Aus dem Lehrstuhl
für Psychiatrie und Psychotherapie
Prof. Dr. R. Rupprecht
der Fakultät für Medizin
der Universität Regensburg

„Modulation of functional connectivity of the motor system through repetitive transcranial magnetic stimulation"

Inaugural – Dissertation
zur Erlangung des Doktorgrades
der Medizin

der
Fakultät für Medizin
der Universität Regensburg

vorgelegt von
Johanna Emma Kreß

2025

Aus dem Lehrstuhl
für Psychiatrie und Psychotherapie
Prof. Dr. R. Rupprecht
der Fakultät für Medizin
der Universität Regensburg

„Modulation of functional connectivity of the motor system through repetitive transcranial magnetic stimulation"

Inaugural – Dissertation
zur Erlangung des Doktorgrades
der Medizin

der
Fakultät für Medizin
der Universität Regensburg

vorgelegt von
Johanna Emma Kreß

2025

Dekan: Prof. Dr. Dirk Hellwig

1. Berichterstatter: Prof. Dr. rer. nat. Jens Volkmar Schwarzbach

2. Berichterstatter: Prof. Dr. med. Ralf Linker

Tag der mündlichen Prüfung: 12. September 2025

CONTENTS

1 ABSTRACT 5

2 INTRODUCTION 8

2.1 The human brain – a huge network of neurons 8

2.1.1 Structural connectivity (SC) 8

2.1.2 Functional connectivity (FC) 9

2.2 Functional MRI as a tool to measure FC 9

2.2.1 Resting-state networks 10

2.3 Repetitive transcranial magnetic stimulation as a tool to change FC 11

2.4 Problem with interpreting the changes in FC caused by rTMS and our approach to a solution 12

2.4.1 Motor evoked potentials (MEPs) as objective readout 12

2.4.2 Aim and hypotheses of our study 14

3 METHODS 15

3.1 Participants 15

3.2 Experimental protocol 15

3.3 MRI data acquisition 17

3.4 Neuronavigation 19

3.4.1 Preparation 19

3.4.2 Application 20

3.5 Repetitive transcranial magnetic stimulation (rTMS) 21

3.6 Preprocessing of the resting-state data 22

3.6.1 Conventional preprocessing steps 22

3.6.2 Additional noise reduction using independent component analysis 23

3.6.3 Splitting the data 24

3.7 Seed-based correlation analysis 24

3.7.1 Correcting for multiple comparisons using TFCE 24

3.8 Dual regression analysis with respect to template maps 25

3.9 Localizing the altered brain areas 27

4 RESULTS 28

4.1 Seed-based correlation analysis: No change in FC through 1 Hz rTMS found 28

4.2 Dual regression analysis: 1 Hz rTMS decreases FC between cerebellum and left thalamus 28

4.2.1 Localization of clusters located in the thalamus based on the thalamic nuclei atlas 29

5 DISCUSSION 32

5.1 Tremor(network) as the linking element: an interpretive approach 33

5.1.1 Structural connection between cerebellum, thalamus, and motor cortex 33

5.1.2 Cerebello-thalamo-cortical pathway as main actor in generation of tremor 34

5.1.3 Cerebello-thalamo-cortical pathway as main target for therapeutic interventions in tremor 36

5.1.4 Tremor patients exhibit altered cerebello-thalamo-cortical FC 36

5.1.5 Similarities between tremor patients and our experiment: an attempt at interpretation 37

5.1.6 Future experiments 40

5.2 Various further aspects 41

5.2.1 FC alterations in the cerebellum as a possible expression of neuroplasticity 41

5.2.2 FC changes located in white matter 42

5.2.3 Possible limitations concerning data analysis 42

5.3 Conclusion 43

6 BIBLIOGRAPHY 45

7 TOOLS 56

DECLARATION I

ACKNOWLEDGMENTS II

1 ABSTRACT

The human brain consists of a huge network of structural linked neurons that enable us to perform higher cognitive functions. In addition to structural connectivity, there is also functional connectivity (FC), a statistical association between time courses of neural activity from different brain regions, that can be measured using functional magnetic resonance imaging (fMRI), even in resting brains. Previous studies have shown that repetitive transcranial magnetic stimulation (rTMS) is not only able to induce frequency-dependent local alterations in cortical excitability (≤ 1 Hz decrease, > 1 Hz increase), but it can also elicit changes in FC in distant brain regions. We aimed to assess the effect of 1 Hz rTMS applied on left primary motor cortex (M1) on resting-state FC. To validate the effectiveness of 1 Hz rTMS in attenuating M1 excitability, we utilized motor evoked potentials (MEPs) as an objective readout measure, revealing a significant reduction in the number of MEPs during the initial 11 minutes post-stimulation in a pre-experiment (reference).

In the main experiment 14 participants underwent 30 minutes of 1 Hz rTMS on left M1, framed by a 22-minute resting-state fMRI scan before and after stimulation.

We performed a two-stage analysis: (1) In the seed-based analysis, we investigated rTMS-mediated FC changes between the target area (left M1) and the rest of the brain. This analysis did not reveal any significant effects. (2) In the following whole brain network analysis, we used a dual regression approach to quantify the characteristics of 10 known template networks in our data. Group statistics unveiled a decrease in FC between the cerebellar component and left thalamus during the first 11 minutes following 1 Hz rTMS.

Interestingly, there exists a structural connection between cerebellum, contralateral thalamus and contralateral motor cortex. This so-called cerebello-thalamo-cortical pathway (or tremor network) is implicated in the development of tremor disorders and is therefore the major target for respective therapeutic interventions. This unexpected anatomical link led us to the following interpretive approach of our results: Previous studies reported changes in FC within this tremor network in tremor patients; hence, the FC change between cerebellum and thalamus we found might be an expression of a compensatory mechanism to the “articifial” tremor induced by rTMS. Further research is required for a potential therapeutic role of rTMS in tremor disorders.

