled.

While our study revealed at best moderate reliability for rTMS induced MEP changes, the true "intrinsic" reliability of rTMS effects on cortical excitability remains unclear. Many confounding factors such as time of the day, gender, age and coil and stimulator type in rTMS-MEP setups can lead to variability and therefore may lower the reliability (Sale et al., 2007; Hanlon & McCalley, 2022). An overview of these factors is provided by various reviews (Ridding & Ziemann, 2010; Pell et al., 2011; Chipchase et al., 2012; Guerra et al., 2020a).

Our study design tried to incorporate many recommendations to reduce variability such as the exclusion of drug intake, the constant time of day for each participant, the use of more than 30 trials to estimate the MEP amplitude and the sample size (Guerra et al., 2020a). Other factors such as genetic pre-screenings (Cheeran et al., 2008) or the use of closed-loop systems to evoke TMS pulses in similar brain-states (Zrenner et al., 2016) were not incorporated in our setting, because we wanted to estimate the reliability of a setting that corresponds to everyday use of rTMS in a clinical or research context. An interesting question for future research concerns the maximal realizable reliability of rTMS and which methodological arrangements are optimal to achieve this. The descriptively higher reliability in the subgroups for 20 Hz indicates potential for improvement.

Thus, more valid MEPs may improve reliability. Input–output slope curve estimation is an approach to determine the optimal stimulation intensity with low risk for ceiling or floor effects (Alavi et al., 2021). At the moment, RMT determination according to Rossini and Rothwell (Rossini et al., 1994; Rothwell et al., 1999) is better investigated, commonly used and showed at least good reliability (Beaulieu

et al., 2017; Nazarova & Asmolova, 2022). But with I-O curves stimulation intensity can be tuned with respect to individual limits, whilst also providing at least good reliability (Therrien-Blanchet et al., 2022).

Furthermore, neuronavigation can ensure a stable position of the coil in relation to the cortical target (Neggers et al., 2004; Schmidt et al., 2015). While some studies postulate increased effects and reliability of rTMS through the use of neuronavigation (Schmidt et al., 2009; Bashir et al., 2011; Chang et al., 2016), others show no further MEP reliability improvement (Jung et al., 2010; Fleming et al., 2012) or no benefit in treatment (Schoisswohl et al., 2019; Hebel et al., 2021). In addition to neuronavigation, collaborative robots (cobots) may presumably further reduce the positioning error (Goetz et al., 2019). However, cobots and neuronavigation systems are still costly and not present in most labs and hospitals. Open-source projects for cobots may increase the availability in the long term (Matsuda et al., 2021). Further research is warranted to confirm whether the utilization of neuronavigation and cobots leads to an improvement in rTMS outcomes.

In general, standardized ways to deal with coil corrections and invalid MEPs are needed. Many papers do not report these provisions, if applied at all (Maeda et al., 2000b; Cincotta et al., 2003; Stinear & Byblow, 2004), which complicates comparisons between dependent variables. In the present study, we addressed provisions by communicating the frequencies of invalid MEPs and coil corrections and by defining criteria for invalid MEPs.

A limiting factor to the results may be interactions between the sessions. In our case, we alternated between 1 and 20 Hz protocols which should evoke opposing neuromodulatory effects according to the lofi-hife heuristic. Therefore, interactions between these protocols like mutually extinguishing effects are possible. Also, reliability assessments with larger sample are needed to reproduce the results with more statistical power.

In conclusion, the increase of objectivity and thus reliability of rTMS protocols is required to fully understand cortical excitability mechanisms and achieve validity. Our findings highlight the relevance of the reproducibility crisis in non-invasive brain stimulation techniques (Amad et al., 2019) by showing only low to moderate test-retest reliability and no clear evidence for the lofi-hife heuristic in 1 and 20 Hz rTMS protocols. These findings further underscore the relevance of uniform setups and transparent methodologies to reduce the sources of variability across experiments (Ridding & Ziemann, 2010; Pell et al., 2011; Chipchase et al., 2012; Guerra et al., 2020a). Valid results are more likely by increasing the reliability and the objectivity of rTMS and single pulse TMS. As the lofi-hife heuristic is based on research containing all this variability, it must be critically reevaluated. Sham-controlled investigations of the effects and reliability of low and high frequency rTMS using bigger datasets as well as longer observation periods are needed.

2.6 Author contributions

MS, BL and SS contributed to study concept and design. KP did the data acquisition and figures. KP and MS processed the data as well as quality check control. CK, MS and KP conducted data analysis. CK, KP, MO, MS, SS and WM performed interpretation and drafted and revised the manuscript. KP, MS and MA took part in participants' recruitment and selection process, clinical evaluation, and monitoring of participants. All authors reviewed the manuscript.

2.7 Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author (CK) on reasonable request.

2.8 Funding

Author SS received funding from the European Union's Horizon 2020 Framework Programme (grant agreement number 848261, UNITI project) and CK, MO and SS received funding from dtec.bw – Digitalization and Technology Research Center of the Bundeswehr (MEXT project). dtec.bw is funded by the European Union – NextGenerationEU.

2.9 Declaration of competing interest

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

2.10 Data availability

Data will be made available on request.

2.11 Acknowledgements

The authors thank J. Mason for linguistic advice, P. Seidel for help with the setup and the volunteers who participated in this study and the test runs.

2.12 Supplementary data

Supplementary Table S1
Intraclass correlation coefficient (ICC) and Pearson's r (r) between session 1 and 2

			ICC	CI – ICC	*r*	CI – *r*
Whole	Mean	1 Hz	0.281	[-0.546, 0.662]	0.162	[-0.211, 0.493]
		20 Hz	0.204	[-0.544, 0.605]	0.123	[-0.248, 0.463]
	Median	1 Hz	0.480	[-0.109, 0.755]	0.322	[-0.043, 0.611]
		20 Hz	0.162	[-0.604, 0.582]	0.097	[-0.273, 0.442]
Q1	Mean	1 Hz	0.056	[-1.05, 0.557]	0.030	[-0.334, 0.386]
		20 Hz	0.001	[-0.789, 0.482]	0.001	[-0.359, 0.361]
	Median	1 Hz	0.406	[-0.26, 0.719]	0.253	[-0.118, 0.562]
		20 Hz	-0.319	[-1.389, 0.321]	-0.166	[-0.497, 0.207]
Q2	Mean	1 Hz	0.087	[-0.984, 0.572]	0.044	[-0.321, 0.398]
		20 Hz	0.519	[0.043, 0.765]	0.404	[0.051, 0.667]
	Median	1 Hz	0.356	[-0.381, 0.697]	0.215	[-0.157, 0.534]
		20 Hz	0.394	[-0.186, 0.701]	0.267	[-0.103, 0.572]
Q3	Mean	1 Hz	0.382	[-0.327, 0.709]	0.241	[-0.131, 0.553]
		20 Hz	0.072	[-0.683, 0.522]	0.047	[-0.319, 0.400]
	Median	1 Hz	0.496	[-0.073, 0.762]	0.340	[-0.023, 0.624]
		20 Hz	0.112	[-0.700, 0.557]	0.068	[-0.300, 0.418]
Q4	Mean	1 Hz	0.469	[-0.136, 0.750]	0.344	[-0.019, 0.627]
		20 Hz	-0.242	[-1.737, 0.421]	-0.151	[-0.485, 0.221]
	Median	1 Hz	0.411	[-0.262, 0.722]	0.293	[-0.075, 0.591]
		20 Hz	0.152	[-0.839, 0.602]	0.123	[-0.248, 0.463]

Notes. Shown are the values for the total measurements as well as for the quarters: quarter 1 (Q1), quarter 2 (Q2), quarter 3 (Q3), quarter 4 (Q4). ICCs and *r* for the mean and median of the amplitudes of motor evoked potentials were calculated separately for the 20 Hz and 1 Hz protocols. Bold values mark moderate/medium reliability/effect size, other values are interpreted as markers of low reliability. CI = 95 % confidence interval.

3 Second study: Retest reliability of repetitive transcranial magnetic stimulation over the healthy human motor cortex: a systematic review and meta-analysis

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The following texts, figures and tables are pre-edited versions of the final article:

Kanig, C., Osnabruegge, M., Schwitzgebel, F., Litschel, K., Seiberl, W., Mack, W., Schoisswohl, S., & Schecklmann, M. (2023). Retest reliability of repetitive transcranial magnetic stimulation over the healthy human motor cortex: A systematic review and meta-analysis. *Frontiers in human neuroscience, 17,* 1237713. https://doi.org/10.3389/fnhum.2023.1237713

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3.1 Abstract

Introduction: Repetitive transcranial magnetic stimulation (rTMS) is used to induce long-lasting changes (aftereffects) in cortical excitability, which are often measured via single pulse TMS (spTMS) over the motor cortex eliciting motor evoked potentials (MEPs). rTMS includes various protocols, such as theta burst stimulation (TBS), paired associative stimulation (PAS) and continuous rTMS with fixed frequency. Nevertheless, subsequent aftereffects of rTMS are variable and seem to fail repeatability. We aim to summarize standard rTMS procedures regarding their test-retest reliability. Hereby, we considered influencing factors such as the methodological quality of experiments and publication bias.

Methods: We conducted a literature search via PubMed in March 2023. The inclusion criteria were the application of rTMS, TBS or PAS at least twice over the motor cortex of healthy subjects with measurements of MEPs via spTMS as a dependent variable. The exclusion criteria were measurements derived from the non-stimulated hemisphere, of non-hand muscles, and by electroencephalography only. We extracted test-retest reliability measures and aftereffects from the eligible studies. With the Rosenthal fail safe N, funnel plot and asymmetry test, we examined the publication bias and accounted for influential factors such as the methodological quality of experiments measured with a standardized checklist.

Results: A total of 15 studies that investigated test-retest reliability of rTMS protocols in a total of 291 subjects were identified. Reliability measures, i.e., Pearson's *r* and intraclass correlation coefficient (ICC) applicable from nine studies, were mainly in the small to moderate range with two experiments indicating good reliability of 20 Hz rTMS ($r = 0.543$) and iTBS ($r = 0.55$). The aftereffects of rTMS procedures seem to follow the heuristics of respective inhibition or facilitation depending on the protocols' frequency, and application pattern. There was no indication of publication bias and influence of methodological quality or other factors on the reliability of rTMS.

Conclusion: Reliability of rTMS appears to be in the small to moderate range overall. Due to a limited number of studies reporting test-retest reliability values and heterogeneity of dependent measures, we could not provide generalizable results. We could not identify any protocol as superior to the others.

3.2 Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation (NIBS) technique with which brain activity can be induced and modulated. By applying TMS via single pulses (spTMS), momentary states of cortical excitability can be assessed; for example, stimulations over the motor cortex can induce a motor-evoked potential (MEP) in the respective contralateral hand muscle (Rossini & Rossi, 1998). TMS applied in a repetitive manner (rTMS) is deployed with either a fixed frequency with common frequencies of 1, 10, or 20 Hz or with complex patterns to induce longer-lasting neuroplastic changes (aftereffects) in the brain (Hallett, 2000; Siebner & Rothwell, 2003). MEPs are also used to capture these aftereffects qualitatively. Literature suggests that changes in cortical excitability after rTMS are depending on stimulation frequency (Fitzgerald et al., 2006). Hereby frequencies at about 1 Hz lead to inhibition of neuronal activity, i.e., lower MEPs after rTMS than before, and stimulation with frequencies over 5 Hz evoke facilitatory aftereffects, i.e., higher MEPs after rTMS than at the baseline. This assumption is referred to as the low frequency inhibitory - high frequency excitatory (lofi-hife) heuristic (Prei et al., 2023). Common patterned rTMS procedures are paired associative stimulation (PAS), whereby electrical stimulation of the respective peripheral muscle (conditioning stimulation; CS) is applied in close relation to the contralateral TMS pulse, and theta burst stimulation (TBS), whereby triplets at 50 Hz are repeatedly delivered with a 5-Hz inter-burst-interval. The latter can be administered as intermittent TBS (iTBS) with a pause of 8 s between 2 s of stimulation or as continuous TBS (cTBS) without breaks. Regarding aftereffects, cTBS is considered to elicit inhibitory effects as well as PAS with an inter-stimulus-interval (ISI) of 10 ms between CS and TMS pulse (PAS_{10}) whereas iTBS and PAS with an ISI of 25 ms (PAS_{25}) tend to be excitatory (Huang et al., 2005; Wischnewski & Schutter, 2016). All of these procedures have been frequently used in both basic and clinical research settings as well as in the treatment of various neurological and psychiatric disorders (Berlim et al., 2013; 2017; Patel et al., 2020; Shulga et al., 2021). However, recent literature shows high inter- and intra-subject variability in rTMS aftereffects, questioning the heuristics of a clear association of inhibition or facilitation with a specific protocol (Fitzgerald et al., 2006).

The variability of TMS and rTMS outcome parameters has been a major topic in the NIBS community (Guerra et al., 2020b; Goldsworthy et al., 2021). Furthermore, with high variability of rTMS aftereffects, their reliability can decrease. As one of the three main quality criteria of scientific experiments, test-retest reliability is important, because it indicates whether a measurement or intervention is precise and can be repeated over time while generating the same output. Reliability is most commonly measured with Pearson's *r* (*r*) and intraclass correlation coefficient (ICC), but both

measures are not always reported. Moreover, there is no consensus on whether rTMS reliability is assessed for the measurements of MEPs after rTMS only (post) or rTMS aftereffects (MEPs from before rTMS application subtracted from MEPs after rTMS). To date, the focus of rTMS research has been primarily on the identification and enhancement of aftereffects, but whether these effects are reproducible over time has been rather neglected. With this review, we aimed to give an overview and classification of test-retest reliability of rTMS procedures. We investigated whether there is a most effective protocol to reliably induce neuroplastic changes in the brain. We conducted a meta-analysis with moderator variables to exclude that study-inherent parameters influence the reliability outcome. Hereby we refer to parameters that can influence aftereffects of NIBS and their variability and depend on the equipment and schedule of laboratories and that cannot be adjusted throughout the experiment. These parameters we wanted to account for are the use of neuronavigation (Herwig et al., 2001; Julkunen et al., 2009), sex of participants (Pitcher et al., 2003), repetition interval (Hermsen et al., 2016), year of publication, excitability of protocol and methodological quality of the study. To assess methodological quality, we chose the checklist by Chipchase et al. (2012). The authors created a checklist via the Delphi procedure that assesses whether publications descriptively "report" and experimentally "control" for participant factors, methodological factors and analytical factors which are observed as likely to influence MEP responses elicited by TMS. With the percentage of applicable items from the checklist, one has an approximate measure of the overall methodological quality of a study ranging from 0 to 100 %. To validate our assessment we checked for interrater agreement. Moreover, we have provided an overview of rTMS aftereffects for each of the protocols within the studies assessing reliability. In order to identify the most effective protocol to induce neuroplastic changes, we compared these protocol-specific aftereffects. Publication bias was examined to assess whether the reliability values of current studies are representative.

3.3 Methods

3.3.1 Inclusion criteria

Author CK performed a literature search in PubMed (latest in March 2023) using the keywords ("rTMS" OR "TBS" OR "theta burst" OR "PAS" OR paired asso* stim* OR repet* transc* magn* stim*) AND (MEP OR motor evoked potentials OR cort* exci* OR plast*) AND (reli* OR reproduc* OR repeat*). No filters or automation tools were applied. Based on the PRISMA flow diagram schema (Page et al., 2021), we extracted articles with experiments that applied (1) any kind of rTMS, TBS or PAS (2) the technique at least twice (3) stimulation area over the motor cortex (4) investigating healthy subjects (5) with measurements of MEPs via spTMS as

a dependent variable. As target muscles we focused on hand muscles to ensure comparability. In the first step, author CK screened records in the PubMed database by title and abstract. Second, authors CK and MO inspected independently the full text for the abstracts screened to confirm eligibility and inclusion in the review. The exclusion criteria were (1) measures derived from the non-stimulated hemisphere, i.e., different stimulation location of rTMS and spTMS, (2) examination of non-hand muscles only, and (3) reports of only electroencephalography measurements. Other search strings did not manage to find all the articles we had included.

3.3.2 Test-retest reliability

For interpreting reliability and conducting the meta-analysis, we only used the studies in which a reliability measure such as ICC or *r* was conducted. Moreover, whenever two dependent measures of the identical session were made or both ICC and *r* values were calculated, we only used one value each for depiction and within the meta-analysis in order to prevent overrepresentation. Preferably we extracted the *r* value over the whole measurement, because it has a fixed range of values whereas ICC calculations need to be correctly selected and reported to exclude biases. Nevertheless, in the summarizing Table 1, all reliability values are listed.

We compiled an overview of reliability values of the different rTMS protocols and interpreted *r* after Cohen (1988), with $r < 0.1$ representing the very small range, $0.1 \leq r < 0.3$ small, $0.3 \leq r < 0.5$ medium and $0.5 \leq r \leq 1$ the large range. ICCs were interpreted after Koo and Li (2016), with ICC of < 0.5 being poor, $0.5 \leq ICC < 0.75$ being moderate, $0.75 \leq ICC < 0.9$ being good, and $ICC \geq 0.9$ being excellent. To assess whether one rTMS protocol might be superior in reliability to others, we conducted the Kruskal-Wallis test.

3.3.3 Influences of rTMS reliability

In a chi-squared test by Hunter and Schmidt (2000), we assessed the homogeneity of reliability values. To identify whether study-inherent parameters influence rTMS reliability measures, we conducted a random effects regression analysis with Fisher's z-transformed reliability values using the following continuous predictors: "methodological quality", "year of publication", "repetition interval of rTMS", and "sex ratio" as well as categorical predictors "neuronavigation" and "excitability of the protocol". Hereby, two authors (CK and MO) assessed the methodological quality via the checklist from Chipchase et al. (2012). To ensure the objectivity of the procedure, we calculated Cohen's kappa (κ) for interrater agreement per study with confidence intervals (CI) (Cohen, 1960). A detailed description of how we applied the checklist can be found in the Supplementary material. To assess the influence of the participants' sex, for each study, the sex ratio of the sample was the ratio of the

number of female participants per male participants.

To investigate publication bias, we calculated the Rosenthal fail safe N (Rosenthal, 1979) and conducted a funnel plot for Fisher's z-transformed reliability values and the respective standard errors derived from the sample sizes. By testing the funnel plot for asymmetry (after Egger et al., 1997), we could assess the influence of publication bias on rTMS reliability. We correlated reliability values with the respective year of publication to assess whether more recent research is able to generate higher reliability of rTMS.

Analyses were run in SPSS (IBM Corp., Version 29) and R (R Core Team, Austria, Version 4.0.5) with the meta package (version 6.2-1) (Schwarzer, 2007). Corresponding syntaxes for the meta-analysis can be found by Field and Gillett (2010).

3.3.4 Aftereffects of rTMS protocols of included studies

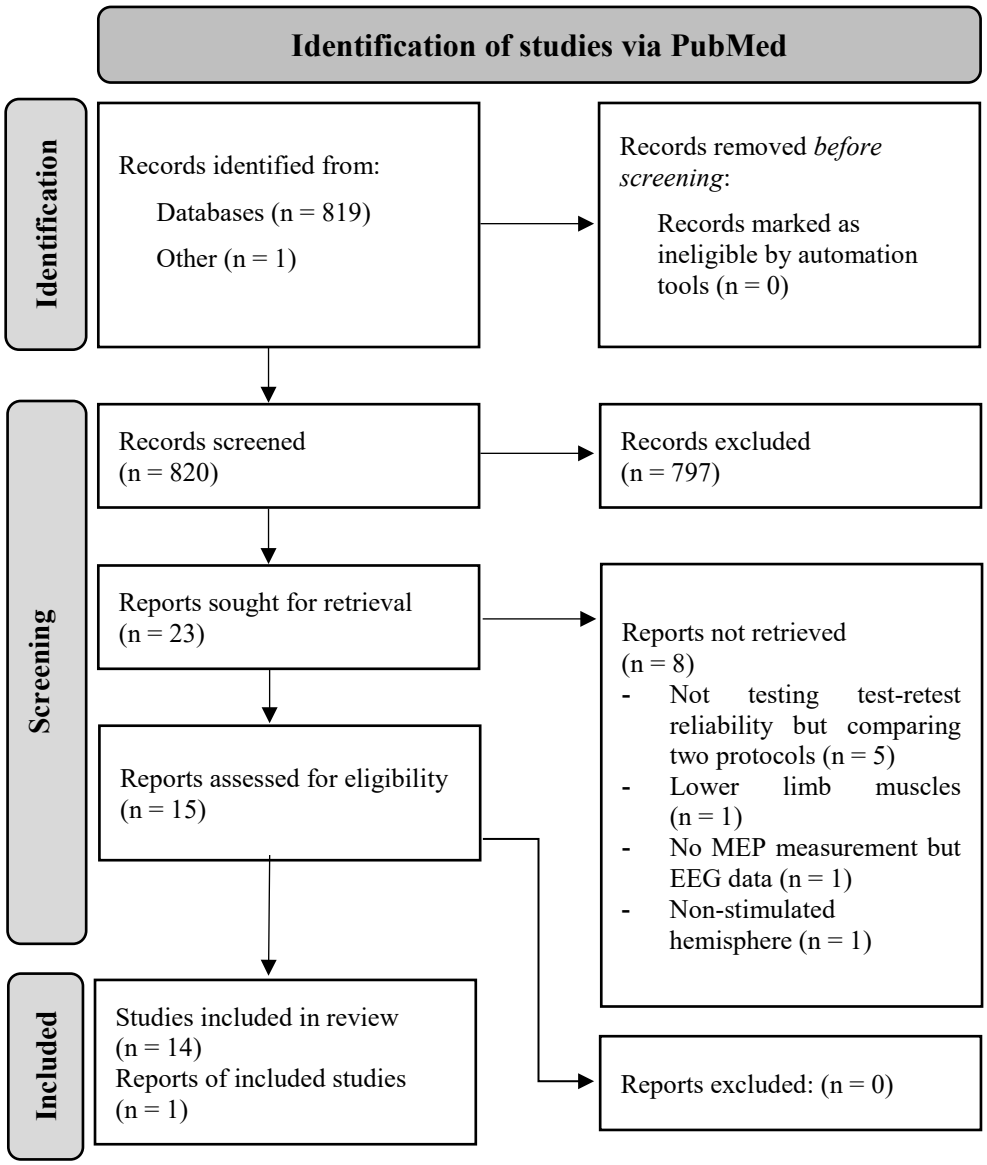
We summarized the aftereffects of rTMS, namely, the percent change from baseline MEP to MEP after rTMS stimulation. With the Kruskal-Wallis test, we tested if rTMS protocols had comparable aftereffects. For those studies that did not provide a mean percent change measure, we recalculated mean changes with the provided descriptive data in the manuscripts.

3.4 Results

3.4.1 Study selection and characteristics

A total of 819 articles resulted from the search in PubMed (latest in March 2023). One preprint was co-authored by CK and included into consideration. In total, 15 articles met the inclusion criteria and were identified as eligible for this review. The detailed procedure can be retraced via the PRISMA flow chart depicted in Figure 1.

Figure 1
PRISMA workflow of how the articles were identified in PubMed via search string and the procedure of identifying the included studies in this review (Page et al., 2021)



The included studies applied continuous rTMS protocols of 1 Hz rTMS (Maeda et al., 2000b; Bäumer et al., 2003; Modugno et al., 2003; Prei et al., 2023), 2 Hz rTMS (Sommer et al., 2002a), 10 Hz rTMS (Maeda et al., 2000b), and 20 Hz rTMS (Maeda et al., 2000b; Cohen et al., 2010; Prei et al., 2023). Moreover, test-retest reliability assessments of patterned rTMS protocols were found: iTBS (Hinder et al.,

2014; Schilberg et al., 2017; Perellón-Alfonso et al., 2018; Boucher et al., 2021), cTBS (Vernet et al., 2014; Vallence et al., 2015; Jannati et al., 2019; Boucher et al., 2021), and PAS_{25} (Fratello et al., 2006; Sale et al., 2007). Two of these studies included sham stimulation (Perellón-Alfonso et al., 2018; Boucher et al., 2021).

The mean sample size over all studies was $n = 17$ (range 4-30, total: 291), with overall 138 women, 143 men, and 10 not applicable. Participants had a mean age of 27 years (range: 18-65 years). The mean test-retest intervals were 13.41 days (range: 6 h – 107 days).

Fratello et al. (2006) reported ICCs for the muscle at which the representative cortical spot was stimulated, i.e., abductor pollicis brevis (APB), as well as one other muscle, the abductor digiti minimi (ADM). For both muscles the authors computed ICCs with the respective post-rTMS measure as well as with the rTMS aftereffects (post-pre). Sale et al. (2007) computed ICCs for a long and a short application of PAS_{25} as well as for the groups that attended sessions in the morning and afternoon respectively. Boucher et al. (2021) reported *r* values for overall measurement of iTBS, cTBS, sham, and ICCs for 5, 10, 20, 30, 50 and 60 min after rTMS application. Hereby, we summarized the ICCs by reporting the minimal and maximal ICC of the respective procedures. Jannati et al. (2019) assessed reliability values from the area under the curve (AUC) of elicited MEPs as well as for the area und the curve of rectified MEPs (|AUC|). Vallence et al. (2015) reported *r* values for two sessions each, i.e., sessions 1 and 2 as well as sessions 1 and 3. The authors also conducted ICC for rTMS aftereffect assessment at stimulus intensities that elicited peak-to-peak MEP amplitudes of 1 mV ± 0.15 mV (SI1mV). Additionally, ICC values for stimulus intensities measured via the input-output curve (IO curve) that evoked MEP sizes halfway between minimal and maximal cortical excitability (SI50), supra-threshold stimulus intensities (150 % RMT) and stimulus intensities evoking maximal MEPs (180 % RMT) were conducted. Prei et al. (2023) reported *r* as well as ICCs of mean and median MEPs over the whole measurement and the respective quarters, whereby we report the overall measures. Table 1 gives an overview of methodological and result parameters of interest.

Table 1

Overview of included studies and values of interest.

References	Protocol	N	Test	Reliability Value	Repetition in days	Observed excitability (rTMS aftereffect)	Sex Ratio (f/m)	NN
Fratello et al. (2006)	PAS_{25}	18	ICC	APB(post): **0.7** ADM(post): 0.62 APB(post-pre): 0.05 ADM(post-pre): -0.003	7	1) **+36.4%**, 2) **+31.7%**	1	no
Sale et al. (2007)	PAS_{25} long, short morning, afternoon	10	ICC	long: **0.68** short: **0.29** morning: 0.39 afternoon: 0.71 long(morning): 0.296 long(afternoon): 0.513 short(morning): 0.011 short(afternoon): 0.812	7	long: **+11%** short: **+51%**	1.55	no
Boucher et al. (2021)	iTBS, cTBS, sham	24	ICC + *r*	iTBS(*r*): **-0.284** cTBS(*r*): **0.298** sham(*r*): **0.149** iTBS(ICC): [-0.22;-0.05] cTBS(ICC): [-0.23;0.51] sham(ICC): [-0.14;0.42]	30	iTBS: **+14.18%** cTBS: **+5.49%** sham: **+18.1%**	0.5	yes
Jannati et al. (2019)	cTBS	28	ICC	AUC: **0.4** |AUC|: 0.46	9.5	1) **-50%**, 2) **-53%**	0.12	yes

References	Protocol	N	Test	Reliability Value	Repetition in days	Observed excitability (rTMS aftereffect)	Sex Ratio (f/m)	NN
Hinder et al. (2014)	iTBS	30	ICC + *r*	ICC: 0.534 *r*: **0.55**	7	**+30.2%**	1.73	yes
Schilberg et al. (2017)	iTBS, sham	27	ICC + *r*	iTBS(ICC): 0.173 iTBS(*r*): **0.097**	7.8	1) **+23.4%**, 2) **+6.4%** sham) **-2.4%**	1.45	yes
Maeda et al. (2000)	1 Hz, 10 Hz 20 Hz	20	*r*	1 Hz: **0.266** 10 Hz: **0.26** 20 Hz: **0.543**	7	1 Hz: 1) **-16.13%**, 2) **-18.5%** 10 Hz: 1) **-6.69%**, 2) **-0.22%** 20 Hz: 1) **+10.8%**, 2) **+24.58%**	1.22	no
Vallence et al. (2015)	cTBS	18	ICC + *r*	*r*(S1, S2): **0.42** *r*(S1, S3): **0.44** SI1mV(ICC): 0.376 SI50(ICC): 0.316 150% RMT(ICC): 0.538 180% RMT(ICC): 0.539	(S1, S2): 11.6 (S1, S3): 22.3	inhibition	1.25	no
Prei et al. (2023)	1 Hz, 20 Hz	30	ICC + *r*	1 Hz(*r*): **0.162** 20 Hz(*r*): **0.123** 1 Hz(ICC): 0.281 20 Hz(ICC): 0.204 median values: 1 Hz(r_{med}): 0.322 20 Hz(r_{med}): 0.097 1 Hz(ICC_{med}): 0.48 20 Hz(ICC_{med}): 0.162	2	no change	2.75	no

Studies without Reliability Value

References	Protocol	N	Test	Reliability Value	Repetition in days	Observed excitability (rTMS aftereffect)	Sex Ratio (f/m)	NN
Vernet et al. (2014)	cTBS	10			107	1) **-44%**, 2) **-56%**	1	yes
Perellón-Alfonso et al. (2018)	iTBS, sham	10			1	1) **+51%**, 2) **+13.27%**, 3) **+53.15%**, 4) **-4.69%**, 5) **+151.75%**	1.86	no
Bäumer et al. (2003)	1 Hz	11, 5			1, 6	excitation after 120 min in session 1	0	no
Cohen et al. (2010)	20 Hz day, night	20			0.5	over day: 1) **+14.94%**, 2) **+14.18%** over night: 1) **+13.29%**, 2) **+29.65%**	0.67	no
Sommer et al. (2002)	2 Hz	6			1	excitation	n.a.	no
Modugno et al. (2003)	1 Hz	4			0.25	1) **+2.68%**, 2) **-14.29%**	n.a.	no

Notes. Overview of the included studies and their methodological properties as well as reliability and aftereffect values. N, number of participants; NN, use of neuronavigation; PAS_25, paired associative stimulation with 25 ms inter-stimulus interval; Long, long application of the protocol; Short, short application of the protocol; Morning, application of protocol in the morning; Afternoon, application of protocol in the afternoon; iTBS, intermittent theta burst stimulation; cTBS, continuous theta burst stimulation; Sham, sham stimulation; day, protocol was applied twice, overday; night, protocol was applied twice, overnight; ICC, intraclass correlation coefficient; *r* = Pearson's *r*; APB, measurement of the abductor pollicis brevis; ADM, measurement of the abductor digiti minimi; Post, reliability of MEPs evoked after rTMS; Post-pre, reliability of MEP aftereffect; AUC, area under the curve; |AUC|, area under the curve of rectified MEPs; (S1, S2), session one in relation to session two; (S1, S3), session one in relation to session three; SI1mV, TMS application with stimulus intensity to evoke 1 mV peak-to-peak MEP amplitude; SI50, TMS application with stimulus intensity that evokes a MEP halfway between minimal and maximal cortical excitability measured via input-output curve; 150 % RMT, TMS application with supra-threshold stimulus intensity; 180 % RMT, TMS application with stimulus intensity evoking maximal MEPs. The column "observed excitability" describes either the mean cortical excitability across all sessions in reference to the baseline activity or if depicted as "1), 2), 3), 4) or 5)" the cortical excitability refers to the change from baseline activity for the respective session. Reliability values printed in bold are depicted in **Figure 2**, and all bold reliability values except the one for sham stimulation are used in the meta-analysis. Aftereffect values in bold are depicted in **Figure 5**.

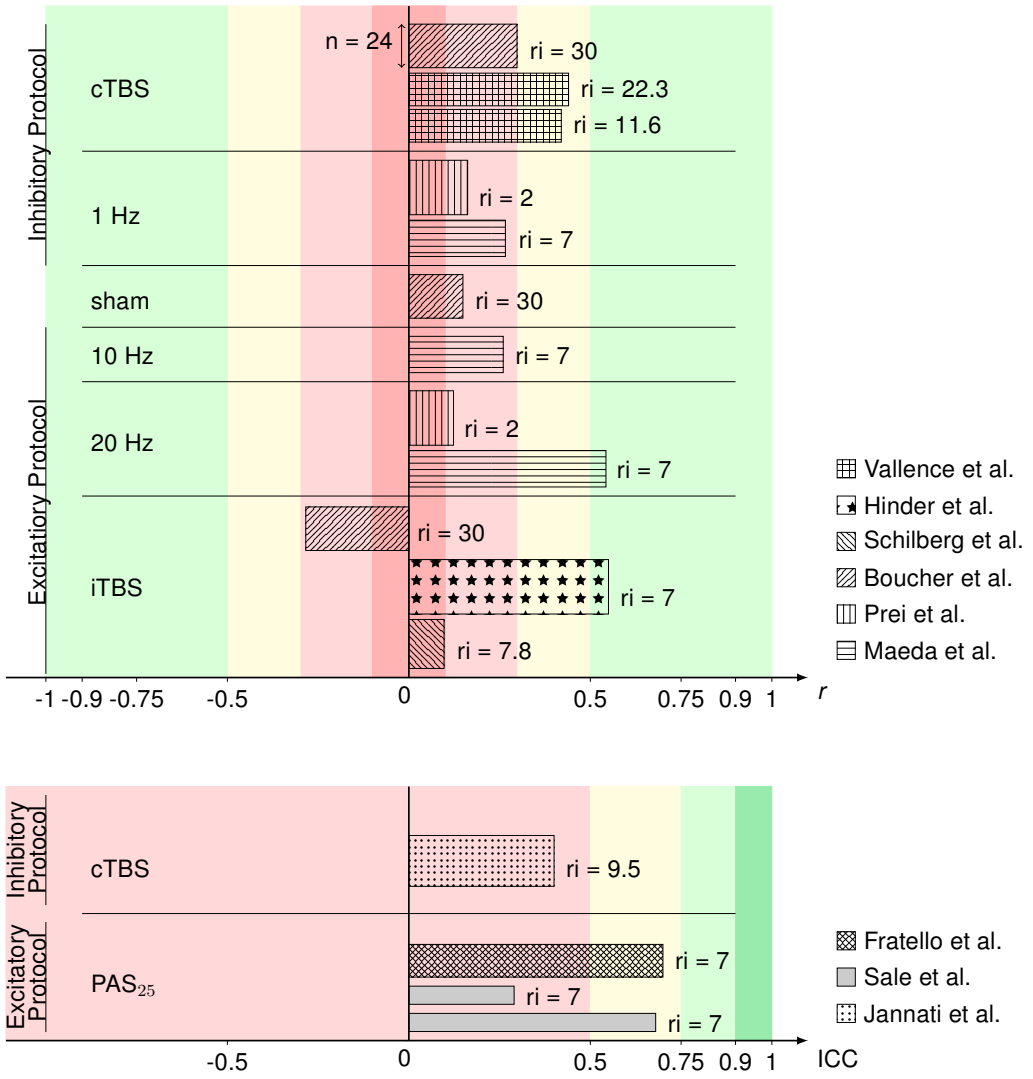
3.4.2 Test-retest reliability

Five of the 15 studies did not report any reliability value but only measures of variance (Sommer et al., 2002a; Bäumer et al., 2003; Modugno et al., 2003; Cohen et al., 2010; Vernet et al., 2014). One study only conducted ICCs for baseline MEPs, but not for MEPs after the rTMS procedure (Perellón-Alfonso et al., 2018). Therefore, these six studies were excluded from the subsequent analyses of reliability, resulting in nine evaluable studies. Both ICC and *r* values were reported in five studies, one publication conducted only *r* and three only ICCs. We preferably extracted *r* values instead of ICC as well as overall reliability for a respective protocol within the studies. Whenever reliability values from the same sessions were calculated, we chose mean MEP amplitudes instead of median (Prei et al., 2023), values derived from the muscle whose cortical representation was stimulated (Fratello et al., 2006) as well as the non-rectified derived parameter (Jannati et al., 2019). Five out of nine studies reported reliability of aftereffect measures, one reported reliability of post rTMS measures (Hinder et al., 2014), two did not state which measure they chose (Sale et al., 2007; Boucher et al., 2021) and one reported both the post and the post-pre measures (Fratello et al., 2006). The highest value was used (post-measure) from Fratello et al. (2006) for depiction and meta-analysis in order to gain most information out of the publication bias investigation.

Figure 2 gives an overview of the included comparable values from evaluable studies combined with a representation of number of participants (sample size) per experiment and the time interval of rTMS repetition. ICCs in this overview of reliability measures ranged from 0.29 to 0.7 and *r* from 0.097 to 0.55 with one iTBS reliability value being in the negative range (-0.284). Reliabilities did not differ between rTMS protocols in analysis via Kruskal-Wallis test ($\chi^2(5) = 5.292,\ p = 0.381$). The exact values can be found in Table 1. According to the classification after Cohen (1988), rTMS reliability yields small to medium effect sizes. The reliabilities of the 20 Hz rTMS protocol (Maeda et al., 2000b) and one iTBS protocol (Hinder et al., 2014) show large effect sizes ($r = 0.543$ and $r = 0.55$, respectively). ICCs also range from poor to moderate reliability values (Koo & Li, 2016). 9 out of 15 rTMS reliability values were interpreted as small or poor, 4 out of 15 as medium or moderate and 2 out of 15 as large effect sizes.

Figure 2

Bar graph of Pearson's r (upper) and ICC values (lower) of the rTMS protocols from the respective articles identified as eligible and comparable in this review



Notes. Reliability values are sorted by protocol and the respective excitability. Patterns of the bars represent in which article the respective values were published. The width of the bars represents the sample size within the respective studies. On the right side of the bars, the (mean or minimum of) number of days between repetition of the rTMS protocol (repetition interval; ri) are depicted. Colors represent the interpretation of *r* (Cohen, 1988) and ICC (Koo & Li, 2016) values as negligible (darker red), poor/low (lighter red), medium/moderate (yellow), good/large (lighter green) or excellent (darker green).

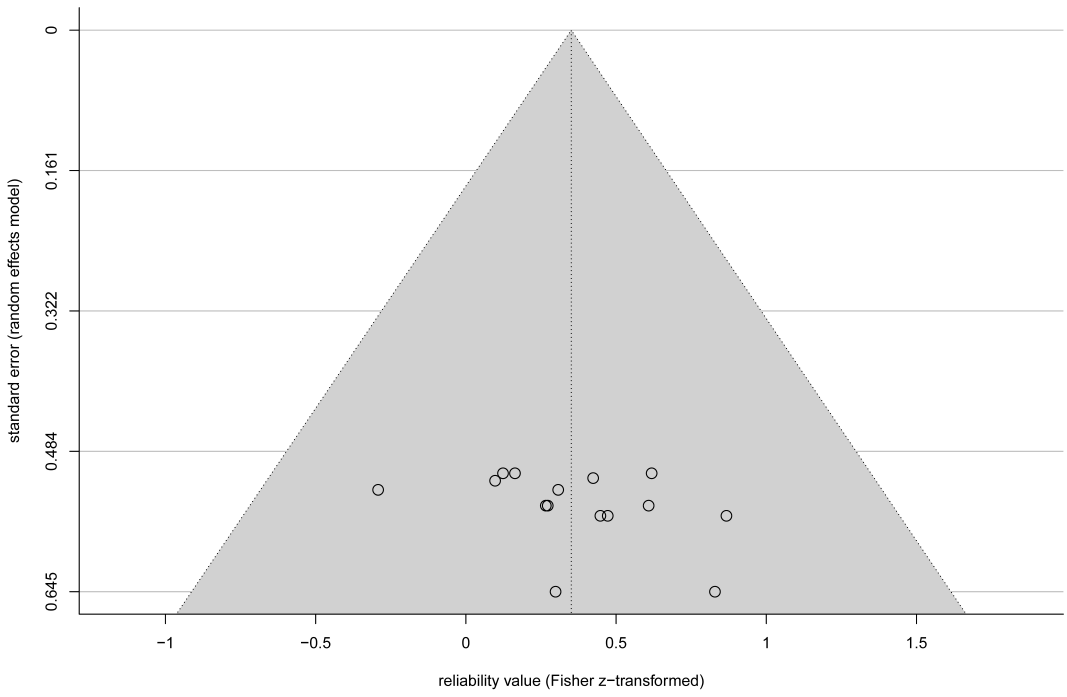
3.4.3 Influences of rTMS reliability

All analyses include both *r* and ICC values because otherwise not all rTMS protocols would be covered. No significant heterogeneity between study reliabilities was found via the chi-squared test ($\chi^2(14) = 20.945,\ p = 0.103$). The random effects regression analysis revealed an overall mean Fisher's z-transformed reliability value

of 0.315 (95 % CI range: 0.168 to 0.449) that is significantly different from zero ($t(15) = 4.45,\ p = 0.001$) in a model without any predictors. By including the continuous and categorical predictors, none of them showed a significant influence (continuous: $t(7) < 1,\ p > 0.442$ and categorical: $\chi^2(1) < 1,\ p > 0.714$). Methodological quality assessed with the checklist by Chipchase et al. (2012) ranged from 30.8 % to 55.8 % and interrater agreement from 0.65 (CI range: 0.5 to 0.82) to 1 (CI range: 1 to 1). Detailed ratings can be found in the Supplementary Tables S1 and S2. Additionally, the goodness of fit of the random effects regression analysis was not significant ($\chi^2(8) = 7.935,\ p = 0.44$). The Rosenthal fail-safe N was 164. The funnel plot, representing the Fisher's z-transformed reliability values on the x-axis and the standard errors from the random effects model on the y-axis, is depicted in Figure 3. With a test for funnel plot asymmetry (after Egger et al., 1997) no significant skewedness was identified ($t(13) = 1.42,\ p = 0.179$). Correlating reliability values with their respective year of publication revealed a negative but non-significant result ($r = -0.475, p = 0.073$), which is shown in Figure 4.

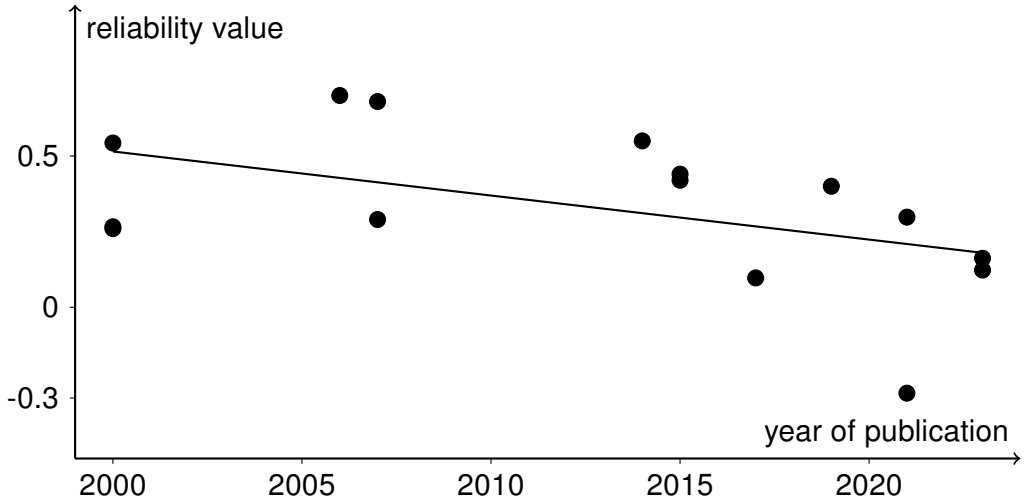
Figure 3

Funnel plot of the standardized effect sizes (Fisher z-transformed values of r and ICC) of the eligible studies plotted against their standard error from the random effects model (circles)



Notes. The diagonal lines (grey background) depict the 95 % confidence interval.

Figure 4
Reliability values as black dots included in the meta-analysis with the year of publication of the respective studies in a scatter plot

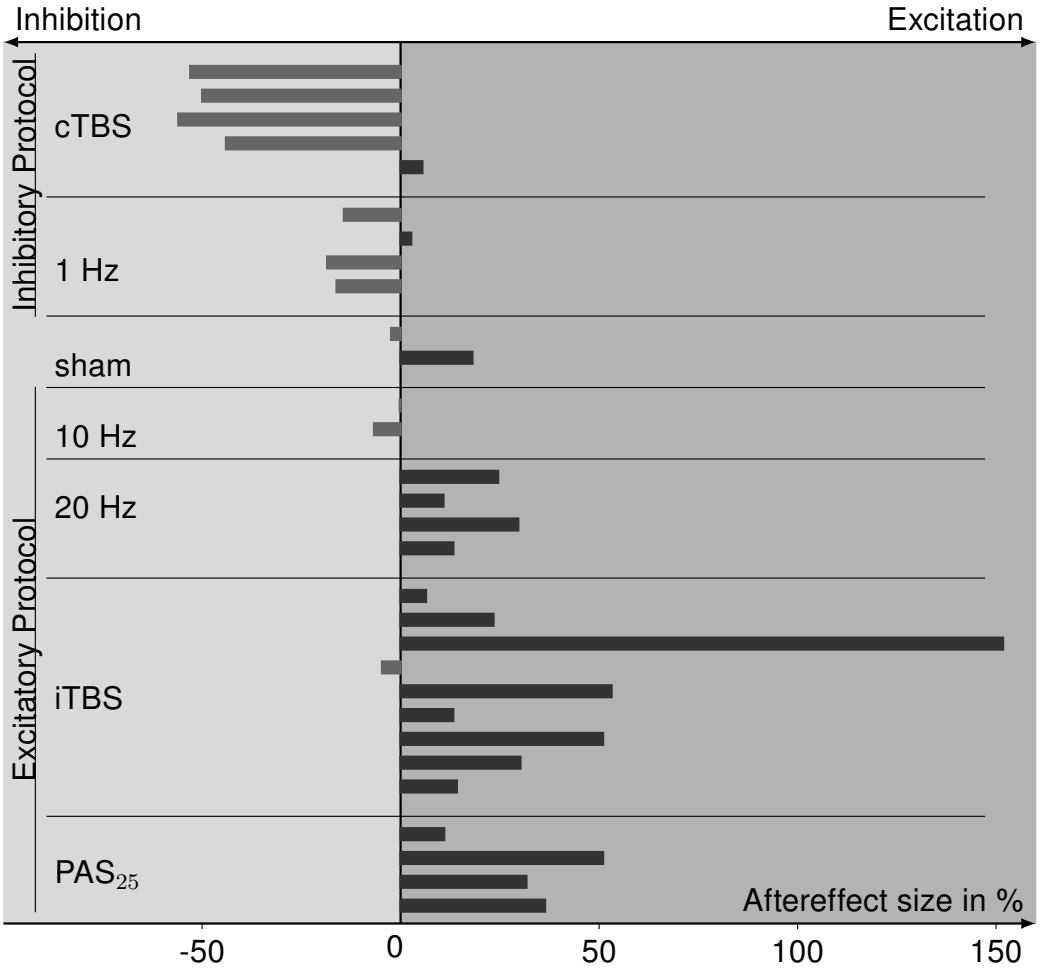


Notes. The negative trend from the correlation analysis is depicted as the black line.