ZUSAMMENFASSUNG (DEUTSCH)

Das menschliche Gehirn besteht aus einem riesigen Netzwerk von strukturell verbundenen Neuronen, die es uns ermöglichen, höhere kognitive Funktionen auszuführen. Neben der strukturellen Konnektivität gibt es die funktionelle Konnektivität (FC), eine statistische Assoziation zwischen Zeitreihen neuronaler Aktivität, die mit funktioneller Magnetresonanztomographie (fMRI) gemessen werden kann, selbst in Gehirnen im Ruhezustand. Frühere Studien haben gezeigt, dass die repetitive transkranielle Magnetstimulation (rTMS) nicht nur in der Lage ist, frequenzabhängig lokale Veränderungen der kortikalen Erregbarkeit hervorzurufen (≤ 1 Hz Abnahme, > 1 Hz Zunahme), sondern auch Veränderungen der FC in weiter entfernten Hirnregionen zu bewirken. Unser Ziel war es, die Wirkung von 1 Hz rTMS, appliziert auf den linken primären motorischen Kortex (M1), auf die FC im Ruhezustand zu untersuchen. Um die Wirksamkeit von 1 Hz rTMS auf die Abschwächung der Erregbarkeit von M1 zu validieren, verwendeten wir motorisch evozierte Potenziale (MEPs) als objektive Messparameter, die in einem Vorversuch (Referenz) eine signifikante Verringerung der Anzahl der MEPs während der ersten 11 Minuten nach der Stimulation zeigten.

Im eigentlichen Experiment untersuchten wir 14 Probanden, von denen jeder 30 Minuten lang mit 1 Hz rTMS über dem linken M1 behandelt wurde, umrahmt von je einem 22-minütigen fMRI-Scan im Ruhezustand vor und nach der Stimulation.

Wir führten eine zweistufige Analyse durch: (1) In der seed-based Analyse untersuchten wir rTMS-vermittelte FC-Veränderungen zwischen der seed-Region (linker M1) und dem übrigen Gehirn. Diese Analyse ergab keine signifikanten Effekte. (2) In der folgenden Analyse aller Hirnnetzwerke verwendeten wir einen dualen Regressionsansatz, um die Eigenschaften von 10 bekannten Muster-Netzwerken in unseren Daten zu quantifizieren. Die Gruppenstatistik zeigte eine Abnahme der FC zwischen der Kleinhirnkomponente und dem linken Thalamus während der ersten 11 Minuten nach 1 Hz rTMS.

Interessanterweise besteht eine strukturelle Verbindung zwischen Kleinhirn, kontralateralem Thalamus und kontralateralem motorischen Kortex. Dieser so genannte cerebello-thalamo-kortikale Nervenstrang (oder Tremor-Netzwerk) ist an der Entstehung von Tremor-Erkrankungen beteiligt und stellt daher den vorwiegenden Angriffspunkt für entsprechende therapeutische Interventionen dar. Dieser

unerwartete anatomische Zusammenhang führte uns zu folgendem Interpretationsansatz für unsere Ergebnisse: Frühere Studien berichteten über Veränderungen der FC innerhalb dieses Tremor-Netzwerks bei Tremor-Patienten; die von uns gefundene FC-Veränderung zwischen Kleinhirn und Thalamus könnte daher Ausdruck eines Kompensationsmechanismus für den durch rTMS induzierten „künstlichen“ Tremor sein. Für eine mögliche therapeutische Rolle der rTMS bei Tremor-Erkrankungen ist weitere Forschung unabdinglich.

2 INTRODUCTION

A network of approximately 86 billion neurons in the human brain (Azevedo et al., 2009) provides the structural basis for our ability to pick up, process and remember countless information every day and our capability to produce an adequate reaction. The nerve cells are interconnected via estimated 100 trillion synapses, from which a widely branched network stretches. Zooming in on the level of single neurons, it is quite well-known how an electric signal is transduced from one cell to the other by means of neurotransmitters. However, at the greater network level, the communication of neurons as well as the propagation and processing of information in the human brain is, even after decades of neuroscientific research, still relatively poorly understood.

What we already know from earlier scientists is that specific brain functions, such as producing speech, are associated with certain brain areas, in this case the inferior frontal gyrus of the dominant hemisphere, the Broca area, named after its discoverer (Broca, 1865). However, this straight attribution cannot explain higher cognitive function such as having a conversation. Furthermore, recent approaches in psychiatry and neurology have revealed that behavioral manifestations of neuropsychiatric diseases do not have their origin in one isolated brain region but represent perturbations in connectivity of brain regions (M. Greicius, 2008). Consequently, much neuroscience research has shifted from focusing on individual brain regions to the interaction between different brain regions.

2.1 The human brain – a huge network of neurons

A network is by definition a system composed of nodes, which are connected through edges. In terms of brain networks, nodes are different brain regions and edges are the axonal connections between nodes. To get a better idea about brain networks and their connectivity the comparison to an air traffic network can be helpful. We use this metaphor in the following to explain two different types of connectivity.

2.1.1 Structural connectivity (SC)

Structural (or anatomical) connectivity simply refers to the existence of white matter tracts interconnecting brain regions. It can be measured using imaging methods such as diffusion tensor imaging (DTI). In the analogy of an air traffic network, the axonal connections correspond to the flight routes that connect the airports of various cities

(corresponding to brain areas). Any disturbance of the flight route such as a volcanic eruption in a certain region can have a major impact on the regional air traffic and beyond. Something similar can be observed in the brain: for example, in the case of multiple sclerosis, lesions of nerve fibers lead to a loss of function depending on the localization of the disruption.

2.1.2 Functional connectivity (FC)

It is not only of interest where flight routes exist, but also how frequently these routes are used. The volume of traffic - a so-called co-activation - between cities is equivalent to what we call *functional connectivity* in the brain. FC is a statistical concept, where two brain regions are considered to show FC if there is a statistical association between the measured brain activities over time (Friston et al., 1993). The similarity of two time courses can be computed by correlating them, which results in a single value between -1 and 1, indicating the strength of FC. A correlation value of 1 shows a perfect positive correlation, whereas a correlation value of -1 describes a perfect negative (inverse) correlation. A correlation value of 0 means that there is no functional relationship at all between the two investigated brain regions.

It is worth highlighting at this stage that FC does not make a statement about direction or causality. FC simply describes the similarity between time courses but cannot tell if the signal of one region is responsible for driving the signal of another region. Furthermore, the presence of FC does not necessarily imply a direct anatomical connection between two brain areas. Correlated activity may for example be mediated by an additional structure relaying information from one area to the other.

2.2 Functional MRI as a tool to measure FC

Magnetic resonance imaging (MRI) is a non-invasive imaging technique used primarily in medical diagnostics to visualize the structure and function of tissues and organs in the body. The concept of MRI is about protons that show resonance to a radiofrequency pulse while being in a strong magnetic field. Since the human body is made up of 70 % of water it contains a lot of protons – the electrically charged particles in the hydrogen nuclei. The strong magnetic field, which is about 60,000 times stronger than the earth’s magnetic field, aligns the spinning (precessing) protons parallel or anti-parallel to the magnetic field lines. A short burst of radio waves deflects the protons along the longitudinal axis and synchronizes the protons to precess “in phase”. The

protons thereafter return to their initial dephased and low-energy state, thereby emitting a signal that is recorded by the MRI scanner. Due to differential water contents different tissues show differential magnetic resonance so that cerebrospinal fluid, for example, can be distinguished from cortical tissue.

What about *functional* MRI? As explained above we need divergent magnetic properties of tissues in order to differentiate them. This applies to oxygenated (diamagnetic) and deoxygenated (paramagnetic) hemoglobin (Pauling & Coryell, 1936). Since cells depend on oxygen, nerve cells in more active brain regions have a higher demand for oxygen. In order to meet that need the blood flow increases; this phenomenon is called the hemodynamic response. Ogawa et al. (1990) were the first to succeed in detecting this blood-oxygen-level-dependent (BOLD) contrast with MRI. Repeatedly sampling BOLD signal over time allows to construct time courses of BOLD signal changes. These time courses indirectly display the underlying neural activity and can be used to compute FC between brain regions.

There are different approaches to investigate FC between brain areas. One of the most commonly used methods is the seed-based correlation analysis, another option is the dual regression approach. Both methods are described in more detail in sections 3.7 and 3.8.

2.2.1 Resting-state networks

Biswal et al. (1995) were the first to acquire fMRI brain scans while the subjects were not performing any active task; they were instructed to relax and not think of anything in particular. This experiment revealed that the measured brain activity did not just show random spontaneous fluctuation but contained information about the brain's functional organization. They observed that, even at rest, the left and right sensorimotor cortex exhibit similar neuronal activity, hence showing resting state FC (Biswal et al., 1995). Subsequent work detected additional resting state networks which turned out to match well previously known functional networks used by the active brain, such as auditory or visual networks (Smith et al., 2009).

Aside from these functional networks, another established resting state network exists, which shows lower levels of activity when the brain is engaged in a specific task, but higher levels of activity when the brain is in a resting mode but awake, like daydreaming. It is called Default Mode Network (DMN) and is composed of a set of

brain regions such as the posterior cingulate cortex, precuneus, medial prefrontal cortex, inferior parietal lobule, and lateral temporal cortex (Raichle et al., 2001).

Many studies have reported that resting-state networks are even well reproducible over different participants (Damoiseaux et al., 2006) and also consistent over time within participants (Fukunaga et al., 2006).

Resting-state FC therefore represents the intrinsic activity of the brain. Many psychiatric and neurologic disorders are found to have altered intrinsic activity. Examples include depression (M. D. Greicius et al., 2007), schizophrenia (Lynall et al., 2010) or Alzheimer's disease (Stam et al., 2006). Achieving a thorough understanding of resting-state FC is therefore crucial for a better comprehension of these diseases and for deriving future therapeutic implications.

2.3 Repetitive transcranial magnetic stimulation as a tool to change FC

Early attempts to perform electric brain stimulation still required opening the subjects' heads (Fritsch & Hitzig, 1870). Over time, more modern techniques allowed a stimulation through the skull – so called transcranial. Whereas P. Merton and H. Morton worked on a direct transcranial electric stimulation via electrodes (TES) (Merton & Morton, 1980), A. Barker and his team from the University of Sheffield came up with an indirect stimulation technique, the transcranial magnetic stimulation (TMS) (Barker et al., 1985). TMS makes use of the physical principle of electromagnetic induction: a rapid changing magnetic field in the TMS coil induces an electric field in the underlying brain tissue, which elicits the depolarization of nerves. For example, a single TMS pulse applied on the motor cortex may allow observing involuntary contralateral finger twitching.

Another milestone was the development of a TMS device that could not only apply a single, but many consecutive pulses within a certain time, called repetitive TMS (rTMS). While single TMS pulses influence the underlying tissue briefly, repeated pulses create changes in cortical excitability that outlast the duration of the stimulation itself. Effects on cortical excitability vary with the frequencies of applied rTMS. These effects can be measured with so-called motor-evoked potentials (MEPs). These are electric potentials derived from a particular muscle elicited by an electric stimulus applied on another part of the motor system. For example, a stimulation of the hand area in the primary motor cortex causes an MEP in the small muscles of the

contralateral hand. Many studies have explored the influence of low (0,1 - 1 Hz) versus high (> 1 Hz) frequency stimulation on cortical excitability. Low frequency stimulation has been mostly reported to produce a transient reduction of MEP size/amplitude (e.g., Romero et al., 2002), high frequency stimulation has been found to mainly induce a transient increase of MEP size/amplitude (e.g., Pascual-Leone et al., 1994).

Several studies using fMRI have shown that the effect of rTMS is not only limited to the stimulated brain area but can induce changes in remote brain regions. In other words, there is evidence that rTMS modulates FC (Eldaief et al., 2011; Chen et al., 2013; Watanabe et al., 2014). According to the study of Eldaief, high-frequency rTMS (in this case 20 Hz) applied to left posterior inferior parietal lobule (lpIPL) decreased FC in Default Mode Network and low-frequency rTMS (in this case 1 Hz) applied to the same region increased FC between lpIPL and hippocampus. Hence, decreased cortical excitability produced an increase in FC, whereas increased cortical excitability led to a decrease in FC.