3.4.4 Aftereffects of rTMS procedures of included studies

From four experiments (Sommer et al., 2002a; Bäumer et al., 2003; Vallence et al., 2015; Prei et al., 2023) we were not able to retrieve information on aftereffect sizes, resulting in 11 studies whose data can be included in a summary of aftereffects (for values see Table 1). The size and direction of aftereffects for each rTMS protocol are depicted in Figure 5. The protocols known to primarily evoke cortical inhibition (cTBS and 1 Hz) mainly show inhibitory effects of MEP amplitudes after rTMS application. Sham stimulation has both aftereffect directions. Excitatory protocols (20 Hz, iTBS, PAS_{25}) mostly evoke cortical excitation, except for the 10 Hz protocol which has inhibitory tendencies. Analysis via Kruskal-Wallis test revealed differences in aftereffects between rTMS protocols ($\chi^2(6) = 20.762,\ p = 0.002$), whereby cTBS had significantly lower effects than 20 Hz rTMS ($p = 0.005$), iTBS ($p < 0.001$) and PAS_{25} ($p = 0.001$) and 1 Hz rTMS had significantly lower aftereffects than 20 Hz rTMS ($p = 0.033$), iTBS ($p = 0.008$) and PAS_{25} ($p = 0.008$). Nevertheless, within excitatory or inhibitory protocols, there were no differences in aftereffects ($p > 0.054$).

Figure 5
Bar graph of aftereffect sizes, i.e., the percent change of MEPs after rTMS relative to pre rTMS (baseline) MEPs of the data collected from the eligible studies and sorted for each rTMS protocol



Notes. Protocols are grouped for inhibitory and excitatory effect expectations according to the TMS-protocol-dependent inhibition-excitation heuristic. Positive aftereffect sizes indicate cortical excitation after rTMS stimulation compared to baseline, whereas negative aftereffect sizes refer to cortical inhibition.

3.5 Discussion

This study provides an overview of test-retest reliability of rTMS procedures. We assessed whether we could identify a procedure to most effective and reliably induce neuroplastic changes in the brain. We identified whether parameters inherent to the respective publication influenced reliability values. To estimate the representativity of reliability values, we checked for publication bias.

A total of 15 studies were found that assessed whether rTMS protocols evoke repeatable cortical reactions over time, i.e., their test-retest reliability. Pearson's *r* and ICC values were interpreted as small in nine and medium in four studies. Only

the reliabilities of the 20 Hz rTMS protocol (Maeda et al., 2000b) and of one iTBS protocol (Hinder et al., 2014) are to be interpreted as large according to Cohen (1988). Nevertheless, there is no evidence to favor one particular rTMS protocol based on higher reliability values since no value showed a significant difference from the mean reliability in the Kruskal-Wallis test. Moreover, the chi-squared test did not confirm a difference between reliabilities, which additionally approves the joint analysis of Pearson's *r* and ICC values. One negative reliability value ($r = -0.284$) for iTBS was identified, meaning that the participants' first application of iTBS resulted in a facilitatory effect, whereas the second application had an inhibitory effect and vice versa (Boucher et al., 2021). The two other experiments assessing iTBS reliability did not show such a relation.

Parameters that depend on the publication, i.e., methodological quality of the study, year of publication, and on experimental design, i.e., excitability of protocol, use of neuronavigation, sex ratio of the sample, and rTMS repetition interval, had no influence on reliability of rTMS. Publication bias did not affect the present reliability values, indicated by the funnel plot and asymmetry test which thus strengthens the credibility of these reliability estimates. Nevertheless, the funnel plot depicts that all reliability values are associated with relatively high standard errors, which are derived from the sample sizes of the studies. The Rosenthal fail-safe N of 164 indicates that if 164 unpublished studies had a nonsignificant reliability parameter, the estimated overall reliability would turn significantly different from zero to non-significant. By correlating reliability values with the respective year of publication we identified a negative trend, indicating that, in the current research study, reliability values decrease. This could be either due to higher publication bias in the past publications or due to increasing variability perhaps induced by plurality of setup equipment and higher accuracy of measures, e.g., TMS stimulators, coils, and electrodes. Moreover, higher objectivity of assessment might lead to reduced reliability values. Thus, further studies are needed with higher sample sizes and a systematic investigation of reliability to strengthen the assumption that no publication bias is present in rTMS reliability studies.

rTMS protocols of our included studies followed the lofi-hife heuristic and association with respective inhibition or facilitation effects. Most of the protocols mainly evoking inhibitory neuronal effects resulted in reduced MEPs after stimulation, and the protocols primarily having excitatory effects produced higher MEPs after stimulation. Only the 10 Hz rTMS protocol (Maeda et al., 2000b) shows contrary results. The Kruskal-Wallis test confirmed that inhibitory rTMS protocols had significantly lower aftereffects than excitatory protocols, whereby 10 Hz rTMS did not differ significantly from both inhibitory and excitatory protocols.

Identification of the rTMS protocol with the most reliable and effective outcome cannot be provided currently. Since reliability values did not differ between protocols

and also within excitatory and inhibitory protocols, aftereffects were comparable, no superiority of certain protocols can be proven. Descriptively, cTBS seems to have better inhibitory aftereffects and reliability than 1 Hz rTMS. For excitatory protocols, iTBS can induce descriptively higher aftereffects than PAS_{25}, 20 Hz and 10 Hz rTMS, but also varies more in reliability.

In contrast to baseline spTMS test-retest reliability values reaching ICCs of 0.86 (Pellegrini et al., 2018), rTMS reliability values tend to be smaller. It is important to note that, to assess rTMS reliability, both rTMS and spTMS need to be applied. Thus, variability in both measures adds up to the resulting rTMS aftereffect reliability value. To assess cortical excitability, IO curves cover the whole spectrum best. Nonetheless, to gain clear insights into brain functions and effective treatment of disorders by rTMS, reliable measurements are necessary at best with reliability values in the large range. On the one hand, this is achieved by identifying and eliminating or controlling parameters that influence the variability of spTMS and rTMS. On the other hand, personalization of applications can be an effective method (Schoisswohl et al., 2021).

Many parameters that influence variability of spTMS and rTMS are already identified, e.g., stimulation intensity and number of applied pulses (Pascual-Leone et al., 1994a; Fitzgerald, 2002; Peinemann et al., 2004; Lang et al., 2006), pulse form (Arai et al., 2005), time of day (Sale et al., 2008), subject-related factors as age (Rossini et al., 1992; Pitcher et al., 2003; Todd et al., 2010; Cueva et al., 2016), genetic factors (Cheeran et al., 2008; Di Lazzaro et al., 2015) and changes in motor activation state (Huang et al., 2008; Iezzi et al., 2008; Goldsworthy et al., 2014). The identified studies assessing rTMS reliability show that, with higher stimulus intensities, cortical inhibition increases during cTBS and perceived stress correlated with larger aftereffects (Vallence et al., 2015). A 20 Hz rTMS application with a night in between resulted in higher aftereffects than stimulation overday (Cohen et al., 2010). Influences on the reliability of rTMS procedures were assessed by Jannati et al. (2019) who showed in an exploratory analysis that age and genotype had an influence on the reliability of cTBS aftereffects. Sale et al. (2007) revealed that PAS_{25} assessment in the afternoon is more reliable than in the morning. To systematically investigate which parameters affect the reliability of rTMS, further studies are needed with more power and randomized and controlled experimental design. A meta-analysis is hereby not sufficient to extract dependable information. To generate comparable data on rTMS reliability, future studies should report both the Pearson's *r* value and ICC with corresponding confidence intervals as well as the model the ICC calculation was based on. It should also be established to compute and report both reliability of post rTMS measures and rTMS aftereffects. Further research on the variability and test-retest reliability of rTMS procedures is needed to identify factors that improve rTMS reliability and estimate maximal reliability values achievable.

Although the induction of expected inhibitory or facilitatory aftereffects by rTMS protocols seems to succeed, high inter- and intra-individual variabilities dominate the results of rTMS experiments (Schilberg et al., 2017), even when controlling for most influencing parameters. In an experiment by Hamada et al. (2013), 50 % of the aftereffect variation after TBS was predicted by a marker for late I-wave recruitment, which is discussed to be a mechanism of neuromodulation (Di Lazzaro et al., 2004). Thus, the other 50 % of variation is not yet explainable, also being not related to age, gender, time of day, and baseline MEP sizes (Hamada et al., 2013). It raises the question, whether rTMS in general leads to the induction of variability in the neuronal responses and thus does not achieve exclusively LTP- or LTD-like plasticity effects. Thus, investigations of variability, e.g., the coefficient of variation in addition to the mean evoked responses could provide explanations. Additionally, all-encompassing sham conditions could reveal unbiased aftereffects.

Another approach to identifying reasons for the variability of rTMS is to investigate patients. For example, patients with Alzheimer's disease characterized by neuronal degeneration and rigidity show higher reliability of rTMS compared to healthy controls (Fried et al., 2017). One explanation might be that in Alzheimer's patients, impairments of cortical plasticity can lead to omitted rTMS aftereffects (Di Lorenzo et al., 2020). Nevertheless, there is also evidence that patients with more severe Alzheimer's disease markers show higher inhibitory aftereffects after 1 Hz rTMS (Koch et al., 2011), which might indicate that neuronal rigidity can be altered by the induction of variability with rTMS. Thus, interpretive approaches should be taken with caution.

The present systematic review and meta-analysis addresses the test-retest reliability of rTMS on healthy individuals and derived findings cannot be transferred to other populations, such as patient groups, or other applications, e.g., stimulation over other cortices than the motor cortex. Participants from the included studies were often right-handed and accordingly did not show a representative sample. Because only a few studies contributed to the analysis of reliability values, the results cannot be generalized and need to be interpreted with caution. Additionally, although eliciting MEPs is a common procedure to investigate cortical excitability, it still represents an indirect measure. There are other markers that hold the potential to estimate reactions of the brain to rTMS in a more direct way, yet, to date, they are studied less frequently and prone to artefacts and noise.

Test-retest reliability of rTMS in the identified studies is mainly small to moderate, with overall scarce experimental assessment. Aftereffects of rTMS protocols mainly followed the respective inhibition or excitation expectation. No protocol is to be favored based on our findings of reliability values and aftereffect sizes. However, the generalizability remains questionable because of limited comparable data. By reporting ICC as well as Pearson's r values of both post-rTMS and aftereffect

measures, studies examining test-retest reliability can contribute to comparability. Additionally, the application of spTMS should be equal, e.g. by assessing IO curves of MEPs. In general, the variability of NIBS outcomes is mirrored in its reliability. Influential factors of both spTMS and rTMS need to be systematically investigated to achieve high and reliable rTMS aftereffects. To establish rTMS procedures in the clinical everyday use of disorder treatment, higher reliability is necessary. With this overview scientists and clinicians can estimate and compare the size and reliability of the aftereffects of rTMS based on current data.

3.6 Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

3.7 Author contributions

CK, SS and MS contributed to the review concept and design. CK performed the literature search and conducted data analysis and visualized the study and drafted the manuscript. CK and MO reviewed included studies and examined the studies' methodological quality. CK, MO, FS, KL, WS, WM, SS and MS revised the manuscript. All authors have read and approved the final version. All authors contributed to the article and approved the submitted version.

3.8 Funding

This research is funded by dtec.bw – Digitalization and Technology Research Center of the Bundeswehr (project MEXT). Dtec.bw is funded by the European Union – NextGenerationEU.

3.9 Conflict of interest

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

3.10 Supplementary material

3.10.1 Methodological quality of included studies

We assessed the methodological quality of the studies with the checklist by Chipchase et al. (2012). From the originally 30 items, with three only assessible for paired-pulse TMS, author CK and MO classified the item "subjects prescribed medication" from the checklist as too little different from the item "use of CNS active drugs" and

merged these into one item resulting in 26 assessed items for single pulse TMS measurements. For rTMS procedures there are currently no factors included in the checklist. Each item was independently checked whether it was experimentally "controlled" , descriptively "reported" or not reported at all – "missing", whereby "controlled" items are also "reported". "Controlled" means that a factor was excluded, e.g., by exclusion criteria, or a factor was balanced e.g., "gender of subjects", or used as a covariate in data analysis. We assume that the term "gender" in the checklist is mistakenly used for "sex", because the female cycle can have an influence on cortical excitability (Inghilleri et al., 2004). Although the checklists authors state otherwise, we considered the item "gender of subjects" as controllable, i.e., by inserting the factor in as a covariate in the analyses and the item "level of relaxation of muscles other than those being tested" as reportable, i.e., with visual monitoring. The percentages for the "reported" items (Percent_R) were calculated by dividing the total number of "reported" items by the total number of the 26 items per study and rater (CK and MO). Equally, percentages of "controlled" items of the checklist (Percent_C) were calculated equivalent to Percent_R. A total percentage (Percent_T) was calculated by calculating the mean of Percent_C and Percent_R of rater 1. The total percentage was considered to represent the overall methodological quality and also used as a covariate in the meta-analysis for accounting of methodological differences between studies. For interrater agreement we calculated Cohen's kappa (κ) per study with confidence intervals (CI) (Cohen, 1960).

3.10.2 Results

Percent_R was on average 73.3 % in a range from 61.5 % to 84.6 %. Percent_C was in the range from 0 % to 38.5 % resulting in an average of 18.5 %. The mean Percent_T was 45.8 %. Detailed percentages of both raters as well as Cohens kappas for interrater agreement are specified in Table S1. Absolute frequencies for each item that was rated as "reported" and "controlled" for all studies are depicted in Table S2. Ten out of 15 studies "controlled" for "time between days of testing" and "size of unconditioned MEP" and seven for "time between MEP trials", being the most "controlled" items. Items that often were neither "reported" nor "controlled", i.e. "missing" were "level of relaxation of muscles other than those being tested" in 14 out of 15 studies, "history of specific repetitive motor activity" in 13 studies and "any medical condition" in 11 studies. κ ranged from 0.65 to 1.

3.10.3 Supplementary tables

Supplementary Table S1

Overview of Cohens kappas and Chipchase percentages of included studies

Study Authors and Year	$Percent_{R1}$	$Percent_{C1}$	$Percent_{R2}$	$Percent_{C2}$	$Percent_{T}$	κ	CI
Fratello et al. (2006)	76.9 %	26.9 %	76.9 %	26.9 %	51.9 %	1	1 – 1
Sale et al. (2007)	80.8 %	30.8 %	80.8 %	30.8 %	55.8 %	1	1 – 1
Boucher et al. (2021)	76.9 %	7.7 %	73.1 %	11.5 %	42.3 %	0.85	0.67 – 1
Vernet et al. (2014)	84.6 %	11.5 %	84.6 %	11.5 %	48.1 %	1	1 – 1
Jannati et al. (2019)	80.8 %	15.4 %	80.8 %	15.4 %	48.1 %	1	1 – 1
Hinder et al. (2014)	73.1 %	15.4 %	73.1 %	15.4 %	44.2 %	1	1 – 1
Perellón-Alfonso et al. (2018)	69.2 %	38.5 %	69.2 %	38.5 %	53.9 %	1	1 – 1
Schilberg et al. (2017)	80.8 %	30.8 %	80.8 %	30.8 %	55.8 %	1	1 – 1
Vallence et al. (2015)	65.4 %	23.1 %	65.4 %	23.1 %	44.2 %	1	1 – 1
Bäumer et al. (2003)	76.9 %	19.2 %	76.9 %	19.2 %	48.1 %	1	1 – 1
Cohen et al. (2010)	69.2 %	11.5 %	65.4 %	11.5 %	40.4 %	1	1 – 1
Maeda et al. (2000)	73.1 %	3.8 %	73.1 %	7.7 %	38.5 %	0.92	0.74 – 1
Sommer et al. (2002)	57.7 %	11.5 %	57.7 %	15.4 %	34.6 %	0.94	0.71 – 1
Modugno et al. (2003)	61.5 %	0.0 %	61.5 %	0.0 %	30.8 %	1	1 – 1
Prei et al. (2023)	76.9 %	23.1 %	76.9 %	26.9 %	50.0 %	0.65	0.5 – 0.82

Notes. This table gives an overview of included studies depicting Cohens kappas (κ), 95 % confidence intervals (CI) of κ and the percentages of experimentally controlled items assessed by rater 1 ($Percent_{C1}$) and descriptively reported items assessed by rater 1 ($Percent_{R1}$) as well as percentages of controlled items assessed by rater 2 ($Percent_{C2}$) and descriptively reported items assessed by rater 2 ($Percent_{R2}$). $Percent_{T}$ are the total percentages per study of rater 1.

Supplementary Table S2

Overview of items from the Chipchase (2012) checklist with the respective absolute frequencies of studies "reporting" and "controlling" for each item

	Rater 1		Rater 2	
	Controlled	**Reported**	**Controlled**	**Reported**
Participant factors				
Age of subjects	1	15	1	15
Gender of subjects	4	14	4	14
Handedness of subjects	6	12	6	12
Use of CNS active drugs	1	3	1	3
Presence of neuro./psych. disorders	2	11	2	11
Any medical condition	0	4	0	4
History of repetitive motor activity	1	2	1	2
Methodological factors				
EMG electrode position/contact	2	13	2	13
Muscle relaxation/contraction	7	14	6	14
Prior motor activity of tested muscle	3	5	3	5
Relaxation of non-target muscles	1	1	1	1
Coil type (size/geometry)	0	14	0	14
Coil orientation	0	13	0	13
Current direction in brain	0	8	0	8
Coil location/stability	2	12	3	12
Stimulator type	0	15	0	15
Stimulation intensity	5	14	5	14
Pulse shape (mono/bi)	0	10	0	10
Optimal hotspot determination	1	13	1	13
Time between MEP trials	8	14	7	14
Time between testing days	13	15	10	15
Subject attention during testing	1	5	1	5
Threshold determination method	1	15	1	15
Number of MEPs recorded	3	15	3	15
Analytical factors				
MEP size determination method	2	14	2	15
Unconditioned MEP size	10	14	10	14

Notes. The assessments of both raters are depicted individually.

4 Third study: Influences of current direction on 1 Hz motor cortex rTMS

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The following texts, figures and tables are pre-edited versions of the final article:

Kanig, C., Osnabruegge, M., Schwitzgebel, F., Mack, W., Schecklmann, M., & Schoisswohl, S. (2025). Influences of current direction on 1 Hz motor cortex rTMS. *Brain Research Bulletin*, 111484. https://doi.org/10.1016/j.brainresbull.2025.111484

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4.1 Abstract

Objective. Neuromodulatory changes induced by repetitive transcranial magnetic stimulation (rTMS) are highly variable and lack replicability. Amongst many influencing factors, the current direction of the stimulation is known to affect rTMS aftereffects. In this study, we investigated the influence of current direction on cortical and peripheral markers of motor cortex plasticity as induced by 1 Hz rTMS as well as the correlation of cortical and peripheral markers. Additionally, we investigated possible confounding variables.

Methods. Twenty-five healthy subjects received 1 Hz rTMS at 110 % resting motor threshold intensity over the left motor hotspot inducing anterior-posterior – posterior-anterior (AP-PA) and posterior-anterior – anterior-posterior (PA-AP) current directions in the brain. Motor evoked potentials (MEPs) and transcranial evoked potentials (TEPs) before and after rTMS were assessed with single pulses. Coil placement was ensured by a neuronavigated robot-assisted setup.

Results. In sum, 1 Hz rTMS resulted in higher amplitudes of MEPs and TEP components N15, N45 and P60 and a reduced amplitude of N100, whereby the induced PA-AP current direction in the brain elicited higher effects. MEP and TEP N15 latency were prolonged and N100 shortened after rTMS. PA-AP current direction elicited stronger changes in latency for MEPs and N15. N45 and MEP correlated in the PA-AP pre rTMS condition with negligible effect size.

Conclusions. Our findings of facilitatory pre-to-post rTMS changes are in contrast to preliminary assumptions that 1 Hz rTMS acts inhibitory. However, since high variability and low reliability of rTMS aftereffects are prominent in the current literature, these results shed light that potential influencing factors need to be better reported, controlled and investigated. We suggest to further investigate effects of stimulation intensity and tiredness of subjects on rTMS. We were able to replicate current direction effects which strengthens the hypothesis of activation of different sets of neurons.

4.2 Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation (NIBS) method to assess cortical excitability (Barker et al., 1985; Hallett, 2000), which is commonly used in research and clinical diagnostics (Hallett, 2000; Di Lazzaro et al., 2004). By delivering a short current pulse through a coil placed over the scalp, TMS produces a rapidly changing magnetic field, which induces an electrical field in the underlying tissue that can lead to depolarization and action potential propagation in the cortical neurons (Di Lazzaro et al., 2018). Through suprathreshold TMS pulses applied over the motor cortex, so-called motor evoked potentials (MEPs) can be derived via electromyography (EMG) from the respective contralateral muscle in the periphery. These are typically used as a marker for cortico - spinal excitability (Pascual-Leone et al., 1998; Di Lazzaro & Rothwell, 2014).