2.4 Problem with interpreting the changes in FC caused by rTMS and our approach to a solution

The fact that rTMS can both increase and decrease cortical excitability makes it difficult to interpret changes of FC in the context of an rTMS experiment. Thus, we need an objective readout, that tells us whether possible observed FC changes can really be attributed to rTMS.

2.4.1 Motor evoked potentials (MEPs) as objective readout

In contrast to other brain areas, the motor cortex/network allows us to derive above-mentioned MEPs, which serve as objective readout with a straightforward interpretation. We therefore chose the primary motor cortex as our rTMS target.

For evaluating the rTMS effect on cortical excitability, we kindly received data from a study carried out by our colleagues Kilian Prei and PD Dr. phil. Martin Schecklmann from the Center for Neuromodulation in Regensburg (Prei et al., 2023). In their study 30 healthy participants underwent four consecutive days of rTMS applied on left motor cortex with a daily alternating frequency of 1 and 20 Hz (e.g., day 1 and 3 = 1 Hz, day 2 and 4 = 20 Hz). Both stimulation protocols contained 1800 pulses, where the 1 Hz pulses were evenly distributed over 30 minutes and the 20 Hz pulses were given in

blocks of 2 s à 40 stimuli followed by 28 s of pause with a total stimulation length of 22 minutes. Their study thus followed the protocols of Eldaief et al. (2011) and complied with the established safety guidelines (Rossi et al., 2009). In each session, MEPs induced by single TMS pulses (applied in irregular intervals between 8 and 12 s over 22 minutes) were recorded before (baseline) and after rTMS application from the right first dorsal interosseous muscle. Figure 1 shows the accumulated data. We observed that as a result of 1 Hz rTMS the number of elicited MEPs was significantly reduced during the first half (approximately 11 minutes) of the post-rTMS run (blue line) compared to the baseline (gray dashed line).

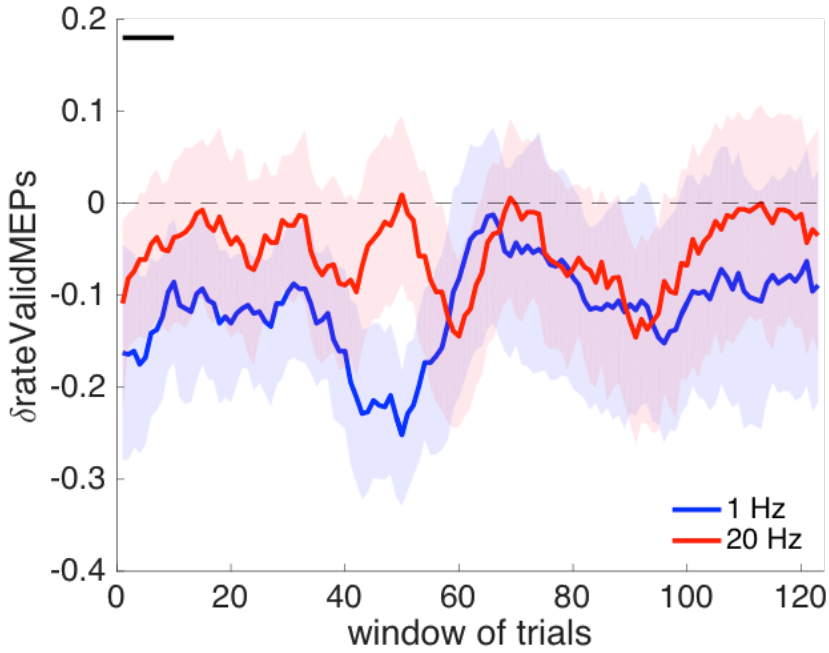

Figure 1. *Depicted here are the effects on MEPs after 1 Hz (blue line) and 20 Hz (red line) rTMS applied on the left motor cortex. For the pre-rTMS session, the number of elicited MEPs was averaged over all subjects; the post-rTMS session was split into 1-minute windows (represented by the short black line in the upper left corner) and thereof computed the relative frequency (number of elicited MEPs/number of applied TMS pulses), in other words the rate of valid MEPs. The two lines now express the difference between the relative frequencies of post- and pre-session. The light patches around the blue and red line represent the 95% confidence interval. Until approximately 11 minutes the blue line shows a significant decrease of the rate of elicited MEPs compared to the baseline (represented by gray dashed line).*
Shared work with Prof. Jens Schwarzbach, taken with his consent.

Usually, the effect of rTMS on cortical excitability is assessed by the size or amplitude of an MEP (Fitzgerald et al., 2006). However, even though we used a common setup, we did not find any alterations of the MEPs' size or amplitude, but in the number of provoked MEPs. The fact that the number of MEPs rose again after 11 minutes suggests a causal effect to the rTMS intervention rather than a measurement error such as a feigned effect due to a slipped coil. We therefore concluded that the number

of evoked MEPs can serve as a valid readout parameter for cortical excitability despite the absent effect on MEP size or amplitude.

2.4.2 Aim and hypotheses of our study

Backed by these results that 1 Hz rTMS indicates to decrease cortical excitability, we now have something to which we can compare our possible rTMS effects on FC in our ensuing experiment. Our study is based on the following two hypotheses:

1. If rTMS changes cortical excitability, it should also change spontaneous fluctuations of neural activity in the targeted area.

2. This localized alteration should lead to downstream changes of regions that are functionally connected, i.e., we should see changes in FC between the targeted area and other functionally connected regions (seed-based FC changes).

For the reasons mentioned above, we selected the motor system as our network of interest. We chose the left primary motor cortex (M1) as our rTMS stimulation site and an rTMS frequency of 1 Hz. In order to capture possible rTMS-induced changes in FC with fMRI, we employed a pre- versus post-stimulation approach.

3 METHODS

3.1 Participants

14 healthy participants (7 female, 7 male) between the age of 20 and 30 years (mean: 24.71; standard deviation: 3.43) without any known pre-existing neurological or psychiatric conditions, without current medication and without any contraindication for MRI took part in the experiment. Subjects provided written informed consent in advance and received financial compensation afterwards. The study was approved by the local ethics committee of the University of Regensburg and complied with the declaration of Helsinki.