Cortical excitability can be directly measured via transcranial evoked potentials (TEPs), which represent cortical responses to TMS pulses and are derived from electroencephalography (EEG; Bergmann et al., 2016). When TMS is applied over the motor cortex, the evoked brain activity is represented by a waveform of positive and negative peaks at consecutive latencies which are referred to as the N15, P30, N45, P60 and N100 TEPs (Bonato et al., 2006; Tremblay et al., 2019; Ahn & Fröhlich, 2021). During this propagation of neuronal signal, TEPs differ spatially, i.e. in topography, and are affected by confounding signal, indicating that different cortical areas and networks are involved in the signal propagation of all peaks (Momi et al., 2021; Zazio et al., 2021; Farzan & Bortoletto, 2022; Zazio et al., 2022). The combined peak-to-peak amplitude of N15 and P30 has been found to correlate with MEP amplitude and thus might reflect the underlying motor cortical excitation (Mäki & Ilmoniemi, 2010; Gedankien et al., 2017). The components N45 and P60 are associated with reafferent motor signals during stimulation of the motor cortex (Mäki & Ilmoniemi, 2010; Petrichella et al., 2017; Ahn & Fröhlich, 2021). N100 is argued to represent inhibitory processes (Rogasch et al., 2013) and motor activity (Roos et al., 2021). Later TEPs like the P180 and N280 were not associated with motor activity (Casula et al., 2014) and showed confounded signal, mainly auditory (Ahn & Fröhlich, 2021), which is why we did not include them in our analyses. Additionally, the M1-P15, a positive TEP peak over contralateral fronto-central electrodes of the stimulated motor cortex was found to reflect cortico-cortical inhibition (Bortoletto et al., 2021; Zazio et al., 2022; Guidali et al., 2023). In contrast to MEPs, TEPs can be elicited by subthreshold stimulation and thus can provide a more sensitive and immediate measure of cortical responses to TMS (Komssi et al., 2004). However, TEPs are also sensitive to confounding activity, such as somatosensory and auditory stimulation (Conde et al., 2019), which further complicates causal interpretation.

In order to alter cortical excitability, TMS pulses are applied in a rhythmic manner

at certain frequencies which is termed repetitive transcranial magnetic stimulation (rTMS) and is a frequently used neuromodulation technique with effects outlasting stimulation offset (Ridding & Rothwell, 2007). Hence, rTMS is capable to induce neuroplasticity and is thus utilized in a wide range of basic science experiments (Fitzgerald, 2002; Todd et al., 2010; Patel et al., 2020) as well as in clinical settings as a therapeutic option for various neuro-psychiatric diseases (Mishra et al., 2011; Lefaucheur et al., 2014).

The underlying mechanisms of inducing neuroplasticity via rTMS have not been fully understood yet. It is suspected that depending on the frequency of rTMS, mechanisms of long-term depression (LTD) or long-term potentiation (LTP) of synaptic strength are accountable (Hallett, 2000; Fitzgerald et al., 2006). Commonly low frequency rTMS is assumed to inhibit cortical excitability, whereas high frequency stimulation acts excitatory (Fitzgerald et al., 2006; Thut & Pascual-Leone, 2010). We refer to this assumption as the lofi-hife heuristic: low frequency inhibitory – high frequency excitatory (Prei et al., 2023). These rTMS effects or pre-to-post changes can be observed for cortico - spinal excitability in the healthy population in increased MEP amplitudes after excitatory high frequency protocols and lower MEP amplitudes after inhibitory low frequency protocols (Pascual-Leone et al., 1994a; Wassermann et al., 1996; Tang et al., 2019). However, these findings are not always reproducible (Prei et al., 2023) and show only low to moderate reliability (Kanig et al., 2023). Due to the high variability of findings, it is advisable to treat the effects of rTMS with caution and to set up experiments as objectively as possible and to systematically investigate possible influencing factors.

Only few studies investigated neuromodulatory effects on TEPs in healthy subjects. Casula et al. (2014) found increased P60 and N100 amplitudes after 1 Hz rTMS over the left motor cortex. Zhou et al. (2022) reproduced this effect partially by evoking an increased N100 and reduced P60. After 0.6 Hz rTMS, an immediate numeric reduction and subsequent significant increase to baseline levels of N45 was found by van der Werf and Paus (2006). During application of 20 Hz rTMS over the left primary motor cortex, increased cortical responses in early TEPs (P5, N8) over electrode C3 were found along with shorter latencies, whereas no differences in P30 and N45 occurred (Veniero et al., 2010).

In sum, rTMS effects are highly variable as can be seen in heterogeneous findings (Thut & Pascual-Leone, 2010; Kanig et al., 2023; Schoisswohl et al., 2024). Contributing factors to this variability are choices in experimental design (Iezzi et al., 2008; Fleming et al., 2012; Pellegrini et al., 2020), physiological (Todd et al., 2010; Di Lazzaro et al., 2015) and also technical parameters (Sommer et al., 2002b; Tings et al., 2005; Lang et al., 2006). Stimulation parameters like induced current direction in the brain are known to influence cortical and cortico – spinal excitability measures: in single pulse TMS, different resting motor thresholds (Kammer et al., 2001;

Davila-Pérez et al., 2018), MEP latency and reliability of MEP amplitude (Davila-Pérez et al., 2018) were found for varying current directions. Casula et al. (2018) reported greater positive TEP peaks for monophasic posterior-anterior (PA) current direction and greater negative TEP peaks for both monophasic anterior-posterior (AP) or biphasic anterior-posterior – posterior-anterior (AP-PA) current direction, while TMS stimulus intensities were overall higher for the AP current direction. Also, topographies of components until 80 ms differed between current direction (Casula et al., 2018). It is discussed that different current directions activate different sets of neurons in the pre- and post-central gyrus (Li et al., 2017; Di Lazzaro et al., 2018). In response to rTMS, MEPs showed higher excitatory pre-to-post changes after 5 Hz rTMS for induced posterior-anterior - anterior-posterior (PA-AP) current direction in the brain than AP-PA pulses (Sommer et al., 2013a). The same pattern of MEP excitation (averaged normalized MEP modulation amplitudes) was found to correlate stronger with peak values of AP depolarizing pulses than PA depolarizing pulses (Halawa et al., 2021). Yet, stronger inhibition after 1 Hz rTMS was found for monophasic PA in contrast to AP induced current in the brain (Goetz et al., 2016). Hereby, it is to be noted that for biphasic pulses the second phase is more effective (depolarizing) than the first, corresponding to the direction of the monophasic pulse phase (Salvador et al., 2011).

In the present study, we investigated the pre-to-post changes of 1 Hz rTMS for default and reversed current direction of a MagVenture MagPro X100 pulse source in several neurophysiological metrics - MEPs and TEPs. We examined the differences between both current directions in rTMS changes as well as the underlying correlations of cortico - spinal (MEPs) with cortical measures (TEPs) to possibly deduce a cortical marker to equally assess the excitability and plasticity effects induced by TMS and rTMS, which then may be used as more proximal categorization variable of rTMS effects. Since findings on TMS and rTMS show only low to moderate reliability (Kanig et al., 2023; Osnabruegge et al., 2023; Prei et al., 2023) we aimed to increase cortical inhibition effects of 1 Hz rTMS by increasing the intensity to suprathreshold level (Fitzgerald, 2002; Lang et al., 2006) and improve the objectivity and reliability of our measures using a modern robot-guided neuronavigated TMS setting (Goetz et al., 2019; Rossi et al., 2021) in combination with a within-subject experimental design.

4.3 Methods

The present experiment was conducted in compliance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the local ethics committee of the University of Regensburg (ethical approval number: 21-2662-1-101). All participants gave written informed consent before study begin.

4.3.1 Participants and exclusion criteria

Our sample included 25 healthy subjects (15 female) aged between 19 and 42 years ($M = 25, SD = 4$). All participants were German-speaking, right-handed ($M = 87.96, SD = 13.67$; Oldfield, 1971) had a mean intelligence quotient of 110.12 ± 11.56, assessed with the German version of the multiple-choice vocabulary intelligence test (MWTB-Q; Lehrl, 2018) and had no neurological, psychiatric or other severe somatic condition, which was examined by a trained clinical professional. Depression, assessed with the Major Depression Inventory (Bech et al., 2001), was not present ($M = 4.28, SD = 2.72, Maximum = 10$) in any subject. Other exclusion criteria were a high stimulation intensity, that would have exceeded our safety requirements (>80 % maximum stimulator output, which produces local sensations that are hard to tolerate), intake of psychoactive substances or medication as well as contraindications with respect to TMS and magnetic resonance imaging (MRI). The latter include ferromagnetic implants and a history of severe brain injuries or epileptic seizures. All participants received monetary compensation.

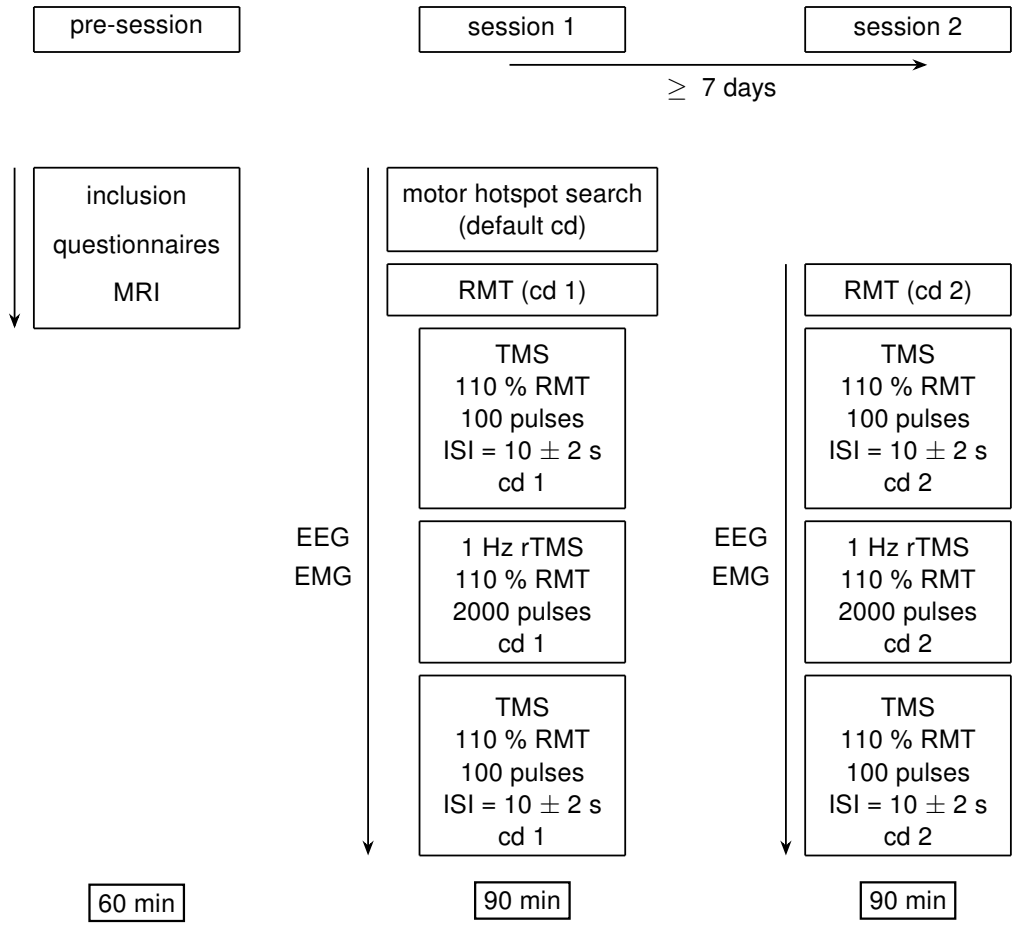
In two of the 25 subjects, EMG data was very noisy (mean MEP-to-baseline-ratio = 0.8 and 0.9) and thus, no MEPs could be identified for the condition before rTMS with reversed current direction in one subject and in the condition after rTMS with default current direction in another subject. Therefore, for MEP analyzes and the correlations, but not TEP analyzes, these two subjects for the respective condition were removed.

4.3.2 Procedure

The experiment consisted of two experimental sessions and a pre-session. In the pre-session, inclusion- and exclusion criteria were checked, informed consent was given, questionnaires were filled out and a T1-weighted MRI scan (MPRAGE 160 slices, 256 × 256, voxel size = 0.977 × 0.977 × 1 mm^3, flip angle 9°, TR/TE/TI = 1910/3.67/1040 ms) was made for the purpose of neuronavigation (3 Tesla; Siemens, Munich, Germany). In an experimental session, all TMS and rTMS stimulations were conducted with one current direction (default or reverse), whereby the starting direction was randomized a priori via number generation. 14 subjects started with default and 11 subjects started with reversed current direction, whereby all participants were blinded to the current direction used throughout the experiment. The experimental sessions started with rating visual analogue scales (VAS) from 1 (minimum) to 10 (maximum) on subjective attention, excitement, and tiredness levels, which was repeated after the session to track changes. Subjects were instructed to remove all electronic devices from their body and clothing, to sit as still as possible, keep their hands relaxed and their eyes on a fixation cross during all measurement procedures. EEG and EMG of the first dorsal interosseous (FDI), abductor pollicis brevis (APB)

and abductor digiti minimi (ADM) muscle were attached and recorded throughout the TMS and rTMS measurements. The motor hotspot for optimal representation of the FDI muscle with default current direction was identified with a grid-based semi-automated method using cobot-assisted neuronavigated TMS setup; for a detailed description see Agboada et al. (2023). Hereby, high and stable MEPs in the FDI were aimed at whilst having relatively less activity in the APB and ADM as well as relatively lowest stimulation intensity. The individual motor hotspot elicited with default current direction was used throughout the whole experiment to ensure that the coil position and thus qualitative course of the induced electric field is comparable between current directions. Additionally, the resting motor threshold defined as 50 % of TMS stimuli resulting in a MEP in the FDI over 50 µV was determined (Rossini et al., 2015). 1 Hz rTMS intervention was made over subjects' individual motor hotspot at 110 % resting motor threshold (RMT) with 2000 pulses for each current direction. These suprathreshold and prolonged stimulation parameters were chosen to enhance the achievable rTMS effect (Maeda et al., 2000a; Fitzgerald, 2002; Peinemann et al., 2004; Lang et al., 2006). Before and after rTMS, 100 single TMS pulses were applied at the individual motor hotspot at 110 % RMT as well, with an inter-stimulus interval (ISI) of 10 s and jitter of 2 s. All TMS pulses were masked throughout the entire experiment by a masking noise composed of 70 % white noise combined with 30 % TMS click noise created with the TMS Adaptable Auditory Control (TAAC) toolbox (Russo et al., 2022) in Matlab (Matlab R2018b; Mathworks, USA), and loudness adapted to individual perception level (max. 85 dB SPL) and delivered through ER-3C 10 Ω Insert Earphones (Etymotic Research Inc., USA) together with an iPod Touch 7^{th} Generation (Apple Inc., Cupertino, California, USA). After the stimulation session, VAS scales were rated again and post questionnaires on perceptions for example of the TMS coil click sound were filled out. The second session was held at least one week after the first session and at the same time of day. It was scheduled the same way as the first session, but the current direction was set to the other condition for all magnetic stimulations. An overview of the experimental procedure is depicted in Figure 1.

Figure 1
Experimental procedure



Notes. After a pre-session, the first experimental session started with motor hotspot search and RMT determination. 100 TMS pulses, 2000 rTMS pulses in 1 Hz frequency and again 100 TMS pulses were administered with the first current direction. Concurrently, EEG and EMG were recorded. The second session was scheduled at least 7 days after and its procedure was the same as the first, but all stimulations were applied with the second current direction. Starting current direction was randomized a priori. MRI = Magnetic Resonance Imaging. Cd = Current Direction. EEG = Electroencephalography. EMG = Electromyography. ISI = Inter Stimulus Interval. RMT = Resting Motor Threshold.

4.3.3 Transcranial magnetic stimulation (TMS)

For all magnetic stimulations, a MagPro X100 stimulator with MagOption and a figure-of-eight Cool-B65 A/P coil (MagVenture A/S, Farum, Denmark) were used. All pulses had a biphasic shape and a pulse width of approximately 280 µs as declared by the manufacturer (MagVenture A/S, Farum, Denmark). The biphasic waveform was chosen to ensure identical stimulation conditions during rTMS with

single pulses before and after (Peinemann et al., 2004). The coil position was held stable throughout the experiment at the hotspot with a $45°$ angle to the midline via neuronavigation software (Localite GmbH, Bonn, Germany) in combination with a collaborative robotic coil holder (cobot; Axilum Robotics, Schiltigheim, France). With this setup, we were able to ensure a continuous placement and alignment onto the participants' hotspot at an accuracy of 2 mm within and across sessions even when small head movements occurred. The two current directions in this experiment refer to the default setting of the MagPro X100 stimulator with an induced current flow of AP-PA in the brain (default current direction) and to the reversed setting, which induced a current flow of PA-AP in the brain (reversed current direction). This parameter can be simply changed in the stimulation parameter settings of the TMS device.

4.3.4 Electromyography (EMG)

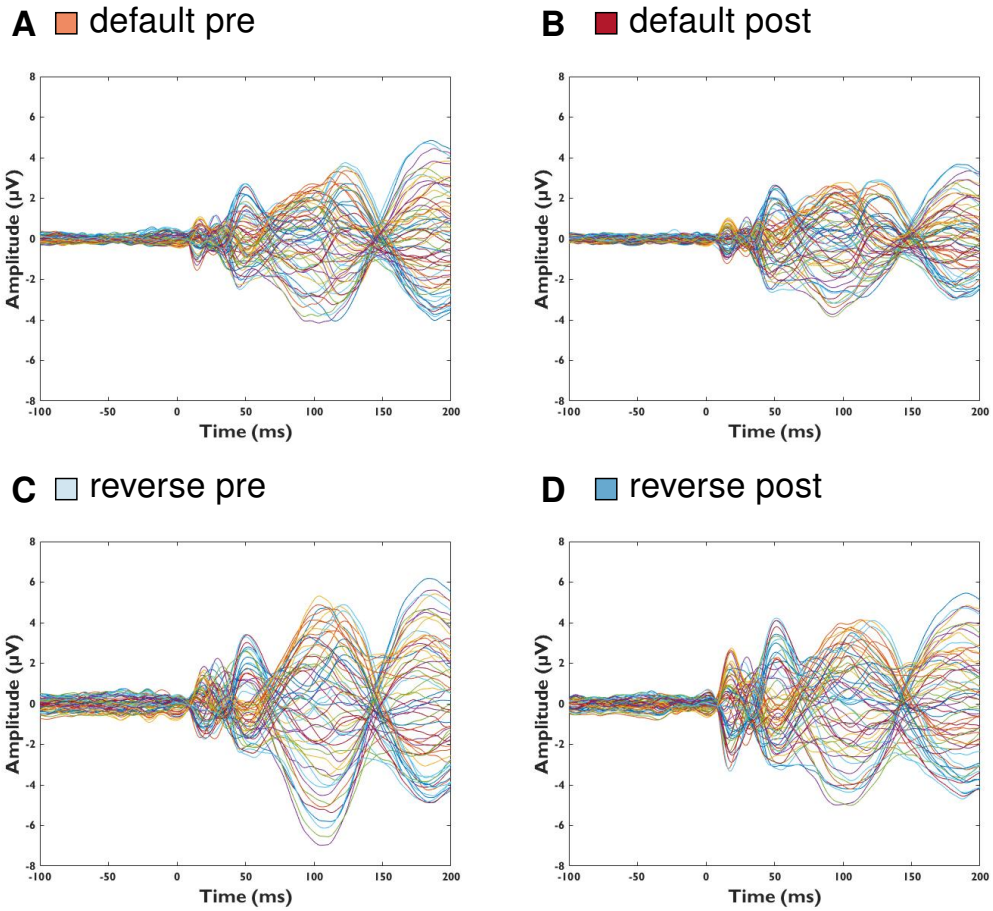
EMG data of the FDI, ADM and APB of the right hand were recorded with Ag/AgCl surface electrodes in bipolar belly-tendon montage (ground: processus styloideus ulnaris) in combination with ActiCHamp with BIP2AUX adapters (Brain Products GmbH, Germany). For MEP analyzes, we only analyzed FDI data. Raw EMG signal from the Brain Vision Recorder (Brain Products GmbH, Germany) was read into and preprocessed with Matlab (R2021b; Mathworks, USA). EMG data was filtered with 4^{th} order two-way butterworth filter for high-pass 10 Hz and low-pass 500 Hz. MEPs were identified in the time window between 10 and 50 ms after the TMS pulse. In order to only analyze valid MEPs, attributable to the brain response to a TMS pulse, for each trial in which the corresponding EEG data was artefact-free, the MEP peak-to-peak amplitude and latency were computed. MEP latency was defined as onset of the first detected peak and extracted at the point where 10 % of the maximal amplitude was reached based on the definition by İşcan et al. (2018). In EMG data where the MEP-to-baseline-ratio was below 1.6, the MEP did not exceed 50 µV or there was muscle activity with ± 100 µV in the 100 ms before the TMS pulse, we did not include these trials in the analyzes. The data was structured corresponding to the TEPs, so that MEP amplitude and latency was extracted per subject and trial for the 100 TMS trials pre and post rTMS. The pre-to-post changes were computed as post minus pre rTMS condition per current direction, subject and trial for MEP amplitudes and latencies.

4.3.5 Electroencephalography (EEG)

EEG data was recorded with the software Brain Vision Recorder version 1.24.0101 (Brain Products GmbH, Germany) together with an ActiCHamp amplifier (Brain Products GmbH, Germany) and a TMS-compatible electrode cap with 64 passive

electrodes (Easycap GmbH, Germany) placed according to the 10-20 location system (Klem et al., 1999). EEG signal was recorded at a sampling rate of 5 kHz and online referenced to FCz (GND: AFz). Impedances were kept below 10 kΩ. Raw EEG signal was read into Matlab (Matlab R2021b; Mathworks, USA) and pre-processed with the EEGLAB toolbox (Delorme & Makeig, 2004) together with the TMS-EEG Signal Analyzer extension (TESA; Rogasch et al., 2017). To identify the TMS artefact, we used the C3 electrode. Afterwards, the data was epoched from 300 ms before to 500 ms after the TMS pulse. Channels that had a kurtosis of $z > 5$ were automatically rejected, resulting in a maximum of 7 rejected channels per subject and condition (10 % of the data). After subtracting the average activity of the overall epoch from every single timepoint within the epoch (demeaning), we removed the TMS artefact in each epoch by replacing the data from 13 ms before until 8 ms after the TMS pulse with zero amplitudes and subsequently interpolated these timepoints via cubic interpolation (Thut et al., 2011). Hereafter, the data was downsampled to 1 kHz. After visual removal of trials with artefacts such as brief muscular activity or eye blinks with a temporal relation to the TMS pulse (mean of 20 % of the trials), further eye blinks as well as related non-neuronal activity that was not identified as electrode noise of muscular activity were identified and removed using fast ICA (toolbox http://research.ics.aalto.fi/ica/fastica/). Hereby, a maximum of 20 % of components were rejected. For reduction of electrode noise and muscle artefacts, we used source-based artefact-rejection algorithms: the source-estimate-utilizing noise-discarding algorithm (SOUND; Mutanen et al., 2018; 2022) and signal-space-projection-source-informed reconstruction (SSP-SIR; Mutanen et al., 2016; Biabani et al., 2019; Mutanen et al., 2022). Default settings were used in the former and for the latter we rejected a maximum of 5 components. The data was filtered using 4^{th} order, two-way Butterworth bandpass (1-100 Hz) and bandstop (48-52 Hz) filters. Lastly, bad channels were interpolated via spherical spline interpolation (Perrin et al., 1989) and data were re-referenced to average. For quality check of the signal, we summarized butterfly plots per condition in Figure 2.

Figure 2
Mean butterfly plots per condition



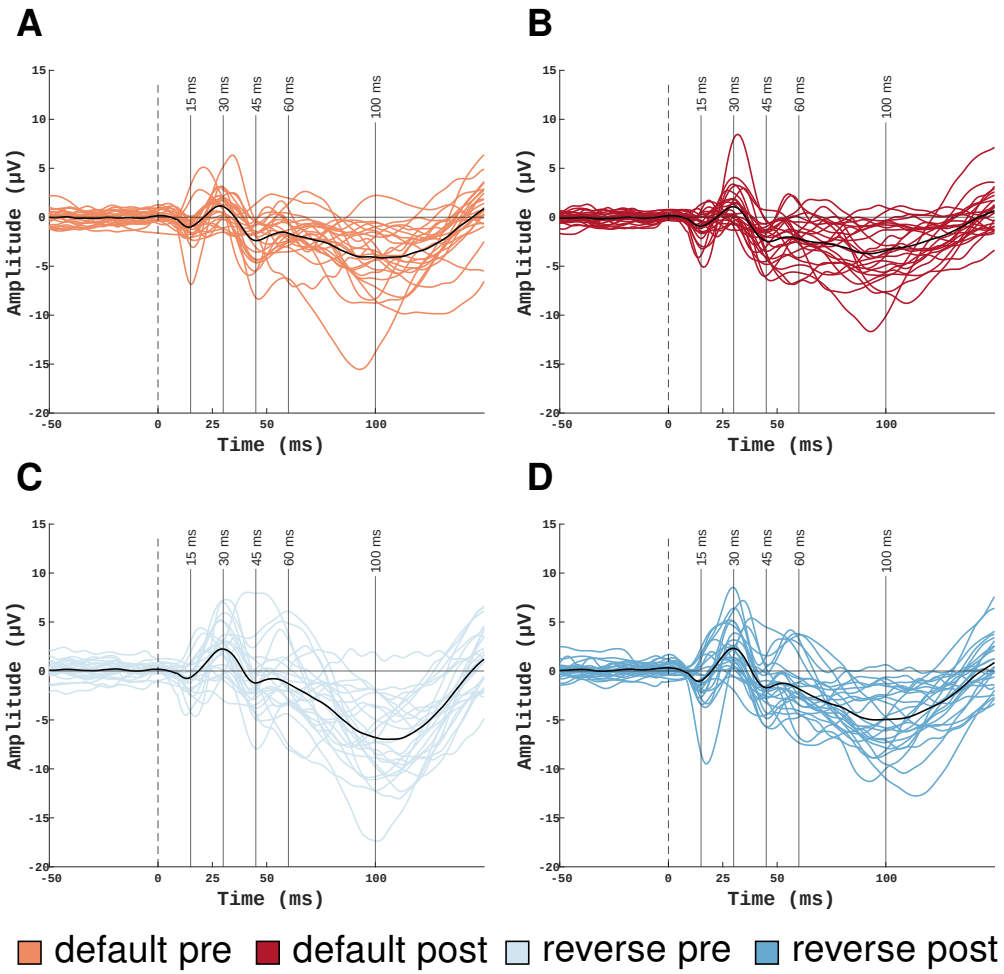
Notes. Figure 2A depicts the butterfly plot of all EEG channels as mean time course over all 100 trials and 25 subjects for the condition pre rTMS with default current direction. Figure 2B represents the butterfly plot of all EEG channels for the condition post rTMS with default current direction. Figure 2C illustrates the butterfly plot of all EEG channels as mean time course for the condition pre rTMS with reversed current direction and Figure 2D shows the butterfly plot of all EEG channels for the condition post rTMS with reversed current direction. All plots share the x-axis from 100 ms before the pulse until 200 ms after the pulse and the y-axis from -8 to 8 µV for comparability.

We extracted TEP amplitudes and latencies per subject and trial for single pulse TMS measurements. Hereby, we wanted to account for the differences of current direction in the topography of TEPs (Casula et al., 2018) whilst comparing the same features within one current direction from pre to post rTMS. Thus, we inspected the same time intervals and EEG electrodes for pre and post rTMS measurements per TEP component and current direction. To achieve this, we extracted the mean TEP latencies ± 5 ms (± 10 ms for N100) from the Cz channel for the pre condition only per current direction and identified the topography clusters of 6 neighboring electrodes with maximal (positive TEPs) and minimal (negative TEPs) activation within these mean latency time intervals. Figure 3 features the mean time courses

over electrode Cz that were used for latency extraction. Figure 4 depicts TEP topographies and summarizes the mean latencies and electrode clusters for each TEP component per current direction. Subsequently, for each subject, trial and condition, we extracted the individual TEP latency at the individual TEP peak within the mean of the identified cluster channels and the TEP amplitude as mean over the cluster channels and individual latencies ± 5 ms or ± 10 ms for N100. To compute the pre-to-post change data we subtracted the pre rTMS condition from the post rTMS condition per current direction, subject and trial for TEP amplitudes and latencies.

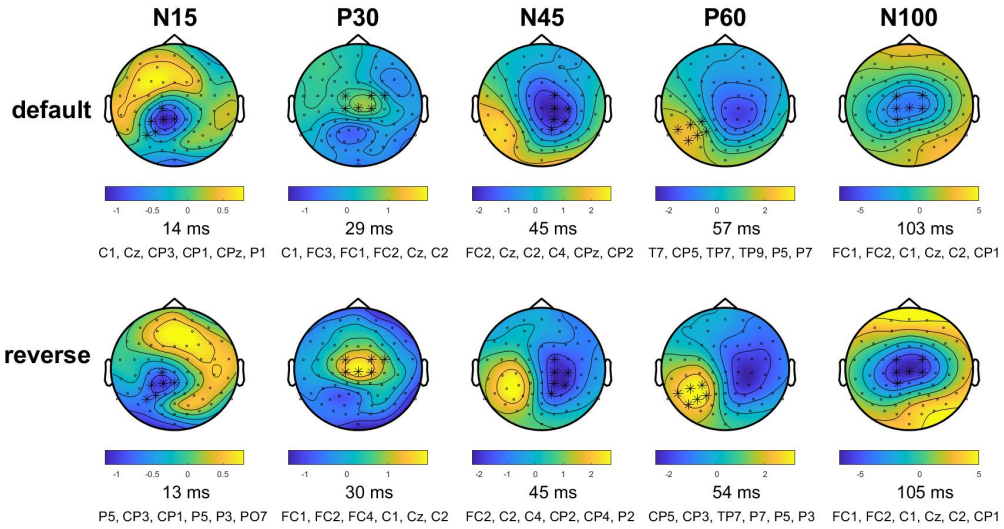
Figure 3

Mean TEP time courses over Cz electrode per subject and overall



Notes. Figure 3A depicts the mean TEP time course for the condition pre rTMS with default current direction (orange). Figure 3B shows the mean TEP time course for the condition post rTMS with default current direction (red). Figure 3C illustrates the mean TEP time course for the condition pre rTMS with reversed current direction (light blue) and Figure 3D represents the mean TEP time course for the condition post rTMS with reversed current direction (blue). Colored lines depict the mean TEP time courses over 100 trials of one subject per condition and the black line represents the mean TEP time course over all subjects for the respective condition.

Figure 4
Topographies of TEP components



Notes. Each column represents one TEP component and rows refer to the current direction. Mean topographies for the conditions before rTMS (pre) are depicted. The six electrodes with the minimal or maximal activation are highlighted as asterisks and written as names below the respective topography plots. Below each TEP component topography and for both current directions the mean latencies identified over Cz are noted.

4.3.6 Statistical analyzes

MEP and TEP data as well as demographic data were analyzed in R (R Core Team, Austria, Version 4.3) with the packages BSDA (Arnholt & Evans, 2023), stats, lmerTest (Kuznetsova et al., 2017) and emmeans (Lenth, 2023). Plots were constructed using ggplot2 (Gómez-Rubio, 2017). MEP and TEP amplitude and latency were analyzed with linear mixed effect models. Hereby, we compared models with the predictors time (pre vs post 1 Hz rTMS), current direction (default vs reverse) and their interaction against the intercept model without predictors in a stepwise selection approach, using AIC, BIC and a Likelihood Ratio test as criteria (Hastie, 2017). Only when all three parameters were lower (AIC, BIC) and significant (Likelihood Ratio test) in the more complex model, it was considered as better model than the one with one predictor less or the intercept model. The variance explained by the resulting models was calculated using marginal and conditional R^2 (Nakagawa et al., 2017). The factor subject was implemented as random effect in all models, so that the full model was as follows: data $\sim$ time + current direction + time $\times$ current direction + (1 | subject). To investigate the differences between default and reverse current direction in changes from pre to post 1 Hz rTMS, we computed the pre-to-post change condition per current direction by subtracting the pre from the post condition per subject and trial for all TEP and MEP components (amplitude

and latency). To analyze the pre-to-post change data of TEPs and MEPs, we tested the full model (data $\sim$ current direction + (1 | subject)) against the intercept model without predictors, congruently. We tested the fixed effects of each final model via expected mean square approach. With post-hoc Tukey *t*-tests and Tukey adjusted *p*-values, we only investigated the contrasts between pre and post conditions per current direction (time | current direction). For the pre-to-post change data, we analyzed the difference between current directions using the same statistical tests. For all analyzes, the level of significance was set at $\alpha = .05$.

Additionally, with paired *t*-tests (*t*), Wilcoxon signed-rank tests (V) or sign tests (S) in case of violation of prerequisites, we analyzed potential current-direction-specific differences in RMT, TMS masking loudness and the perceived loudness of the TMS click during stimulation. We investigated changes from pre to post rTMS as well as differences in current direction for attention, excitement and tiredness via Friedman tests (time $\times$ current direction) and post-hoc paired *t*-tests or sign tests.

With the repeated measures correlation coefficient (Bakdash & Marusich, 2017; 2019), we additionally correlated MEP latencies with TEP latencies as well as MEP amplitudes with TEP amplitudes for all pre, post and pre-to-post change data. We wanted to look at all the data to map any relationship between MEPs and TEPs, even if they are not equally transformed by rTMS. Thus, we corrected α for all possible combinations that we investigated (5 TEP components [N15, P30, N45, P60, N100] $\times$ 3 conditions [pre, post, change] $\times$ 2 current directions [default, reverse] $\times$ 2 derivations [amplitude, latency] = 60). We used the R package rmcorr, that includes subject as random factor in the correlations.

4.4 Results

RMT for default current direction ($M = 50.76$, $SD = 9.207$) was significantly lower than for the reverse current direction ($M = 61.16$, $SD = 9.114$; $t(24) = -8.291$, $p < .001$). Yet, the loudness of the masking noise did not differ between current directions ($S = 9$, $p = .424$, $n = 25$), referring to about 75 dB SPL ($M_{default} = 10.52$, $SD_{default} = 2.084$, $M_{reverse} = 11.28$, $SD_{reverse} = 1.621$). Neither did the participants' perception of loudness change ($V = 65$, $p = .897$, $n = 25$; $M_{default} = 3$, $SD_{default} = 1.601$, $M_{reverse} = 3.22$, $SD_{reverse} = 1.948$). In analysis of the VAS scales, time had a significant effect on tiredness ($F(1, 72) = 6.141$, $p < .05$, $\eta_p^2 = .079$), whereby tiredness levels were higher after rTMS than before ($M_{pre} = 4.52$, $SD_{pre} = 2.16$, $M_{post} = 5.42$, $SD_{post} = 2.34$, $t(49) = -2.534$, $p < .05$). Also on excitement levels, time had a significant effect ($F(1, 72) = 11.233$, $p < .01$, $\eta_p^2 = .135$), whereby excitement was lower after rTMS than before ($M_{pre} = 2.22$, $SD_{pre} = 1.36$, $M_{post} = 1.71$, $SD_{post} = 0.81$, $S = 21$, $p < .01$, $n = 25$). Concerning attention, the main effect of time was also present in the

Friedman test ($F(1, 72) = 3.98$, $p < .05$, $\eta_p^2 = .052$). But the post-hoc sign test did not reveal significant differences between pre and post rTMS ($M_{pre} = 6.79$, $SD_{pre} = 1.74$, $M_{post} = 6.25$, $SD_{post} = 1.78$, $S = 27$, $p = .088$, $n = 25$). No main effect of current direction or any interaction effect for tiredness, excitement or attention reached significance.

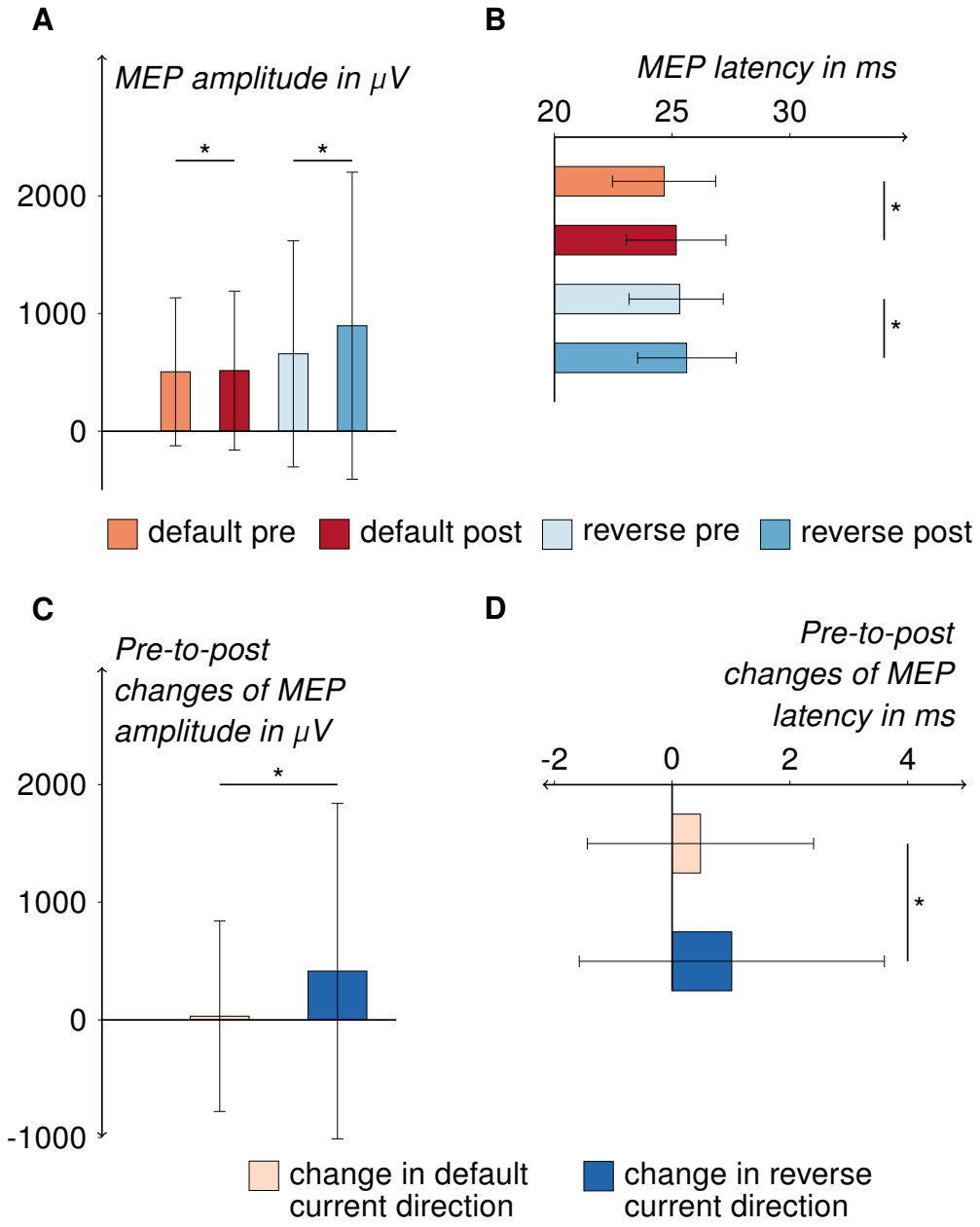
4.4.1 MEPs

For MEP peak-to-peak amplitude, the fixed effects of time, current direction and interaction of time × current direction were significant via expected mean square approach. Post-hoc Tukey *t*-tests showed that MEP amplitude was significantly higher after rTMS than before in both default ($t(6619) = -2.118,\ p = .034$) and reversed current direction ($t(6617) = -8.828,\ p < .001$). In analysis of the pre-to-post changes, current direction was a significant fixed effect. The pre-to-post change from lower to higher amplitude was larger for the reversed current direction than for default ($t(2382) = -6.354,\ p < .001$).

For MEP latency data, the fixed effects of time, current direction and interaction of time × current direction were significant. Latency was prolonged after 1 Hz rTMS with both default ($t(6613) = -8.629,\ p < .001$) and reversed current direction ($t(6612) = -4.77,\ p < .001$). Current direction was a significant fixed effect for pre-to-post changes in MEP latency. The pre-to-post change from shorter to longer latency was higher for the reversed current direction than for default ($t(2375) = -4.332,\ p < .001$). Descriptive MEP mean and standard deviation values are depicted in Figure 5 along with the respective significant difference results from the linear mixed effect model analyses. The linear mixed effect models that were identified to have the best fit along with statistics on significant fixed effects as well as marginal and conditional R^2 are listed in the Supplementary Table 1. Supplementary Table 2 summarizes all post-hoc Tukey *t*-tests and contains estimated mean values. Supplementary Figure 1 depicts the mean MEP time courses and those for each subject per condition.

Figure 5

MEP amplitude and latency and their respective pre-to-post rTMS changes



Notes. Figure 5A depicts the mean MEP amplitude per condition (orange = pre rTMS with default current direction, red = post rTMS default, light blue = pre rTMS with reversed current direction, blue = post rTMS reverse). Figure 5B shows the mean MEP latency per condition with congruent colors. Figure 5C depicts the MEP amplitude change from pre to post 1 Hz rTMS for default (light orange) and reversed current direction (dark blue) and Figure 5D represents the MEP latency pre-to-post change per current direction with congruent colors. Error bars represent the standard deviations. Asterisks indicate significant differences ($p < .05$) between conditions, as resulted from the linear mixed effect model Tukey post-hoc tests.

4.4.2 TEPs

For N15 amplitude data the fixed effects of time, current direction, and time × current direction were significant. Post-hoc Tukey *t*-tests revealed no difference between pre and post rTMS for the default current direction ($t(8954) = -1.403,\ p = .161$), but with reversed current direction, the N15 amplitude was larger, i.e. more negative after rTMS than before ($t(8955) = 12.436,\ p < .001$). The model for pre-to-post N15 amplitude changes had a significant fixed effect of current direction. Pre-to-post N15 amplitude changes were significantly larger for the reversed than the default current direction ($t(4039) = 9.479,\ p < .001$), revealed by the post-hoc Tukey *t*-test. Hereby, the descriptive direction of the effect was different for default (reduction of amplitude) than reversed current direction (enhancement of amplitude).

For N15 latency data significant fixed effects were time, current direction, and time × current direction. N15 latency was not different from pre to post rTMS with the default direction ($t(8954) = -1.403,\ p = .161$), but was significantly prolonged after rTMS than before with the reversed current direction ($t(8955) = 12.436,\ p < .001$). The significant fixed effect for the data of pre-to-post changes in N15 latency was current direction. Post-hoc *t*-tests revealed that the pre-to-post changes were significantly larger for the reversed than the default current direction, meaning that latency was significantly more prolonged after 1 Hz rTMS than before for reversed current direction than N15 latency was shortened after 1 Hz rTMS than before for the default current direction.

Concerning P30 amplitude and latency data the fixed effect of current direction was significant in the respective optimal model. For both amplitude and latency of P30 pre-to-post change data there was no significant fixed effect. Thus, no post-hoc *t*-tests were conducted for P30 amplitude and latency nor the respective pre-to-post change data.

The fixed effects of time, current direction, and time × current direction were significant for N45 amplitude data. Post-hoc Tukey *t*-tests revealed no difference from pre to post rTMS in the default condition ($t(8954) = 0.53,\ p = .597$), but significantly larger, i.e. more negative N45 amplitude after rTMS than before in the reversed current direction ($t(8955) = 5.459,\ p < .001$). Also, for the pre-to-post N45 amplitude change data, a significant fixed effect of current direction was present. The pre-to-post N45 amplitude changes, i.e. more negative N45 amplitude after rTMS than before, were larger for reversed than default current direction ($t(4049) = 3.58,\ p < .001$).

No significant fixed effect was identified in the models for N45 latency data and pre-to-post change data of N45 latency. Thus, no post-hoc *t*-tests were computed for N45 latency and the respective pre-to-post change data.

Significant fixed effects for the P60 amplitude data were time, current direction,

and time × current direction. Post-hoc Tukey *t*-tests revealed no difference from pre to post rTMS for default current direction ($t(8954) = -0.214,\ p = .831$), but for reversed current direction a larger P60 amplitude was shown after rTMS than before ($t(8954) = -6.622,\ p < .001$). For the P60 amplitude pre-to-post change data the fixed effect of current direction was significant. Hereby, the pre-to-post enhancement in P60 amplitude was significantly larger in the reverse than in the default current direction ($t(4042) = -4.772,\ p < .001$).

Concerning P60 latency, the fixed effect of current direction was significant and no significant fixed effect was identified for the P60 data of pre-to-post changes in latency. Since no significant fixed effects of time and current direction were present in the models for P60 latency and P60 latency pre-to-post change, respectively, no post-hoc *t*-tests were conducted.