3.2 Experimental protocol

The experiment encompassed three sections: a pre-MRI session, repetitive transcranial magnetic stimulation (rTMS) and a post-MRI session. In the pre-session, we acquired a high-resolution T1-weighted structural scan, a resting-state scan (rs-scan), a sequence with a finger-tapping task for determining the rTMS stimulation site and a diffusion-weighted imaging scan (DWI). Following these scans, participants underwent 30 minutes of 1 Hz rTMS in a room adjacent to the scanner. After rTMS, the subjects were immediately brought back into the scanner for a post-rTMS rs-scan. The time between the end of rTMS and the beginning of the subsequent rs-scan was on average 172.36 s with a standard deviation of 16.75 s. Additional information on subjects, such as their associated timings, can be found in the table below.

Subject #	Sex	Age	RMT (%)	Stim (%)	tt-Return (s)
1	male	30	52	57	135
2	female	29	56	61	170
3	female	29	50	55	155
4	male	28	51	56	171
5	female	28	49	53	183
6	male	24	45	50	162
7	female	24	45	45*	172
8	male	24	57	62	195
9	male	24	50	55	172
10	female	22	58	63	205
11	male	21	58	64**	170
12	male	22	42	45***	182
13	female	21	48	53	175
14	female	20	58	64	166
MEAN	**-**	**24.71**	**51.36**	**55.93**	**172.36**
SD	**-**	**3.43**	**5.37**	**6.43**	**16.75**

Table 1. *This table includes subject characteristics as well as their respective stimulation parameters and timings during the experiment.*
RMT (%) = resting motor threshold (in % of maximum stimulator output). Stim (%) = stimulation intensity (in % of maximum stimulator output). tt-Return (s) = time-to-return (end of rTMS until begin of scanning in seconds). SD = standard deviation.
** Participant 7 felt discomfort toward stimulation above 100 % of RMT, thus we used the RMT for stimulation intensity.*
*** Although participant 11 showed a very strong twitching of his index finger to the TMS stimuli, no MEPs were observed. Despite this discordance we decided to include this subject due to obvious strong physical reactions.*
**** Participant 12's reaction to TMS with his individual RMT-intensity was extreme, thus we stimulated with less than 110 % of RMT to reduce head movement.*
Table adapted with the consent of Philipp Seidel, for original see Seidel, 2019.

3.3 MRI data acquisition

For our experiment we used the research MRI of the University of Regensburg, a 3T Siemens Prisma (Siemens Healthineers, Erlangen) scanner with a 64-channel head coil (Siemens Healthineers, Erlangen), located at the district hospital Regensburg.

To minimize the participants' head movements, their heads were stabilized with foam pads. Because of the scanner's high sound level, we provided the subjects with earplugs. Furthermore, we measured participants' heart and breathing rates with a pulse oximeter and a breathing belt, respectively.

The first scan acquired in the pre-stimulation session was a T1-weighted structural MPRAGE (Magnetization Prepared Rapid Gradient Echo) scan, which we used for later co-registration with the functional data and for 3D reconstruction for neuronavigation (see section 3.4). Sequence details are listed in table 2.

Next, we instructed our subjects to close their eyes, let their mind wander, and try not to fall asleep during a 22-minute T2*-weighted echoplanar imaging (EPI) resting-state sequence (Auerbach et al., 2013).

The following finger-tapping scan (task-based EPI sequence) was required as a localizer for determining each individual's stimulation site (left M1) and therefore the seed region of interest (ROI) for the seed-based analysis. We therefore told the participants to clearly tap their either right or left thumb and index finger in a rough 2 Hz pace according to the visual cue ("RIGHT INDEX FINGER" or "LEFT INDEX FINGER") on the screen placed at the head end of the scanner bore, which participants saw via a mirror on the head coil. A central fixation cross on the display indicated the end of a finger tapping block. The task was split into eight blocks, each composed of 16 s of fixation cross followed by 16 s of right- or left-hand finger tapping. After the last block we added 16 s of fixation to ensure that the BOLD-signal of the last block could get back to baseline. Four blocks of right and four blocks of left index finger were randomized for each subject. For the presentation of this task we used the software A simple framework (Schwarzbach, 2011), which is based on psychophysics toolbox (Brainard, 1997) for MATLAB.

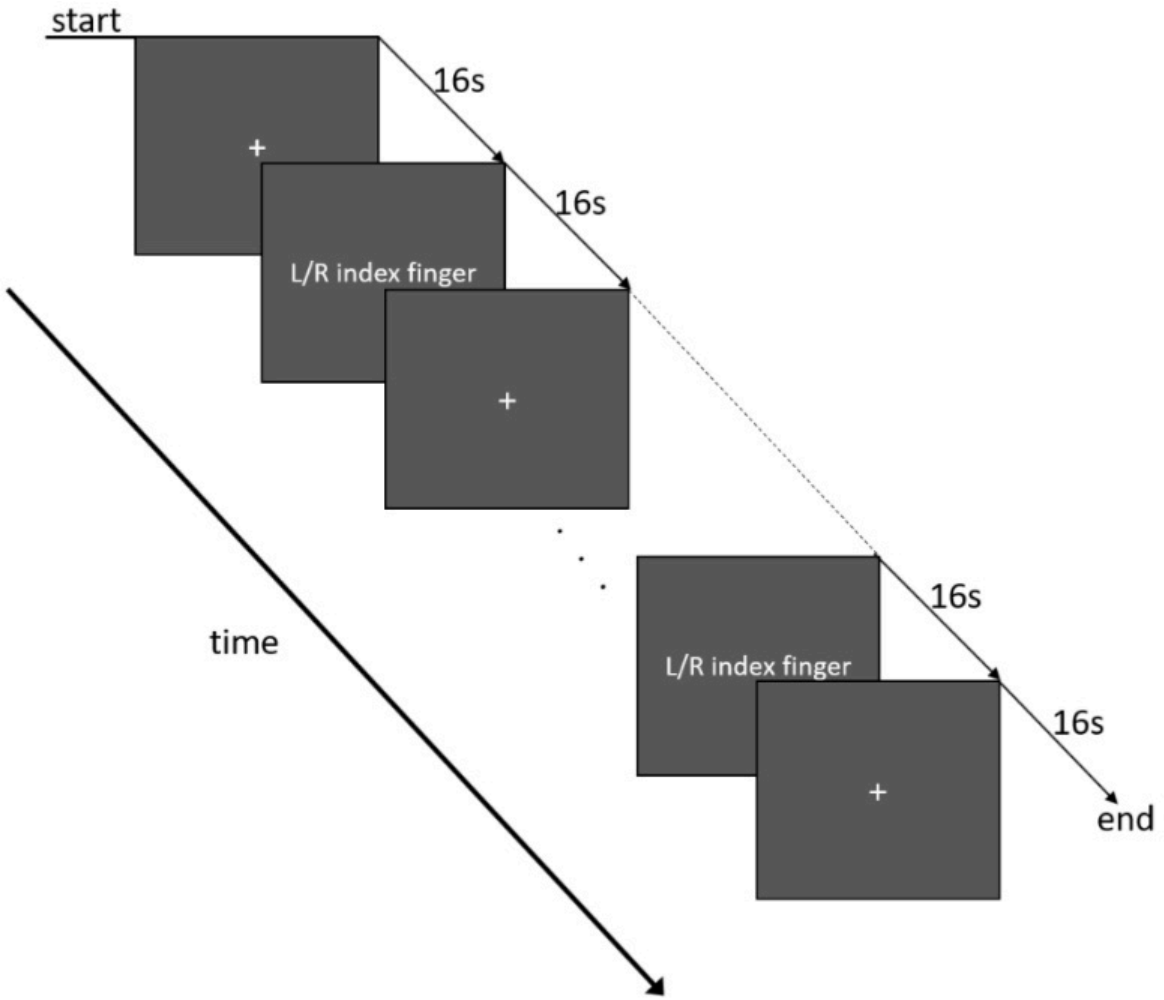

Figure 2. *In order to find the individual location of primary motor cortex, each participant performed a finger-tapping-task. Four blocks of left and four blocks of right finger tapping (16 s per block) were conducted in random order, always alternated by 16 s of a fixation cross.*
Figure used with the consent of Philipp Seidel, for original see Seidel, 2019.

The last scans in the pre-stimulation session were multiple diffusion-weighted imaging (DWI) sequences, which we acquired for a different project.

After the 1 Hz rTMS we performed another 22-minute T2*-weighted EPI resting-state scan with the same parameters and instructions as in the pre-session.

Further information about the scanning parameters is listed in the following table.

		MRI sequence		
		Structural	rs-fMRI	task-fMRI
Sequence parameters	Repetition time (TR) in ms	1910	1000	2000
	Echo time (TE) in ms	3.67	30	30
	Flip angel in degrees	9	60	75
	Voxel size (isotropic) in mm	1	3	2
	Field of view in mm²	250	192	192
	Acquisition matrix	256 x 256	64 x 64	96 x 96
	Number of slices	160	44	46
	Total number of volumes	1	1320	144
	Multiband acceleration factor	-	4	2
	Slice acceleration factor	2	-	-
	Receiver bandwidth (Hz/Px)	180	2368	2368
	Partial fourier	-	-	7/8

Table 2. *Depicted here are the most important parameters of the three MRI sequences we performed (structural, rs-fMRI and task-fMRI).*
Table adapted with the consent of Philipp Seidel, for original see Seidel, 2019.

3.4 Neuronavigation

Our experiment required the precise positioning of the TMS coil above the primary motor cortex (M1). In order to optimally find this defined brain region in each individual, we used a neuronavigation system. Neuronavigation enables real-time tracking of the TMS coil position in relation to the brain area to be stimulated. Previous work has shown that neuronavigation-guided TMS using an individual functional MRI scan may increase statistical power (Sack et al., 2009).

The system we used is called BrainVoyager TMS Neuronavigator (Brain Innovation BV, The Netherlands). It consists of the BrainVoyager QX and the BrainVoyager TMS Neuronavigator software (both Brain Innovation BV, The Netherlands) as well as the corresponding hardware CMS20 (Zebris Medical GmbH, Germany), an ultrasound-based position measurement system.

3.4.1 Preparation

Neuronavigation needs a virtual 3D representation of the participant's head and brain, based on an acquired structural T1 scan. By use of BrainVoyager QX, we first removed

the non-brain tissue to get a surface reconstruction of the brain with its gyri and sulci. Second, we created a head mesh, a reconstruction of the head surface. After making the head mesh transparent, we overlaid the 3D-reconstructed brain and head. In the last step, we projected the statistical map from the finger tapping task onto the reconstructed brain and used a threshold such that we saw a patch of high statistical scores corresponding to right finger tapping. The final 3D reconstruction was loaded into the BrainVoyager TMS Neuronavigator software.

3.4.2 Application

After the participants had settled comfortably in a special TMS chair, they were equipped with three little ultrasound transmitters at the face, two at the forehead and one on the nasal bridge. Furthermore, we attached four ultrasound transmitters to the handle of the TMS coil, which were continuously transmitting ultrasound waves picked up by a receiver in front of the participant. For co-registration of the head it is necessary to choose anatomical landmarks as reference points, both in virtuality and reality. With a Digitizer Pen (equipped with two ultrasound transmitters) we tagged the spatial coordinates of the nasion and both incisurae intertragicae of the ears as previously determined in the 3D head reconstruction. Afterwards, the real and the virtual TMS coil needed to be co-registered with five reference points on it in a similar manner.

Once the co-registration was completed, we placed the coil at the participant's head and were now able to watch the virtual coil moving in real time on the screen while moving it in reality. A virtual beam, perpendicular to the coil, indicated the magnetic field of the TMS coil. Using a positioning arm we adjusted the coil in such a way that the beam was optimally hitting our searched stimulation site, the left sided M1.