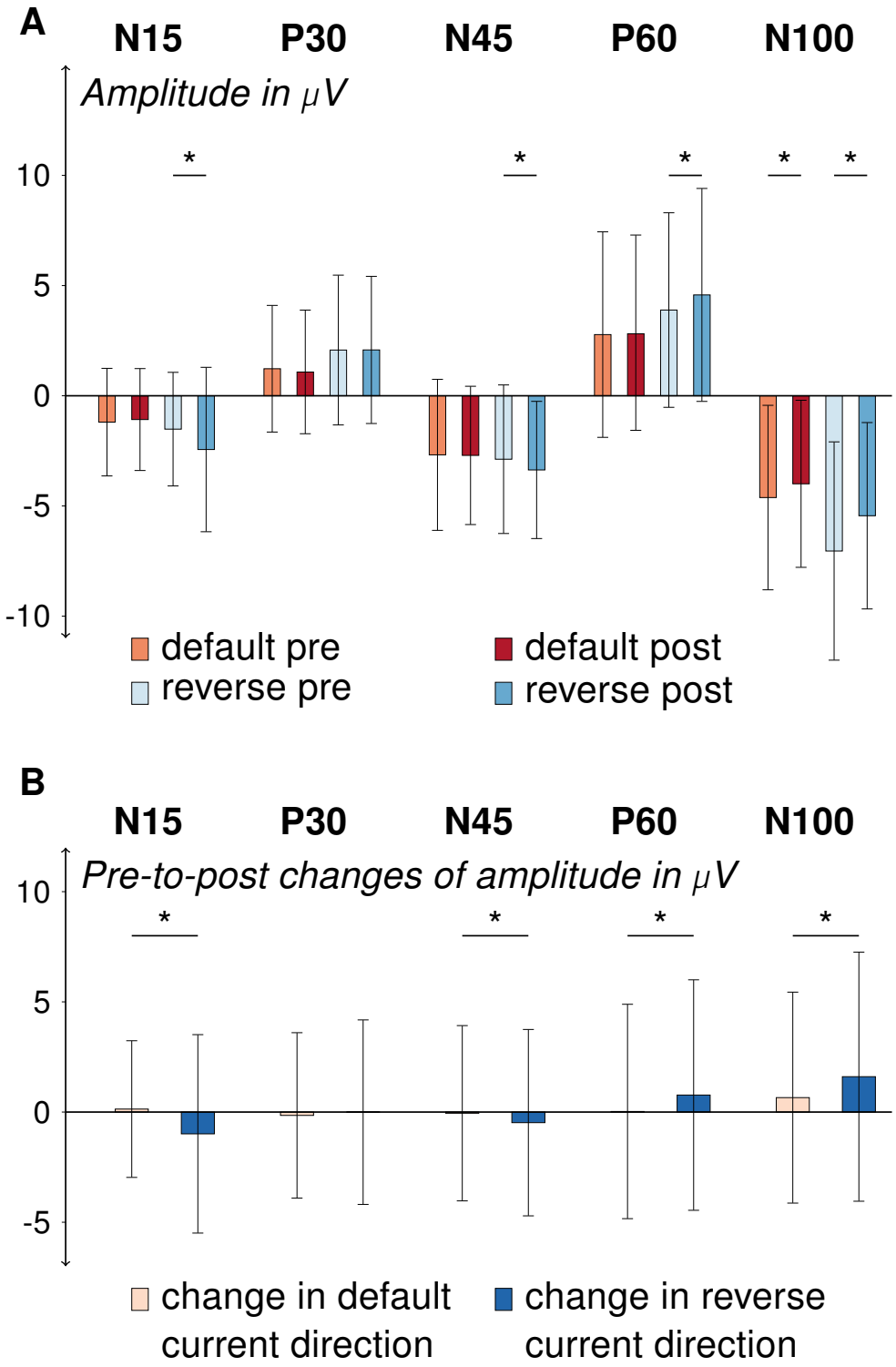
All fixed effects (time, current direction, and time × current direction) were significant for the N100 amplitude data. Post-hoc Tukey *t*-tests revealed a significantly smaller N100 amplitude, i.e. less negative after than before rTMS in both default ($t(8954) = -5.767,\ p < .001$) and reversed current direction condition ($t(8954) = -14.461,\ p < .001$). For the pre-to-post change data of N100 amplitude, the optimal model showed a significant fixed effect of current direction. Post-hoc Tukey *t*-tests revealed that the reduction of N100 amplitude, i.e. becoming less negative from pre to post rTMS, was significantly larger in the reversed than default current direction ($t(4040) = -5.754,\ p < .001$).

The fixed effects of time and current direction were significant for N100 latency data. N100 latency was shortened after rTMS than before in both default ($t(8955) = 6.485,\ p < .001$) and reversed current direction ($t(8955) = 6.485,\ p < .001$). For the N100 latency pre-to-post change data there was no significant fixed effect and thus, no further tests were carried out.

For detailed inspection, descriptive mean TEP amplitudes and their standard deviations are depicted in Figure 6 along with significance indications resulted from the linear mixed effect model analyses. Figure 7 features TEP latency mean and standard deviation values with the significance indications from the model fitting analyses. Linear mixed effect models that were identified by the model fitting procedure to have the best fit on TEP data as well as statistics on significant fixed effects and marginal and conditional R^2 are listed in the Supplementary Table 1. As summary, post-hoc Tukey *t*-tests and estimated mean values are shown in Supplementary Table 2.

Figure 6

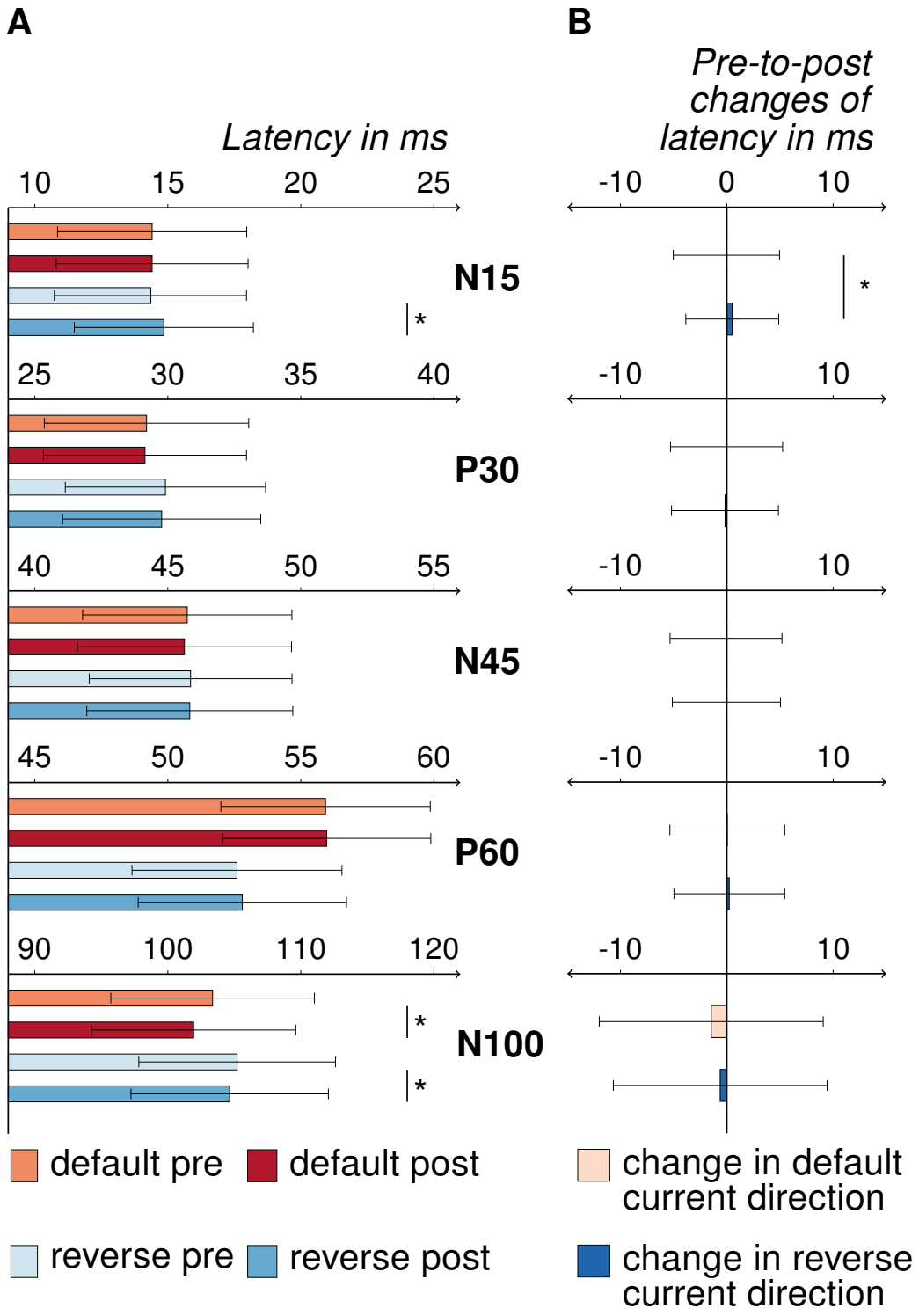
TEP amplitudes per condition and pre-to-post rTMS changes per current direction



Notes. Figure 6A depicts the mean amplitude per condition (orange = pre rTMS with default current direction, red = post rTMS default, light blue = pre rTMS with reversed current direction, blue = post rTMS reverse), which are faceted per TEP component. Figure 6B shows the TEP amplitude changes from pre to post 1 Hz rTMS per current direction, whereby default is depicted in light orange and reversed current direction in dark blue. Error bars represent the standard deviations. Asterisks indicate significant differences ($p < .05$) between conditions, as resulted from the linear mixed effect model Tukey post-hoc tests.

Figure 7

TEP latencies per condition and pre-to-post rTMS changes per current direction



Notes. Figure 7A shows the mean TEP latency per condition (orange = pre rTMS with default current direction, red = post rTMS default, light blue = pre rTMS with reversed current direction, blue = post rTMS reverse) and faceted per TEP component. Figure 7B depicts the TEP latency change from pre to post 1 Hz rTMS per current direction. Hereby, the default current direction change is depicted in light orange and the change for reversed current direction in dark blue. Error bars represent the standard deviations. Asterisks indicate significant differences ($p < .05$) between conditions, as resulted from the linear mixed effect model Tukey post-hoc tests.

4.4.3 Correlation of MEPs and TEPs

We observed a significant but negligible correlation of peripheral and central electrophysiological measures for the amplitudes of the N45 with MEPs pre rTMS for the reversed current direction ($r = 0.088, p < 0.001$). All other correlations did not reach significance.

4.5 Discussion

In 25 healthy subjects we investigated the pre-to-post changes of interventional 1 Hz rTMS over the motor cortex on cortico – spinal and cortical excitability via MEPs and TEPs. 100 single TMS pulses were applied prior and after 2000 pulses of 1 Hz rTMS on two days separated by at least one week. For all magnetic stimulations per day we used one of two different current directions that refer to the default and reversed setting in the MagVenture MagPro X100 stimulator (MagVenture A/S, Farum, Denmark), inducing AP-PA (default) and PA-AP (reverse) currents in the brain, respectively. Linear mixed effect models were used to analyze differences between pre and post rTMS for each current direction as well as differences in current direction of the pre-to-post 1 Hz rTMS changes. We additionally investigated correlations of MEPs with TEPs and differences between current direction conditions in the RMT, masking noise loudness and TMS coil click perception as well as VAS data.

Pre-to-post 1 Hz rTMS changes in amplitude and latency were prominent in both MEPs and TEPs, however the amplitude of the P30 did not show any influence by rTMS in general or current direction. Also TEP latencies only revealed pre-to-post differences in the N15 and N100 component. In the derivations, when significance level was reached, these pre-to-post changes were larger when elicited with the reversed than the default current direction, although for N15 amplitude and latency the descriptive direction of change was not equal between current directions.

MEP amplitudes increased from before to after 1 Hz rTMS in both current directions, but the reversed current direction showed a larger increase in the pre-to-post changes than the default current direction. This finding indicates that in our experimental setup, 1 Hz rTMS did not act inhibitory as assumed by the lofi-hife heuristic and other previous research (Pascual-Leone et al., 1994a; Wassermann et al., 1996; Tang et al., 2019; Schoisswohl et al., 2024), but rather had a facilitatory effect on cortico - spinal excitability. Since not all factors that contribute to rTMS effects have been identified, one can only speculate about reasons for the derivations of our results from the heuristic. These could be either due to experimental decisions, technical stimulation or intrapersonal parameters. Firstly, in our experiment the stimulation intensity was suprathreshold (110 % RMT) in contrast to other experiments using subthreshold intensity (van der Werf & Paus, 2006; Goetz et al., 2016; Zhou

et al., 2022) and the number of applied pulses was higher in our procedure than in others (van der Werf & Paus, 2006; Goetz et al., 2016; Zhou et al., 2022). Yet, literature suggests that higher intensities and longer stimulation duration enhance neuromodulatory effects (Maeda et al., 2000a; Fitzgerald, 2002; Lang et al., 2006), thus we would not have expected a contrary result to the expected direction but rather an enhanced one. Metaplasticity effects for example of the effect of higher stimulation intensity may have contributed to our findings. Previous research hereto has found individual intensity dependence of inhibitory or excitatory effects of cTBS (Sasaki et al., 2018). Thus, further investigation of intensity dependence of 1 Hz rTMS is needed, since it likely affected both the individual reactions as well as the comparability of rTMS effects between studies. The rationale that higher intensities evoke higher effects seems to be dependent on the stimulation parameters. Secondly, we used biphasic pulses for all magnetic stimulations, but monophasic pulses were found to be more effective in modulating cortico - spinal excitability than biphasic pulses (Sommer et al., 2002b; Arai et al., 2005; Tings et al., 2005; Goetz et al., 2016). Yet, also for biphasic stimulations, inhibitory 1 Hz rTMS effects were found (Wassermann et al., 1996; Taylor & Loo, 2007). Pulse width was found to also influence 1 Hz rTMS effects with longer pulses (120 µs) resulting in excitation and shorter pulses (40 µs, 80 µs) resulting in inhibition (Halawa et al., 2019), which might explain our excitation effect with a pulse width of 280 µs. Yet, since pulse widths are not typically reported in the experimental procedures and little is known about the influence of all phase components, we cannot directly compare our results to previous research. Thirdly, it is known that subject-specific parameters influence cortical and cortico - spinal excitability and neuromodulatory responses (Guerra et al., 2020b). Factors such as age (Bashir et al., 2014), handedness (Triggs et al., 1994), genetics (Di Lazzaro et al., 2015) and intrinsic state (Stefan et al., 2004) are found to contribute to TMS response differences between and within participants. The influence of sex on TMS and subsequent excitability measures appears to be negligible (Livingston et al., 2010; Cueva et al., 2016). Although we know, that also attention (Conte et al., 2008) influences the efficacy of NIBS induced excitability, in our experiment we tried to eliminate this factor by instructing the participants to look at the fixation cross while keeping the stimulated hand at rest and assessing attention along with tiredness and excitement in the VAS scales. Hereby, the Friedman tests showed no differences in attention from pre to post rTMS, but increased tiredness and reduced excitement levels after rTMS than before, indicating that the subjects were getting familiar with the procedure, but also showed fatigue. This might have influenced the facilitation of cortico - spinal excitability as well, since increases in MEP amplitude were found for small reductions in alertness levels, i.e. wake to drowsy before sleep (Noreika et al., 2020). During sleep, on the other hand, a reduction of MEP amplitude has been demonstrated in the literature (Avesani et al., 2008).

In summary, due to the complexity of parameters that influence neuromodulatory effects, it is likely that a combination of the discussed parameters is responsible for the high variability of experimental findings and thus the non-conformity of our results to the lofi-hife heuristic.

Concerning the differences of MEP amplitudes between current directions, the found excitatory 1 Hz rTMS effect was even more pronounced for the reversed than for the default current direction, which corresponds to findings of 5 Hz rTMS (Sommer et al., 2013a). For 1 Hz rTMS the opposite effect was found; monophasic PA, corresponding to the dominant phase of the MagVenture default current direction elicited stronger inhibitory effects than monophasic AP (corresponding to reverse) current direction (Goetz et al., 2016). Our findings mainly align with the previous literature, indicating that the induced PA-AP (reversed) current direction acts more effectively than the induced AP-PA (default) current direction onto neuromodulatory mechanisms in the brain (Sommer et al., 2013a; Halawa et al., 2021). Yet, results for the inhibitory 1 Hz rTMS protocol seem to be directed oppositely (Goetz et al., 2016). Although the RMT and thus stimulation intensity between current directions differed significantly, we are confident to have induced comparable physiological responses over the exact same cortical position since the stimulation intensity is matched to the individual RMT per condition. Differences in current direction should therefore only occur based on the underlying cortical structures and their interaction with the magnetic field. Since for the reversed current direction the stimulation intensity was significantly higher, it is possible that with the elicited higher field strength also more neurons might be recruited for the reversed current direction.

MEP latency was significantly prolonged after rTMS than before for both current directions. The literature mainly reports no differences in MEP latencies after rTMS in both inhibitory and facilitatory rTMS protocols (Lorenzano et al., 2002; Arai et al., 2005; Gilio et al., 2009; Sommer et al., 2013b). Yet, during one facilitatory 5 Hz rTMS protocol, in which MEP amplitudes were increased, MEP latencies were found to be shortened (Tings et al., 2005). The reasons why in our experiment MEP latencies were prolonged after 1 Hz rTMS could be diverse. Some findings indicate that stimulation at a suboptimal hotspot prolongs MEP latency due to an increase of indirect transsynaptic propagation (Fuhr et al., 1991). Since our experimental setting included automatized placement of the coil with a cobot-assisted neuronavigation system, we can rule out large spatial deviations from the initial hotspot. Another explanation might be the increased tiredness of our participants after the rTMS application than before. It was found that sleepiness and sleep prolonged MEP latency compared to wakefulness (Avesani et al., 2008).

Also for MEP latency the reversed current direction showed a larger pre-to-post change than the default current direction. This finding is in line with results that showed that MEP latencies were shorter for monophasic PA, corresponding to

the dominant phase of the default current direction, than monophasic AP pulses, corresponding to the dominant phase of the reversed current direction (Tings et al., 2005; Hamada et al., 2013; Davila-Pérez et al., 2018; D'Amico et al., 2020a; Guidali et al., 2023), as well as biphasic AP-PA TMS single pulses (Davila-Pérez et al., 2018). Different latencies for current directions indicate an activation of different neural elements, such as later I-waves (Di Lazzaro et al., 2001) and sets of neurons (Li et al., 2017; Di Lazzaro et al., 2018).

TEP amplitudes that showed a significant pre-to-post change were mainly enhanced after inhibitory 1 Hz rTMS. Hence, N15 and N45 amplitude were more negative after 1 Hz rTMS than before and P60 was more positive after rTMS than before. N100 amplitude was the only component to be reduced after 1 Hz rTMS in both current directions, i.e. having a less negative amplitude after rTMS than before. Although this pattern shares one similarity to the study that found increased P60 (Casula et al., 2014) after 1 Hz rTMS, the differences in outcomes predominate: increased N100 (Casula et al., 2014; Zhou et al., 2022) and reduced P60 (Zhou et al., 2022) show opposite findings to ours. In the literature on 1 Hz rTMS and TEPs, rTMS inhibited MEP amplitude (Casula et al., 2014) or showed no influence (van der Werf & Paus, 2006; Casula et al., 2014; Zhou et al., 2022). Thus, it seems as if our results did not reproduce the inhibitory effects of 1 Hz rTMS of other experiments. Yet, when comparing our data to facilitatory protocols, contrary to null results of the N45 amplitude from the 20 Hz rTMS experiment by Veniero et al. (2010), our data showed an enhancement of the N45 amplitude elicited with reversed current direction, which corresponds to the current direction elicited by the Magstim Super Rapid stimulator (Orth & Rothwell, 2004) used in the experiment by Veniero et al. (2010). Since N100 is suspected to represent inhibitory processes (Premoli et al., 2014; Casula et al., 2024), a reduction of N100 after rTMS as in our findings could be interpreted as reduction of inhibition or enhancement of facilitation. As N45 is influenced by the inhibitory neurotransmitter GABA(A) (Premoli et al., 2014) and P60 by the excitatory neurotransmitter glutamate (Belardinelli et al., 2021) and both amplitudes were larger after rTMS than before, we cannot say with certainty that in our experiment only cortical excitability was increased. Maybe increased cortical and cortico – spinal excitability was just the dominant finding.

Within all significant pre-to-post rTMS changes for the respective TEP components, the reversed current direction elicited a stronger effect than the default current direction, concordant to our MEP amplitude results. Although, it is to be noted that for the N15 component, only the pre-to-post changes in amplitude and latency for the reversed current direction were significant and that the pre-to-post change elicited with the default current direction descriptively went in the opposite direction. Contrary to our results, in previous literature, biphasic current directions corresponding to the MagVenture default current direction (inducing a current direction of AP-PA

in the brain) elicited larger negative TEP amplitudes, corresponding to N45 and N100, than the reversed current direction (PA-AP; Casula et al., 2018). Yet, when comparing the results for monophasic pulses that correspond to the second phase of biphasic pulses, to our findings, the monophasic AP current direction congruent to reverse (PA-AP) elicited more negative TEP amplitudes than the PA current direction congruent to default (AP-PA) (Casula et al., 2018). For positive TEP components comparable to P30 and P60, Casula et al. (2018) found larger amplitudes for default than reversed current direction. For the M1-P15, the AP current direction also elicited higher amplitudes than the PA current direction (Guidali et al., 2023). Our data proposes an overall enhancement of the induced rTMS neuromodulatory changes in TEP amplitude by the reversed current direction in comparison to default. This phenomenon might be affected by the overall stronger induced electrical field for stimulations with reversed current direction due to higher stimulation intensities. In an experiment with prefrontal intermittent theta-burst stimulation by Krile et al. (2023), with 120 % RMT the N120 was more negative than elicited with 110 % RMT. Yet, higher dosage does not always result in stronger effects, since with increased number of pulses in 1 Hz rTMS, no linear change of amplitude was found for MEPs and most TEP components (Schoisswohl et al., 2024). Thus, a dose-response relationship of intensity and duration of rTMS should be further investigated. It might be that other parameters such as attention also influence TEP components for example N100 amplitude (Kaarre et al., 2018). Although in our experiment, the interaction effect of time and current direction did not reach significance, the interaction of attention, current direction and neuromodulatory responses should be thoroughly investigated in future research.

We found significantly prolonged TEP latencies after rTMS than before for N15 in the reversed current direction and significantly shortened latencies after rTMS than before for N100 in both current directions. No such findings were reported in previous literature. Since MEP latency was also prolonged after 1 Hz rTMS in our experiment, this prolongation of N15 might be due to the current direction effect and difference of acquired sets of neurons (Li et al., 2017; Di Lazzaro et al., 2018). And thus, tiredness may not only influence MEP latency but also TEP latency. Contrary to our findings, Roos et al. (2021) found a relationship with higher MEPs and prolonged N100, but no effect of 1 Hz rTMS was investigated. A shortened latency after rTMS than before of TEP component N100 as in our experiment could reflect a trajectory effect of the rTMS procedure on neuronal projections and consecutive heightened plasticity, but further investigation is needed to replicate results and identify reasons for this latency difference.

The pre-to-post change of TEP latency was only different between current directions in the N15 component, revealing that the N15 latency elicited by reversed current direction was more prolonged after 1 Hz rTMS than before than the N15

latency elicited by default current direction which was shorter after 1 Hz rTMS than before. Our finding for the N15 latency current direction difference, likewise to the MEP latency results, resembles the findings from M1-P15 (Guidali et al., 2023) and could be caused by the different sets of neurons that are recruited with different current directions (Li et al., 2017; Di Lazzaro et al., 2018). Another reason might also be the different stimulation intensity and thus induced electric field as well as muscle recruitment which might affect signal recovery. Since no other pre-to-post change of TEP component latency was influenced by current direction, maybe this activation of different sets of neurons only manifests in early TEP components and for later TEPs the accumulative neuronal propagation overshadows this difference.

Although both EEG and EMG derivations are used to examine excitability in TMS and plasticity in rTMS, we only found a significant correlation of the MEP and N45 amplitude elicited with reversed current direction before rTMS. Yet, this correlation remained negligible ($r = 0.088$). Thus, we cannot infer to an equally suitable cortical marker of TMS and rTMS effects, compared to the cortico – spinal derivation, i.e. MEP, yet. Previous literature also indicated that the N45 component is associated with motor activity (Ahn & Fröhlich, 2021), especially elicited with suprathreshold intensity rather than subthreshold intensity (van der Werf & Paus, 2006). Yet, correlations were also found between MEP and other TEP amplitudes like N15-P30 or P60 (Mäki & Ilmoniemi, 2010; Gedankien et al., 2017; Bigoni et al., 2024) and other experiments found no correlation of MEPs and TEPs (Bonato et al., 2006; Casula et al., 2014). The finding of low correlation in our experiment along with heterogeneous findings may refer to mediation effects of subject internal processes, such as brain state (Bigoni et al., 2024), alertness or tiredness (Noreika et al., 2020).

With regard to our hypotheses, we did not find inhibitory effects of 1 Hz rTMS. On the contrary, our results show pre-to-post rTMS changes in the excitatory direction and share similarities with findings from experiments investigating high frequency rTMS. However, the differences in current direction are mainly concordant with previous study findings, indicating that the reversed current direction achieved larger effects than the default current direction (Sommer et al., 2013a; Goetz et al., 2016; Halawa et al., 2021). Although different sets or neurons are activated by different current directions (Li et al., 2017; Di Lazzaro et al., 2018), the induced rTMS effect was mainly similarly directed. Since for the treatment of neuro-psychiatric diseases like tinnitus, the current direction seems to determine the success of the treatment (Schoisswohl et al., 2023), it might be worth to further investigate the reasons for larger rTMS effects.

4.6 Limitations

Limitations to our findings are mainly due to restrictions on comparability of the current direction conditions. To ensure that differences in topography and TEPs do not occur because of different hotspots and thus recruited cortical regions, but because of differences in current direction within the same brain region, we decided to determinate the individual motor hotspot only with default current direction. But to enhance comparability between the current direction conditions, we assessed the RMT at the hotspot with each current direction separately. Since the RMT for default was significantly less than for reversed current direction, we have different physical but probably physiological equal stimulation intensities for the current directions, which may cause a systematic error in our data. Additionally, findings across the current literature are difficult to compare due to differences in the experimental setup and stimulation parameters. Investigation of other current directions (for example lateral to medial) can additionally give insight into direction specific reactions to rTMS procedures. Whereas induced current directions can be directly or indirectly derived from the methods, other parameters such as stimulation intensity and channels as well as pipelines used for TEP and MEP preprocessing and extraction are very variable (Rogasch et al., 2022). Also, different pulse sources are not directly comparable in pulse width, induced electrical field strength and derived parameters (van Doren et al., 2015; Osnabruegge et al., 2024). In our experiment, since we investigated both TEPs and MEPs simultaneously, we decided for suprathreshold TMS stimulation for all measurements, whereas other experiments stimulated with subthreshold rTMS (van der Werf & Paus, 2006; Casula et al., 2014; Goetz et al., 2016; Zhou et al., 2022). Thus, our EEG data might be biased by additional somatosensory input (Paus et al., 2001).

4.7 Conclusion

In summary, we elicited excitatory effects with suprathreshold 1 Hz rTMS applied with 2000 biphasic pulses at a pulse width of 280 µs over M1 that were more pronounced in the reversed current direction than in the default direction. The findings on pre-to-post rTMS changes are mainly contrary to the current literature. Yet, findings on the difference between current directions were mainly according to the literature. Despite having chosen stimulation parameters based on experiments that showed enhancement of inhibitory effects, like suprathreshold intensity (Fitzgerald, 2002; Lang et al., 2006) and longer duration (Maeda et al., 2000a), no reproduction of 1 Hz rTMS effects was possible. Thus, we call upon a more detailed inspection of confounding variables in TMS and rTMS research: Firstly, although confounding factors like subject-related variability, differences in experimental setup and stimulation parameters are known to influence both TMS and rTMS measures (Guerra et al.,

2020b), their individual extent and interaction with other parameters needs to be disentangled. For example, differences in stimulation of the cortex and assessment of MEPs and TEPs during versus before and after rTMS could bias the derived excitability, like inhibition during and excitation after stimulation dependent on monophasic or biphasic stimulation (Halawa et al., 2019). Secondly, exact replication of previous findings should be encouraged for future experiments, with a detailed description of experimental setup, stimulation and preprocessing of data, since many findings were found to not be transferable to other laboratories and setups (Héroux et al., 2015; Gutiérrez-Muto et al., 2023). Thirdly, both the induced excitability and plasticity effects of TMS and rTMS along with the corresponding influences of the confounding factors should further be investigated on their reliability. Currently, low to moderate reliability of rTMS effects (Prei et al., 2023) as well as individual differences of rTMS responses (Schoisswohl et al., 2024) are predominant in the literature. Above all, care must be taken when using rTMS in therapy or other clinical use on the basis of the lofi-hife heuristic assumptions. Our findings suggest that expected inhibitory changes from pre to post 1 Hz rTMS application remain absent or invert to contrary effects, which in the worst case could deteriorate the patients' symptoms. Thus, personalized application could increase the therapeutic effect (Schoisswohl et al., 2021). Additionally, since the set current direction of pulse sources often differs (van Doren et al., 2015), in order to achieve better responses, researchers or clinical personnel may consider adjusting the current direction settings.

4.8 Author contributions

Florian Schwitzgebel: Writing – review & editing. Mirja Osnabruegge: Writing – review & editing, Methodology, Investigation, Conceptualization. Carolina Kanig: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Stefan Schoisswohl: Writing – review & editing, Supervision, Methodology, Conceptualization. Martin Schecklmann: Writing – review & editing, Supervision, Methodology, Conceptualization. Wolfgang Mack: Writing – review & editing, Supervision, Funding acquisition.

4.9 Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author (CK) on reasonable request.

4.10 Funding

This work was funded by the dtec.bw – Digitalization and Technology Research Center of the Bundeswehr (MEXT project). dtec.bw is funded by the European

Union – NextGenerationEU.

4.11 Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

4.12 Supplementary material

Supplementary Table 1

Component	Optimal Model	R^2_m	R^2_c	Time	Current Direction	Time × CD
MEP amplitude	Time + CD + Time × CD + (1 | Subject)	.024	.243	$F(1, 6614) = 58.219,\ p < .001$	$F(1, 6632) = 114.905,\ p < .001$	$F(1, 6615.9) = 20.39,\ p < .001$
N15 amplitude	Time + CD + Time × CD + (1 | Subject)	.034	.206	$F(1, 8951.4) = 61.882,\ p < .001$	$F(1, 8951.6) = 222.256,\ p < .001$	$F(1, 8951.4) = 96.79,\ p < .001$
P30 amplitude	CD + (1 | Subject)	.019	.200		$F(1, 8951.5) = 215.55,\ p < .001$	
N45 amplitude	Time + CD + Time × CD + (1 | Subject)	.007	.179	$F(1, 8951.4) = 18.127,\ p < .001$	$F(1, 8951.6) = 44.59,\ p < .001$	$F(1, 8951.4) = 12.346,\ p < .001$
P60 amplitude	Time + CD + Time × CD + (1 | Subject)	.026	.344	$F(1, 8951.2) = 23.657,\ p < .001$	$F(1, 8951.3) = 307.05,\ p < .001$	$F(1, 8951.2) = 20.824,\ p < .001$
N100 amplitude	Time + CD + Time × CD + (1 | Subject)	.062	.315	$F(1, 8951.3) = 205.78,\ p < .001$	$F(1, 8951.3) = 568.21,\ p < .001$	$F(1, 8951.2) = 38.96,\ p < .001$
MEP latency	Time + CD + Time × CD + (1 | Subject)	.029	.392	$F(1, 6609.1) = 91.732,\ p < .001$	$F(1, 6619.9) = 193.337,\ p < .001$	$F(1, 6610) = 8.9035,\ p < .01$
N15 latency	Time + CD + Time × CD + (1 | Subject)	.003	.116	$F(1, 8951.7) = 13.111,\ p < .001$	$F(1, 8951.9) = 6.376,\ p < .05$	$F(1, 8951.7) = 12.406,\ p < .001$
P30 latency	CD + (1 | Subject)	.008	.086		$F(1, 8952.3) = 74.372,\ p < .001$	
N45 latency	1 + (1 | Subject)	.0	.129			
P60 latency	CD + (1 | Subject)	.144	.2		$F(1, 8952.6) = 1612.8,\ p < .001$	
N100 latency	Time + CD + (1 | Subject)	.026	.077	$F(1, 8952.7) = 42.066,\ p < .001$	$F(1, 8953.1) = 212.622,\ p < .001$	

Component	Optimal Model	R^2_m	R^2_c	Current Direction
MEP effect amplitude	CD + (1 | Subject)	.015	.176	$F(1, 2380.3) = 40.432,\ p < .001$
N15 effect amplitude	CD + (1 | Subject)	.017	.231	$F(1, 4037.7) = 89.887,\ p < .001$
P30 effect amplitude	1 + (1 | Subject)	.0	.035	
N45 effect amplitude	CD + (1 | Subject)	.003	.031	$F(1, 4047.3) = 12.824,\ p < .001$
P60 effect amplitude	CD + (1 | Subject)	.005	.079	$F(1, 4041.2) = 22.778,\ p < .001$
N100 effect amplitude	CD + (1 | Subject)	.007	.120	$F(1, 4039.5) = 33.115,\ p < .001$
MEP effect latency	CD + (1 | Subject)	.006	.259	$F(1, 2373.6) = 18.786,\ p < .001$
N15 effect latency	CD + (1 | Subject)	.003	.026	$F(1, 4049.3) = 12.921,\ p < .001$
P30 effect latency	1 + (1 | Subject)	.0	.019	
N45 effect latency	1 + (1 | Subject)	.0	.012	
P60 effect latency	1 + (1 | Subject)	.0	.009	
N100 effect latency	1 + (1 | Subject)	.0	.015	

Notes. Per MEP and TEP component as dependent variable, the significant fixed effects are listed with respective test statistics. Marginal (R^2_m) and conditional (R^2_c) R^2 are listed for the respective optimal model.

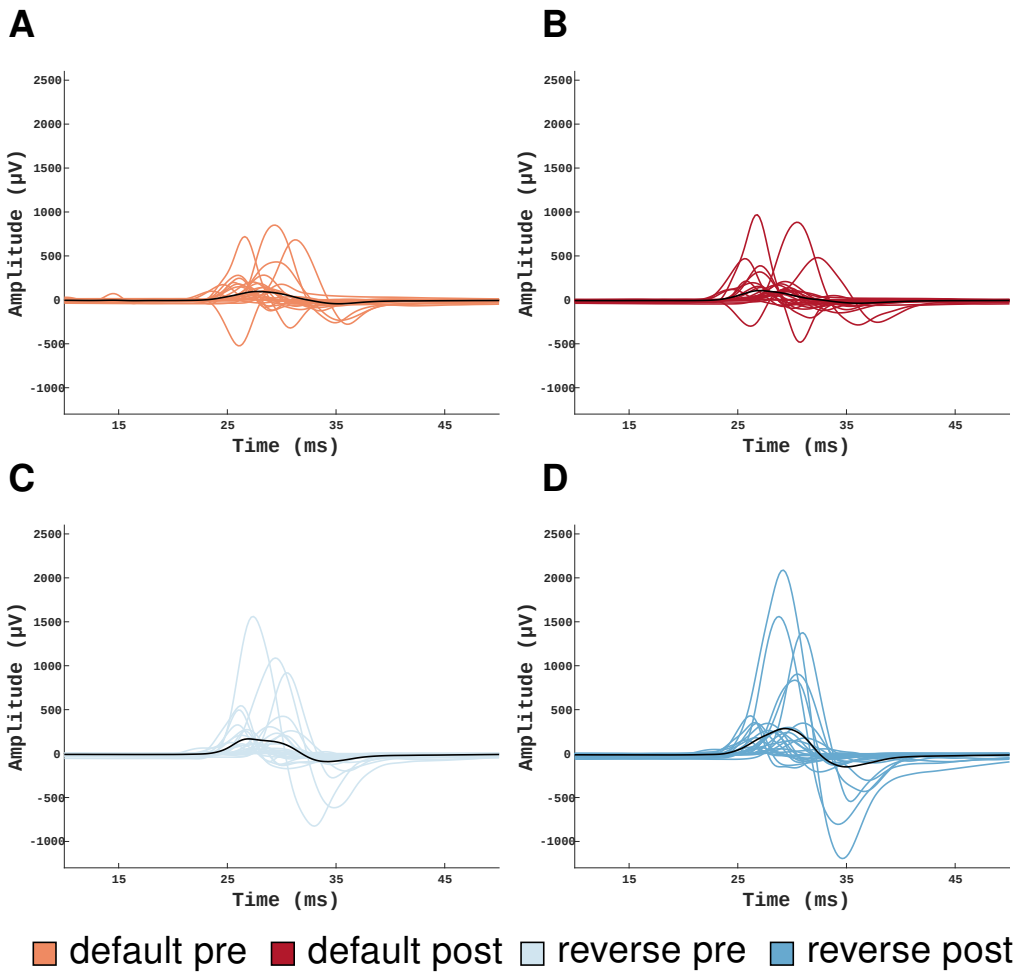
Supplementary Table 2

Component	Default CD: Pre - Post		Reverse CD: Pre - Post		Pre-to-post Change: Default - Reverse	
	μ_{pre}, μ_{post}	Tukey t-test	μ_{pre}, μ_{post}	Tukey t-test	$\mu_{default}, \mu_{reverse}$	Tukey t-test
MEP amplitude	439, 503	$t(6619) = -2.118$, $p = .034$	577, 829	$t(6617) = -8.828$, $p < .001$	108, 401	$t(2382) = -6.354$, $p < .001$
N15 amplitude	-1.19, -1.08	$t(8954) = -1.403$, $p = .161$	-1.46, -2.43	$t(8955) = 12.436$, $p < .001$	0.123, -0.899	$t(4039) = 9.479$, $p < .001$
P30 amplitude						
N45 amplitude	-2.64, -2.69	$t(8954) = 0.530$, $p = .597$	-2.84, -3.33	$t(8955) = 5.459$, $p < .001$	-0.048, -0.507	$t(4049) = 3.580$, $p < .001$
P60 amplitude	2.76, 2.78	$t(8954) = -0.214$, $p = .831$	3.78, 4.53	$t(8954) = -6.622$, $p < .001$	0.010, 0.742	$t(4042) = -4.772$, $p < .001$
N100 amplitude	-4.63, -4.00	$t(8954) = -5.767$, $p < .001$	-6.97, -5.37	$t(8954) = -14.461$, $p < .001$	0.675, 1.570	$t(4040) = -5.754$, $p < .001$
MEP latency	0.0247, 0.0252	$t(6613) = -8.629$, $p < .001$	0.0254, 0.0257	$t(6612) = -4.770$, $p < .001$	0.00065, 0.00103	$t(2375) = -4.332$, $p < .001$
N15 latency	0.0144, 0.0144	$t(8954) = -0.070$, $p = .944$	0.0143, 0.0148	$t(8955) = -5.018$, $p < .001$	-0.000026, 0.0005	$t(4050) = -3.593$, $p < .001$
P30 latency						
N45 latency						
P60 latency						
N100 latency	0.103, 0.102	$t(8955) = 6.485$, $p < .001$	0.105, 0.104	$t(8955) = 6.485$, $p < .001$		

Notes. Post-hoc Tukey *t*-test statistics with Tukey adjusted *p*-values are listed per MEP and TEP component. Estimated values (μ) are specified for the compared conditions within each *t*-test. CD = current direction.

Supplementary Figure 1

Mean MEP time courses per subject and overall



Notes. Supplementary Figure 1A depicts the mean MEP time course for the condition pre rTMS with default current direction (orange). Supplementary Figure 1B represents the mean MEP time course for the condition post rTMS with default current direction (red). Supplementary Figure 1C illustrates the mean MEP time course for the condition pre rTMS with reversed current direction (light blue) and Supplementary Figure 1D shows the mean MEP time course for the condition post rTMS with reversed current direction (blue). Colored lines depict the mean MEP time courses over 100 trials of one subject per condition and the black line represents the mean MEP time course over all subjects for the respective condition.

5 Concluding discussion

Not only have TMS and rTMS derived measures been prone to individual variability (Sommer et al., 2002a; Guerra et al., 2020b), but heterogeneous experimental results (Osnabruegge et al., 2023) question the reliability of TMS and rTMS protocols and thus the effectivity of their application. Contrary to other clinical and therapeutic interventions such as pharmacological products, to date, there is no standardized procedure to either apply TMS and rTMS protocols in combination with stimulation parameters (Gutiérrez-Muto et al., 2023), preprocess and analyze derived measures (de Cheveigné & Nelken, 2019; Rogasch et al., 2022) or report side effects, adverse events and serious adverse events, i.e. abnormal and harmful reactions to the intervention (Giustiniani et al., 2022). Thus, the present thesis was made with the attempt to give an insight into the current situation of typical rTMS protocols with regard to their effects and reliability, as well as to give concrete application prospects with the help of the investigation of the influencing parameter current direction.

5.1 Summary

With the help of three studies, this dissertation shows that firstly an exact reproduction of published results and a validation of the lofi-hife heuristic was not possible, that secondly although other published rTMS effects seem to follow the heuristic, test-retest reliability is low throughout rTMS studies and that thirdly the influence of stimulation parameters such as current direction seems high.

5.1.1 First study: Limited evidence for reliability of low and high frequency rTMS over the motor cortex

The first study (Prei et al., 2023) assessed rTMS effects of a low (1 Hz) and a high (20 Hz) frequency protocol twice with MEP amplitudes derived from single TMS pulses from before and after the rTMS intervention. The application of rTMS was closely oriented to the clinical practice, i.e. no neuronavigation was used and coil placement adjusted after deviations from the marked point or a series of absence of EMG responses. In analysis of the mean and median values per subject, no effects for both the low and high frequency rTMS protocol were prominent, which might be due to influential variables such as the intrinsic state (Stefan et al., 2004) or others (Guerra et al., 2020b). To further elaborate the effects of 1 and 20 Hz rTMS, we analyzed single-subject responses and found that more than a quarter of the participants responded significantly according to the lofi-hife heuristic and more than half descriptively. Only one participant reacted significantly according to the heuristic in all four measurements, which further highlights the variability of rTMS effects. We conducted Chi-square tests to reveal correspondences of the

first and second session of rTMS application. Hereby, no associations were found, except for descriptive changes from pre to post 1 Hz rTMS, whereby in both sessions more participants showed the expected decrease of MEP amplitude compared to an increase. Yet, test-retest reliability values of *r* and ICC remained in the low to moderate range. Only when analyzing subsamples with higher data quality, i.e. at least 75 % of valid trials, no manual coil correction needed and both, higher but infrequent reliability values for the 20 Hz rTMS protocol were reached. Overall, reliability values of 1 Hz rTMS were similar to previous research, but reliability for 20 Hz rTMS in our experiment was lower (Maeda et al., 2000b). Although stimulation parameters used for the present experiment were evaluated as inducing larger rTMS effects and reliability by the literature (Nojima et al., 2013; Jannati et al., 2019), no such tendency was depicted within our data. That only for 20 Hz rTMS a subgroup with higher data quality achieved higher reliability values might be due to higher influences of discomfort, pain and muscle twitching in comparison to low frequency stimulation (Kaur et al., 2019).

Limitations to this study such as no use of neuronavigation, possible interaction between the rTMS procedures because of a short inter session interval or subject-specific influences due to cognitive states were noted, discussed and incorporated within the third study.

5.1.2 Second study: Retest reliability of repetitive transcranial magnetic stimulation over the healthy human motor cortex: a systematic review and meta-analysis

The second study (Kanig et al., 2023) investigated current literature on the test-retest reliability of rTMS protocols and summarized accompanying rTMS effects within a scope of review and meta-analysis. Except from a 10 Hz rTMS intervention, which showed inhibitory effects, all inhibitory (1 Hz and cTBS) and facilitatory rTMS protocols (20 Hz, iTBS, PAS_{25}) evoked expected effects according to the lofi-hife heuristic. Yet, reliability values of *r* and ICC mainly (in 13 out of 15 studies) remained in the low to moderate range. Overall, the identified studies had homogeneous reliability values with a mean value of 0.315, which is still in the lower range. In comparison to TMS measures elicited with single pulses that show reliability values up to 0.86 (Pellegrini et al., 2018), the rTMS reliability values are influenced by both TMS and rTMS variability, which should be identified and eliminated further in order to gain higher results. The study furthermore evaluated possible influences to rTMS reliability such as the methodological quality of the experiment, assessed via checklist (Chipchase et al., 2012), the year of publication, the repetition interval of the rTMS protocol, the sex ratio of the investigated sample, and categorical predictors such as the use of neuronavigation and excitability of

the rTMS protocol. None of these factors contributed significantly to the reliability of rTMS as shown in the meta-analysis. Yet, more studies with higher power and larger sample sizes are needed to validate this finding. By systematically assessing influences on rTMS effects and reliability within the particular experiments, results showed higher inhibition effects with higher stimulation intensity and stress (Vallence et al., 2015), as well as higher facilitation effects with sleep in between sessions (Cohen et al., 2010) along with higher reliability values in the afternoon (Sale et al., 2007), in younger participants and those with a specific BDNF genotype (Jannati et al., 2019). Lastly, the publication bias was examined and interpreted to not reveal a major influence. Still, a negative trend occurred for the correlation of reliability and year of publication, indicating that with the plurality of setups and possibly higher objectivity the reliability of rTMS measures suffers. In turn, this means that researchers should find parameters to increase reliability also within these more objective and differentiated setups and samples.

To accommodate the plurality of setups, the third study was set up with the assessment of 1 Hz rTMS in dependency of the two current directions that are typically used for biphasic rTMS interventions, but do not equally correspond to the default setting of the pulse source (van Doren et al., 2015).

5.1.3 Third study: Influences of current direction on 1 Hz motor cortex rTMS

The third study (Kanig et al., 2025) assessed MEP and TEP amplitudes and latencies before and after 1 Hz rTMS for both AP-PA (default) and PA-AP (reverse) current direction. Contrary to the lofi-hife heuristic, higher MEP amplitudes were observed along with higher amplitudes for the TEP components N15, N45 and P60 and a reduced N100 amplitude, which indicates that 1 Hz rTMS induced rather facilitatory than inhibitory effects in the CE and CSE measures. Yet, influential variables such as pulse configurations or subject-inherent differences in the factors assessed by VAS, namely excitement, referring to the individual cognitive activation, and tiredness might have also contributed to the opposite findings from the literature. The latency of MEPs in both current directions and the TEP component N15 in reverse were prolonged and the latency of the N100 was shorter after rTMS than before. Previously published data especially on TEP latency is scarce, and thus comparisons are difficult on rTMS effects. MEP latency on the other hand usually was not modulated by rTMS, thus a prolongation might be due to influential factors such as sleepiness (Avesani et al., 2008). Current direction had an influence on MEPs and some TEP components: Pulses with reverse current direction in the brain elicited higher rTMS effects in MEP and TEP (N15, N45, P60, N100) amplitude and MEP and N15 latency. This finding is predominantly in accordance with previous literature, yet some results

from amplitude investigations of other studies seem to point to the opposite direction (Goetz et al., 2016; Casula et al., 2018). Since the RMT was significantly higher in the reverse than the default current direction, the interpretation of current direction differences needs to account for this possible confounding effect. Other possible confounding variables, such as loudness of the TMS masking, perceived loudness of the coil click and attention, excitement and tiredness were investigated as well. Although after the rTMS procedure, participants were more tired, less excited and in tendency less attentive, no current direction effect was prominent in the analyses. Yet, in discussion of rTMS effects, such concurrent findings need to be kept in mind. The correlation analysis between MEPs and TEPs revealed a significant relationship between MEP and N45 amplitude, but this only occurred in the condition before rTMS with reversed current direction and had a negligible effect size, which is why no clear association between CE and CSE measures can be derived from this dataset.