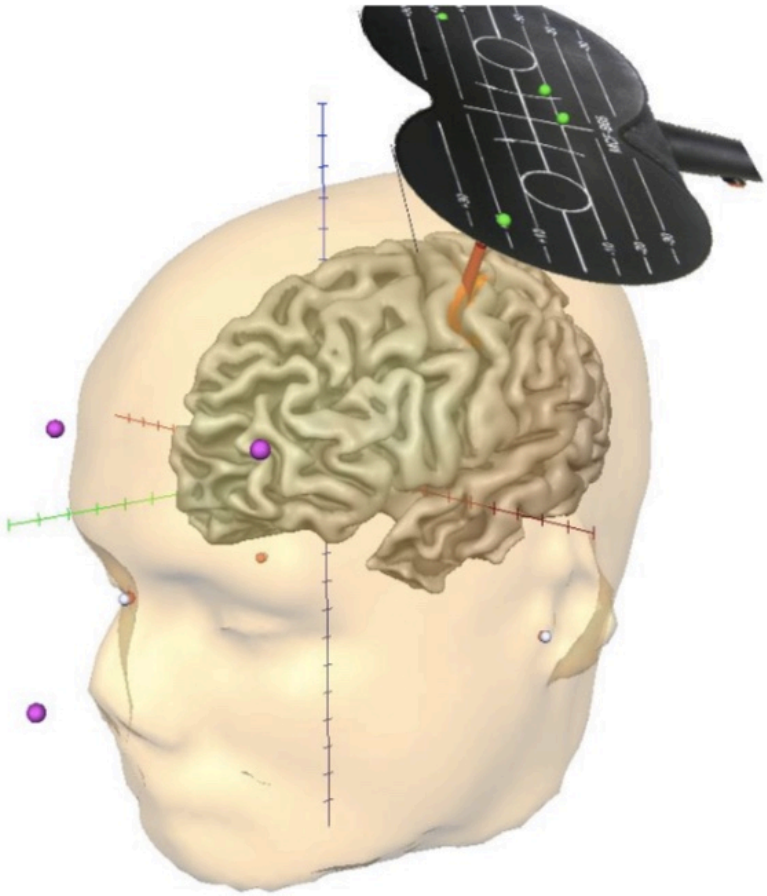

Figure 3. *This picture shows the 3D reconstruction of a participant's head and brain with the neuronavigated TMS coil placed over the functionally identified left primary motor cortex (orange region). The grey dots on the head mesh are reference points that set up the virtual individual's spatial coordinate system. Their real-world equivalent is determined with a digitizing pen (orange dots). The coordinate system of the virtual and real head is then co-registered (overlay of grey and orange dots). The purple dots represent the ultrasound senders, which are attached to the participant's face and are continuously transmitting ultrasound waves to a respective receiver. After co-registration, the recorded information from the ultrasound transmitters enables the software to detect the head's real-time location in space. Furthermore, the TMS coil is co-registered in the same way: reference points are specified in virtuality and reality (again with the digitizing pen; green dots), which are then overlaid. The stimulation coil is also equipped with ultrasound transmitters, thus the location of the coil can be tracked in real-time. This allows the optimal positioning of the coil and hence an optimal stimulation.*
Figure used with the consent of Philipp Seidel, for original see Seidel, 2019.

3.5 Repetitive transcranial magnetic stimulation (rTMS)

For rTMS we used a MagPro X100 (Medtronic, Denmark) TMS device and an MCF-B65 (Medtronic, Dublin, Ireland) figure-of-eight coil. In order to detect the MEPs, we attached four surface electrodes to a participant's right hand: one on the muscle belly and one on the tendon insertion of the first dorsal interosseous muscle as well as two reference electrodes on the radial and ulnar styloid processes.

Before the actual stimulation, we identified each subject's individual resting motor threshold (RMT) by applying single TMS pulses with varying intensity to the left primary

motor cortex (M1) and simultaneously counting the elicited MEPs. Based on recommendations of Rossini and colleagues, we defined the RMT as the minimum pulse intensity necessary to elicit MEPs with a peak-to-peak amplitude of at least 50 μV in 4 out of 8 consecutive pulses (Rossini et al., 1994). Following Eldaief et al. (2011), we likewise chose a pulse intensity of 110% of each participant's individual RMT and applied 1800 pulses of 1 Hz rTMS over the course of 30 minutes. Furthermore, we followed the common safety guidelines for rTMS (Rossi et al., 2009). The respective participants' stimulation parameters can be discerned in Table 1 in section 3.2.

3.6 Preprocessing of the resting-state data

FC analysis, in particular of resting-state data, is eminently vulnerable to structured noise. The reason is that FC methods aim to find similarities in the BOLD signal between different brain regions and many kinds of noise may imitate such similarities. For example, a deep breath or pulsating intracranial vessels can affect multiple brain areas at the same time and would hence mistakenly be identified as FC. In order to avoid such noise driving our findings, we aimed to remove as much structured noise as possible with preprocessing, before proceeding with the main analysis.

For preprocessing and analyzing our fMRI data we used the FMRIB Software Library (FSL), version 6.0.0 (Oxford Centre for Functional MRI of the Brain, Oxford, UK; Smith et al., 2004) as well as the CoSMoMVPA toolbox (Oosterhof et al., 2016) for MATLAB (The MathWorks, Inc., Natick, MA, USA).

3.6.1 Conventional preprocessing steps

After converting the data from DICOM to NifTI format using the tool dcm2niix as part of the program MRIcroGL (Chris Rorden, McCausland Center for Brain Imaging, University of South Carolina), we carried out structural preprocessing with FSL, to obtain a high-resolution structural brain as reference for each subject. This included bias-field correction (using FAST, Zhang et al., 2001), brain extraction (using BET, Smith, 2002), tissue-type segmentation (cerebrospinal fluid, gray matter, and white matter; using FAST, Zhang et al., 2001), and non-linear image registration (using FNIRT, Andersson et al., 2007) to the Montreal Neurological Institute (MNI) 2 mm standard brain.