Overall, the high variability of TMS and rTMS measures is consistent across all studies. Even when accounting for some of the influential factors and following recommendations of previous studies, no high nor stable effects were achieved in the studies contributing to the present thesis.

5.2 Discussion of rTMS effects

The studies presented within this dissertation were not able to replicate previous findings that low frequency rTMS elicits an inhibitory effect whereas high frequency rTMS acts facilitatory. This could be due to various causes:

In the first study, only half of the participants responded according to the heuristic descriptively and only one participant showed significant changes in CSE for both 1 and 20 Hz rTMS. As stated in the respective discussion section, influential factors such as the participants' intrinsic state or others might have contributed to this variability of responses. Within such experiments, not all factors can always be sufficiently controlled for and additional variables might not have been identified yet (Guerra et al., 2020b). Hereby, the extent and direction of influence on both TMS and rTMS measures would be beneficial to be able to estimate how important it is to include the factors as experimental covariates or for example in a therapeutic setting to improve symptoms (Ridding & Ziemann, 2010). The second study included in this thesis summarized that although the rTMS aftereffects were mainly according to the heuristic, except the 10 Hz rTMS protocol, aftereffect size varied between experiments and protocols. Other experiments found that only 50 % of rTMS aftereffect variation can be predicted for now and that the other 50 % is still in need to be explained (Hamada et al., 2013). It might be that with rTMS applications, not solely LTP- or LTD-like effects are produced, but that in general variability is induced and dependent on the influential factors, LTP or LTD effects occur predominantly.

Thus, contrary effects within and between subjects could appear dependent on the influential variables.

This possible explanation additionally raises the consideration of applying more individualized versus generalized TMS and rTMS protocols. Applications that are tailored to a person's particular response have the advantage to be effective per definition, which might refer to individual adjustment of eliciting CE measures (Beck et al., 2024) or individualized treatment (Schoisswohl et al., 2021). Yet, in comparison to generalized protocols or standard procedures such as a coil orientation of $45°$ to the midline (Daskalakis et al., 2006; Balslev et al., 2007; Hamada et al., 2013; D'Amico et al., 2020b) or an entire treatment plan (Cole et al., 2020), individual settings cannot be used for general deductions on the effects of TMS and rTMS per se which makes optimization of protocols more difficult. Additionally, individualization versus generalization often also demands the available setup, time and money. Although standardized rTMS protocols are available and yield promising treatment effects (Cole et al., 2020), in comparison to pharmaceutical drugs that undergo a stepwise procedure to get approval for distribution of the local pharmaceutical authorities like Food and Drug Administration (United States of America) or the Bundesinstitut für Arzneimittel und Medizinprodukte (Germany), rTMS still needs proof of efficacy as well as large cohort studies to be recognized as treatment (Foucher et al., 2007; Guerra et al., 2020a). Hereby, proof of efficacy refers to the clinical significance of the treatment result, i.e. improvement of symptoms until remission of the disease.

The third study within this thesis also found contrary effects than predicted by the lofi-hife heuristic, whereby 1 Hz rTMS acted facilitatory and not inhibitory on both CE and CSE measures. Although previous literature was used as a basis for experimental and methodological decisions, these findings could not all be reproduced by our data. This might be due to insufficient accuracy and detailed description of the experimental setup and procedure of the experiments to be compared with. Hereby, the plurality of setups, pulse sources and stimulation parameters between laboratories aggravate comparability (van Doren et al., 2015; Gutiérrez-Muto et al., 2023; Osnabruegge et al., 2024). For example, electrical properties in a setup like the line voltage differ between laboratories, especially between European or Asian countries, where the line voltage is at 50 Hz, and American countries, where the line voltage is at 60 Hz. Thus, during preprocessing shifted filters need to be applied to clean the data from this background noise, which in turn can affect the raw signal as well (Hernandez-Pavon et al., 2022). The pulse sources as such often differ in electrical configuration such as the capacitors, electrical circuits and transistors and coil shape and windings (Gutiérrez-Muto et al., 2023). Thus, the induced electrical field in the brain is not always comparable between pulse sources (Nieminen et al., 2015). And even if the pulse sources might be identical, the use of neuronavigation and a cobot which can improve objectivity, accuracy of coil placement and transferability of the

hotspot across sessions, are not yet part of the standard equipment, because high costs are involved which not every laboratory can afford (Jung et al., 2010; Matsuda et al., 2024).

Additionally, since no golden standard of stimulation parameters is set, applications of TMS and rTMS highly differ in stimulus intensity, current direction, number of pulses, inter trial and session interval etc. An accurate replication of these parameters thus depends on the description within the publication. Within our third study it seems that we were able to reproduce the main findings on current direction influences on TMS and rTMS. Yet, it might be that the used stimulation intensity and thus the strength of the induced $\mathbf{E}$-field, which were higher for the reversed current direction, contributed to these findings. Therefore, an exact differentiation between the influences of current direction and strength of the induced $\mathbf{E}$-field is necessary. Also, other factors that contribute to TMS and rTMS variability should be disentangled in order to derive direct dependencies on CE and CSE measures. For example, within one experimental session, which often lasts up to several hours, the participants' cognitive state often changes. In our third experiment, participants were more tired and less excited after the rTMS session, which might also contribute to the contrary outcomes as stated in the respective discussion section. By reducing the time of intervention or giving the participant pauses in between measurements or implementing brain-state dependent measures (Bergmann et al., 2016; Zrenner et al., 2016), this bias may be circumvented. Furthermore, relatively small sample sizes and number of repetitions may bias the findings on CE and CSE measures by reduced statistical power. Thus, both new research with accurate replication of previous results as well as large scale meta analyses of existing literature may contribute to identifying reasons for variability of rTMS effects within and between experiments. One obstacle to carrying out these replications to further investigate the validity of rTMS effects lies in the journal publishing and grant proposal requirements to generate new findings instead of mere reproduction of effects (Makel & Plucker, 2014).

A major goal in NIBS research is to find measures that are least influenced by third factors and reflect TMS and rTMS effects as direct as possible. Although within scientific experiments the objectivity is maintained rigorously and reliability is aimed to increase, solutions in TMS and rTMS applications with zero interference and a high signal-to-noise ratio have not been found yet. Even within CE and CSE measures, there is no consensus on which parameter reflects the "true" stimulation effect. In our third study, we investigated which CE and CSE parameter correlated to find out which measures may reflect the same stimulation effect. Yet, only for the reversed current direction before rTMS, N45 and MEP amplitude correlated with negligible effect size. This finding hints to the need of a less influenceable parameter. In investigation of M1, iTEPs promise to be less influenced than current

CE and CSE measures (Beck et al., 2024). Therefore, to date, rTMS effects might be absent or contrary to expected results due to biased derived measures. However, in other human science disciplines, the dependent variables such as reaction times, eye-tracking data or data derived from questionnaires can be equally biased. As an example, in clinical practice, rTMS effects on patients and concurrent symptoms are often measured with questionnaires (Dragon et al., 2024), such Major Depression symptoms with the MDI (Cuijpers et al., 2007). Although both neurophysiological (MEPs and TEPs) and subjective (questionnaire) data are used to investigate rTMS effects (Berlim et al., 2017; Cole et al., 2020; Li et al., 2023), a comparison of effects, treatment outcomes or remission rates between any of these data needs to be treated with caution since they measure different systems and influential factors affect them differently. Especially results of MEP and TEP amplitude and latency do not seem to correlate, which was found in the third study (Influences of current direction on 1 Hz motor cortex rTMS). Measurements should therefore be adjusted to the research question and a proper sham condition be introduced depending on which parameter is being examined to ensure validity of the results.

Of course, it might also be that the validity of the lofi-hife heuristic is low and that we need more complex predictive tools to categorize TMS and rTMS effects.

5.3 Discussion of rTMS reliability

Reliability of rTMS effects has been identified as low to moderate throughout all protocols as well as in our first study for 1 and 20 Hz rTMS in particular. Despite only investigating applications over the motor cortex on healthy individuals in our second study, we can conclude that even for this homogeneous sample and well investigated stimulation position reliability was rarely in the high range.

Reason for these low to moderate reliability values could be that the influential parameters of stimulation, experimental setup and subjects are not excessively investigated and need to be controlled for experimental designs and analyses of both TMS and rTMS applications (Guerra et al., 2020b). In detail, because reliability values of measures of single TMS pulses are more often in the higher levels (Osnabruegge et al., 2023), these variability influences seem to have greater impact on repetitive TMS pulses and concurrent plasticity effects, which is why especially rTMS variability needs to be investigated further and disentangled from TMS variability when investigating rTMS reliability. Both experiments with randomly controlled trials and meta-analyses of existing literature contribute to that. For example, in our second study we found that parameters like methodological quality of the study and year of publication, as well as excitability of the protocol, i.e. whether the rTMS procedure acts inhibitory or facilitatory according to the lofi-hife heuristic, use of neuronavigation, sex ratio of the sample, and rTMS repetition interval, did not affect

the reliability. Yet, it might be that the included experiments were too few to give a dependable result, since the goodness of fit was not significant in the Chi-squared test. Other parameters are yet to be investigated.

In the first study, significant reliability values of the 20 Hz rTMS protocol were achieved when assessing a subgroup of subjects with higher data quality, i.e. at least 75 % valid MEPs. As discussed in the respective section within the study, the discomfort and muscle twitching that can accompany higher frequency protocols (Kaur et al., 2019) may have contributed to more invalid MEPs and thus the lower reliability. More valid MEPs may also be achieved by using neuronavigation (Bashir et al., 2011; Chang et al., 2016) or by adjusting the standards of CE/CSE (MEP) acquisition, preprocessing, analyzing and reporting with addressing the variability:

The main probed measure, CSE, is a parameter easily to be biased (Ridding & Ziemann, 2010; Pell et al., 2011; Guerra et al., 2020a). Not only interindividual differences but also state dependent factors, such as concurrent motor activity and attention influence its outcome, which always has to be accounted for during measurements (Ridding & Ziemann, 2010; Guerra et al., 2020b). To assess CE directly at the scalp via EEG is one attempt to purify the measure from more indirect interferences during signal propagation (Guerra et al., 2020a). Yet, even after a few milliseconds, the original cortical reaction to the TMS pulse is contaminated by sensory, somatosensory and auditory afferences (Nikouline et al., 1999; Malcharek et al., 2011; Alhussaini et al., 2018; Conde et al., 2019; Rocchi et al., 2021). To avoid these, very early responses, such as the iTEPs might give further and less biased insights into TMS and rTMS effects and lead to increased reliability (Beck et al., 2024). Yet, for now, dependent measures such as I-O curves that portray CSE more detailed and are less prone to ceiling and floor effects in comparison to MEPs elicited with a certain intensity, might contribute to investigating reliability measures more robustly and in a more detailed way.

In our analyses from the first study, we saw that using a measure of central tendency that better represents skewed distributions such as the median in comparison to the arithmetic mean resulted in slightly higher reliability values. Of course, this finding is immanent to the concept that reliability is a measure of variances (Koo & Li, 2016) and by reducing the variance artificially with a parameter less sensitive to variances, reliability increases. Still, it sheds light to the discussion of outlier handling in TMS and rTMS derived measures (Héroux et al., 2015; Guerra et al., 2020b). To logarithmize a variable, just to fit it into a desired analysis can be more critical than to define a "valid", i.e. physiologically and interpretative plausible, interval a priori for example for MEP amplitudes, and adapt the analysis to the data (Feng et al., 2014).

In general, the concept of reliability comprises several aspects, such as test-retest reliability, parallel-test reliability and consistency (Bajpai & Bajpai, 2014).

When investigating rTMS reliability, it is not only important to consider the rTMS measure which should be examined, but also the form and measure of reliability. We aimed to investigate test-retest reliability in our experiments to address the stability of rTMS effects over time and used both *r* and ICC as measures. Reliability depends on both the variability of the measure and the variability of the error term (Cohen, 1988). In the classical testing theory, only random errors are considered (Lord & Novick, 2008), but usually systematic errors (biases) are included in the equation (Krippendorff, 1970). Although systematic errors do not bias measures of consistency, as the ICC, and merely change the linear equation in any *r* measure, they change the true value and thus affect the validity of a measure (Krippendorff, 1970). The importance of error term analysis can be seen when measuring the electrical properties of a TMS pulse: For example differences in pulse width within and between pulse sources yield very low variance, but pulses administrated to a human scalp evoke reactions with much higher variance (Osnabruegge et al., 2023; 2024). Thus, different measurements and underlying mechanisms contain varying error terms that bias the outcome. Although some mechanisms of TMS are roughly outlined, since not all of them, nor their exact effects, are (Siebner et al., 2022), both systematic and random errors cannot be clearly identified and restricted in TMS research and thus prevent reaching high reliability levels. With this in mind, the interpretation of reliability should be reconsidered for reliability analysis: In comparison to other areas of research, such as informatics or mathematics, perfect reliability, indicated with the value 1 for *r*, cannot be achieved due to the immanent variability of natural and vivid entities (Meyer et al., 2001). And although the interpretation of *r* by Cohen (1988) and ICC by Koo and Li (2016) is also accounting for behavioral data, its validity is not proven yet.

5.4 Limitations

Within our studies, we have tried to incorporate influential factors on the variability of TMS and rTMS as much as possible. Either by controlling for their influences by systematically modifying the variable, i.e. current direction, by assessing it via questionnaires, e.g. tiredness, attention and excitement, or by including it in the analyses as covariate, e.g. methodological quality of the study in the Chi-square test or subject as random variable in the linear mixed effect models. We also have followed the recommendations from the literature, e.g. on the use of stimulus intensities (Fitzgerald, 2002; Lang et al., 2006), number of pulses within rTMS protocols (Maeda et al., 2000a; Nojima et al., 2011) and ITI of single TMS pulses (Osnabruegge et al., 2023). Still, we cannot exclude interactions of these factors or influences of others. Further research with larger sample sizes is needed to get further insight into their contributions to TMS and rTMS.

Larger sample sizes are generally aimed at in NIBS research to increase statistical power. We tried to account for this with a sample size of 30, which should be sufficient to detect effects according to the central limit theorem as mentioned in the first study. In the third study, although not having investigated 30 participants, we used the linear mixed effect models to increase the power of our analyses that hereby were also able to account for the individual variability by including all repetitions within subjects and conditions. Nevertheless, since the marginal and conditional R^2 of the linear mixed effect models are relatively low, the power of the investigated 1 Hz rTMS procedure along with the current direction influence seems to be lower than expected and thus, even higher sample sizes as well as further replications of data would be beneficial to investigate in order to identify underlying rTMS effects. Since statistical power is not only determined by sample size, but also effect size, significance level and data variability (Cohen, 1988), larger sample sizes are only one part to identify higher effect and reliability values. Conversely, lower data variability by reducing random and systematical measurement errors and thus higher reliability as well as higher effect sizes contribute to higher statistical power. To increase statistical power in overall TMS research, all components should be considered, which highlights the importance of effect and reliability investigations.

The preprocessing and analysis methods used in our studies were mainly based on current literature (Rogasch et al., 2017; Hernandez-Pavon et al., 2022). Especially the choice of EMG and EEG filtering and artifact rejection have been investigated and approved. Yet, a few adjustments had to be made due to the data characteristics, for example to interpolate the TMS pulse artifact in EEG data preprocessing. Hereby, deviances from the literature may occur and bias our results. Also the use of individual latency intervals to extract the TEP component amplitudes from induce deviances within the data. Still, we chose to implement this approach to account for interindividual differences and thus being able to disentangle the rTMS effects from individual variability within our analyses.

In the two conducted experiments, the balancing act between personalization and generalization was a challenge. We endeavored to find a way in the middle and kept the setup general along with the generalizable hotspot search approach (Agboada et al., 2023) in the third study, and focused on implementing the individual influence during the analyses. For that we used Chi-square tests of individual responses in the first study and linear mixed effect models with the random factor subject in the third study. Other studies kept parameters constant, such as the stimulation intensity at e.g. 70 % MSO (Fregni et al., 2006), or TEPs are extracted at a cluster of electrodes defined a priori (Casula et al., 2014). This discrepancy between choices of generalization and personalization parameters within and across studies might also be a reason for failed replication of results and might potentially hinder the finding of reliable rTMS effects.

As in all laboratory environments, the experiments conducted for this thesis are prone to the influence of investigator and analyzer. Although we tried to implement a highly objective environment by controlling the coil position either by additional analyses or via use of a cobot navigation, adjustments throughout the experiments such as telling the subject to focus on relaxing the hand or participant-investigator interactions may have influenced the outcome. Thus, rTMS effects, concurrent reliability and also the validity of results could also be dependent on the laboratory environment.

5.5 Recommendations for future research

Since both rTMS effects and rTMS reliability did not show the desired outcomes, a more detailed but also broader investigation of those parameters is necessary.

If one follows the literature in the previous recommendations for the use of rTMS with maximum effects, one should stimulate at a laboratory with neuronavigation (Ahdab et al., 2010) and to increase objectivity, use a cobot with grid search of the individual hotspot (Littmann et al., 2013; Agboada et al., 2023). Higher stimulation intensity (Fitzgerald, 2002; Lang et al., 2006; Vallence et al., 2015) and a PA-AP current direction induced in the brain (Sommer et al., 2013a) are found to evoke higher cortical plasticity. Shorter inter-session intervals can lead to potentiation of rTMS effects (Maeda et al., 2000b) and administration in the afternoon (Sale et al., 2007), with enough sleep (Cohen et al., 2010) and high attention (Stefan et al., 2004) are beneficial to reach larger effects. Participants should be younger (Cueva et al., 2016), more active (Cirillo et al., 2009) and should not have the BNDF polymorphism Val66Met (Cheeran et al., 2008). Yet, hereby interactions between the variability influences as well as the low repeatability of previous literature should be treated with caution.

Reliability of rTMS effects can be increased by adjusting the factors that increase the effects themselves, just as stated in the section above. Following the recommendations of the literature higher reliability can be achieved by assessing rTMS in the afternoon (Sale et al., 2007; 2008), in younger people (Cueva et al., 2016), without the BDNF polymorphism (Cheeran et al., 2008) and by analyzing the MEP p2p amplitude instead of AUC (Brown et al., 2017) or TEPs with longer and later time windows (Gogulski et al., 2024).

In basic science, the first step to enhancing rTMS effects and reliability is to accurately communicate the stimulation and methodological parameters used throughout the experiment. Hereby, a standardized method, such as using validated questionnaires (Giustiniani et al., 2022) and ensuring high quality of overall methodology (Chipchase et al., 2012) would be worthwhile in order to make exact replications of rTMS interventions possible. Uniform nomenclature of parameters, such as current

direction induced in the brain instead of flow in the coil or an accurate description of the stimulation intensity as $\frac{dI}{dt}$ instead of an incomparable arbitrary scale as % MSO would contribute to this standardization.

Furthermore, to promote communication between researchers and laboratories and thus enable comparable results and avoid misunderstandings in nomenclature, collaborations between researcher groups and contributing data to large data sets (Corp et al., 2020) is a major contribution to enhancing rTMS effects and reliability and identify good and omit bad practices (Héroux et al., 2015; Gaffney et al., 2023). Thus, in our research group, we have launched the Annual Regensburg Transcranial Evoked Measures Interactive Symposium (ARTEMIS) to get in contact with other researchers, discuss current findings and exchange experience on problems during data acquisition, preprocessing and analysis.

Not only the interaction with other neuroscientists should be the goal, but also with people coming from different backgrounds, such as electrical engineers, physiologists, biologists, pharmacists and clinicians (Gaffney et al., 2023). In further understanding the underlying mechanisms of TMS and rTMS on cell level or in models and animals, also rTMS effects and reliability can be enhanced.

By investigating influential factors on TMS and rTMS on a large scale (Corp et al., 2020) with special focus on the differentiation between the influences on the effects and their reliability, a more detailed view on the mechanisms within the human brain can be provided. Hereby, realistic sham conditions should be incorporated (Gordon et al., 2021) and the assessment of different dependent variables considered, that might be more reliable and less prone to noise than the common CSE and CE measures MEPs and TEPs (Beck et al., 2024).

In cognitive sciences, current investigations with rTMS should be cautious with subsequent interpretation of rTMS effects and consider its low to moderate reliability. For now, TMS remains one of the only tools next to tES to be able to engage and disengage brain regions briefly without noteworthy side effects or damage to the tissue (Jahanshahi & Rothwell, 2000). Thus, its improvement of efficacy and reliability with further understanding of influential factors would be highly beneficial. To further disentangle the influential factors on rTMS effects and reliability, cognitive research along with its methods contributes to understanding the neuropsychological basis.

Clinical applications of TMS and rTMS would also benefit from such effect and reliability improvements. Since as diagnostic and therapeutic tool, magnetic stimulation has been used quite frequently (Berlim et al., 2013; Cao et al., 2018; Schoisswohl et al., 2021; Chen et al., 2023), and patients profit from its low side effect profile (Clarke et al., 2006), one could efficiently combat widespread diseases such as Major Depression by improving rTMS effects either individually or generally and providing comprehensive care, possibly also at home with smaller devices. For

now, further differentiation of rTMS effects, identification of concurrent influences and improvement of reliability can be achieved by investigating patient groups (Koch et al., 2011; Fried et al., 2017).

5.6 Concluding remarks

TMS and rTMS can be mighty tools to alter cortical plasticity and improve current brain functions or even help recovering dysfunctional networks. But in order to establish magnetic stimulation as standard cognitive or clinical intervention, there is still a long way to go. Findings from the present dissertation show that rTMS effects are not always reproducible, also challenging the common heuristic that low frequency rTMS acts inhibitory, whereas high frequency rTMS elicits facilitatory effects. Yet, higher effects were achieved with the stimulation parameter current direction induced from posterior-anterior to anterior-posterior in the brain. Additionally, reliability of rTMS ranges mainly from low to moderate, indicating that improvements for both efficacy and reliability of rTMS are necessary. Further research is needed, optimally in analysis of large samples and with investigating the influential effects on rTMS efficacy and reliability of stimulation parameters, experimental setup parameters and subject related parameters. Until then, uniform nomenclature and generalized or individual-specific methodology along with technological advances may pave the way to an effective and reliable intervention.

Personally, I have benefited greatly from an experienced environment with excellent researchers who helped me throughout the planning, preparation and execution of experiments. With their support also to collaborate and interact with other more skilled researchers, it was very easy to familiarize with the nomenclature and specific procedures, to being able to identify approaches for improvement. Despite eliciting highly variable effects, as a participant yourself you can easily feel and understand the mechanisms of TMS on your own body. But keeping one's state constant throughout an experiment that lasts more than an hour is merely impossible. I believe that with the combination of findings of personalized applications and large data sets, rTMS can improve to levels of other interventional and therapeutic efficacy.

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