For the subsequent preprocessing of our functional data we used FSL's FMRI Expert Analysis Tool (FEAT, Woolrich et al., 2001). First, because of unavoidable head

movements of the participants during scanning, it carries out a motion correction by using the middle brain volume as reference volume, to which all other volumes are spatially registered (6 degrees of freedom (DOF); using the tool MCFLIRT (Jenkinson et al., 2002)). Next, we performed slice-timing correction to account for the small differences in the acquisition time of the slices. We further carried out brain extraction (again using BET, Smith, 2002) and applied high-pass temporal filtering (cutoff = 100 s) which aims to eliminate the very low frequencies (< 0.01 Hz) from the data. This drift – a very slow change in the baseline BOLD signal over time – is attributed to scanner-related noise. We then applied a 5 mm full-width-at-half-maximum (FWHM) Gaussian filter for spatial smoothing. In a final step, using FLIRT (Jenkinson & Smith, 2001) each participant's functional image was linearly co-registered to its respective structural scan (6 DOF) and then, using FNIRT, non-linearly co-registered to the MNI 2 mm standard brain (12 DOF).

3.6.2 Additional noise reduction using independent component analysis

For further noise reduction after the conventional preprocessing steps we employed an *independent component analysis* (ICA). This data-driven approach decomposes the whole-brain resting-state BOLD dataset into several spatially structured components. Some of the components represent structured noise such as motion, blood vessels, cerebrospinal fluid or other acquisition-related artifacts (Griffanti et al., 2014). They can be identified and then removed from the data.

The tool FSL provides for automatic classification and removal of motion-related ICA components is called ICA-AROMA (ICA-based Automatic Removal Of Motion Artifacts; Pruim et al., 2015). It includes the decomposition into independent components using MELODIC (Beckmann & Smith, 2004), automatic component classification and data denoising. Removing the noise components from the data can either be carried out in an aggressive or a non-aggressive manner. The aggressive approach removes all components that are not clearly classified as signal, risking the loss of some components with mixed proportions of signal and noise. The more conservative non-aggressive approach on the other hand keeps all components that show any signal even if this might lead to some more noise in the data. In order to preserve as much signal as possible we employed non-aggressive denoising. Lastly, the denoised data were warped to MNI 2 mm standard space.

3.6.3 Splitting the data

Since 1 Hz rTMS is expected to decrease the number of elicited MEPs during the first half of the post-rTMS run, we split each subject's pre- and post-rTMS run into two halves (pre1, pre2, post1, post2). With a total scanning duration of 22 minutes per run, each part thus lasts 11 minutes.

3.7 Seed-based correlation analysis

To see if 1 Hz rTMS applied to left M1 changes the connectivity between left M1 and the rest of the brain, we first defined a seed region (= region of interest, ROI) in the stimulated area. We therefore identified the voxel with the maximum z-score (in the contrast right vs. left finger tapping from each participant's task-fMRI) and generated a binary spherical ROI with a radius of 3 (in voxel size) around it. Using this binary mask, we extracted the BOLD time courses of the resting state data and averaged them over all voxels of the seed region. To see how this averaged seed time course relates to the rest of the brain, we computed the Pearson correlation coefficients between the seed time course and the time courses of all other voxels for both parts of the baseline (pre) and TMS (post) condition. After Fisher z-transforming the correlation maps we investigated the difference between the two conditions using a paired t-test ("pre1 - post1" and "pre2 - post2").

3.7.1 Correcting for multiple comparisons using TFCE

Voxel-wise analysis of brain images requires a high number of statistical tests and therefore runs the risk of a high number of false positives. To reduce the likelihood of reporting false positives, the resulting statistical maps must be corrected for multiple comparisons (Bennett et al., 2009). Commonly used correction methods threshold the statistical maps either in a voxel-based (e.g., Family-wise Error rate correction or False Discovery Rate correction) or in a cluster-based way (Friston et al., 1994). Voxel-based thresholding searches for the maximum statistic value, whereas the cluster-based thresholding looks for the spatial extent of contiguous voxels, hence the maximum size of a cluster. Both described methods only focus on one dimension, either maximum statistical value or maximum cluster size. In the case of voxel-based correction, a cluster with relatively low statistical values may be eliminated despite having a large spatial extent. In the case of cluster-based correction, a small cluster may be excluded despite having strong statistical values. In contrast, we employed the *Threshold-Free*

Cluster Enhancement (TFCE, Smith & Nichols, 2009) correction because it allows to consider both the maximum statistical value and the maximum cluster size. The TFCE statistic uses unthresholded statistical maps and computes each voxel's individual so-called TFCE-score based on the values of the surrounding voxels. The result is that isolated high-score voxels are down-weighted and relatively low-score voxels in large clusters are up-weighted or, as the method's name implies, enhanced. Hence, we computed TFCE-scores for our t-statistic.

Since the calculated TFCE-scores do not follow a known parametric distribution, they must be turned into p-values using non-parametric statistics. In our case, we used permutation testing, which uses the data itself to generate a null distribution under the assumption that the null hypothesis is true (i.e., there is no difference in FC between pre- and post-session). This distribution is constructed by randomly mixing up (permuting) the subjects many times, such that they don't correspond to their labels (pre/post) anymore. If the null hypothesis were true and rTMS did not influence FC, it would not matter whether a subject is assigned to the pre- or post-session. Hence, we performed 5000 iterations of a Monte Carlo resampling procedure using the CoSMoMVPA toolbox (Oosterhof et al., 2016).

3.8 Dual regression analysis with respect to template maps

Furthermore, we wanted to find out, if 1 Hz rTMS applied to M1 as part of a functional network caused changes in the sensorimotor network itself or in other functional networks. We therefore chose a method called *dual regression analysis* (Beckmann et al., 2009; Nickerson et al., 2017), which allowed us to investigate differences in the structure of these networks before and after the stimulation. As the name suggests, the approach consists of two subsequent multiple regression analyses. The model input for the first stage consisted of each subject's preprocessed functional dataset (pre/post) as well as the ten ICA-based functional network maps from S. M. Smith et al. (2009) respectively an updated version from Tahedl & Schwarzbach (2023).

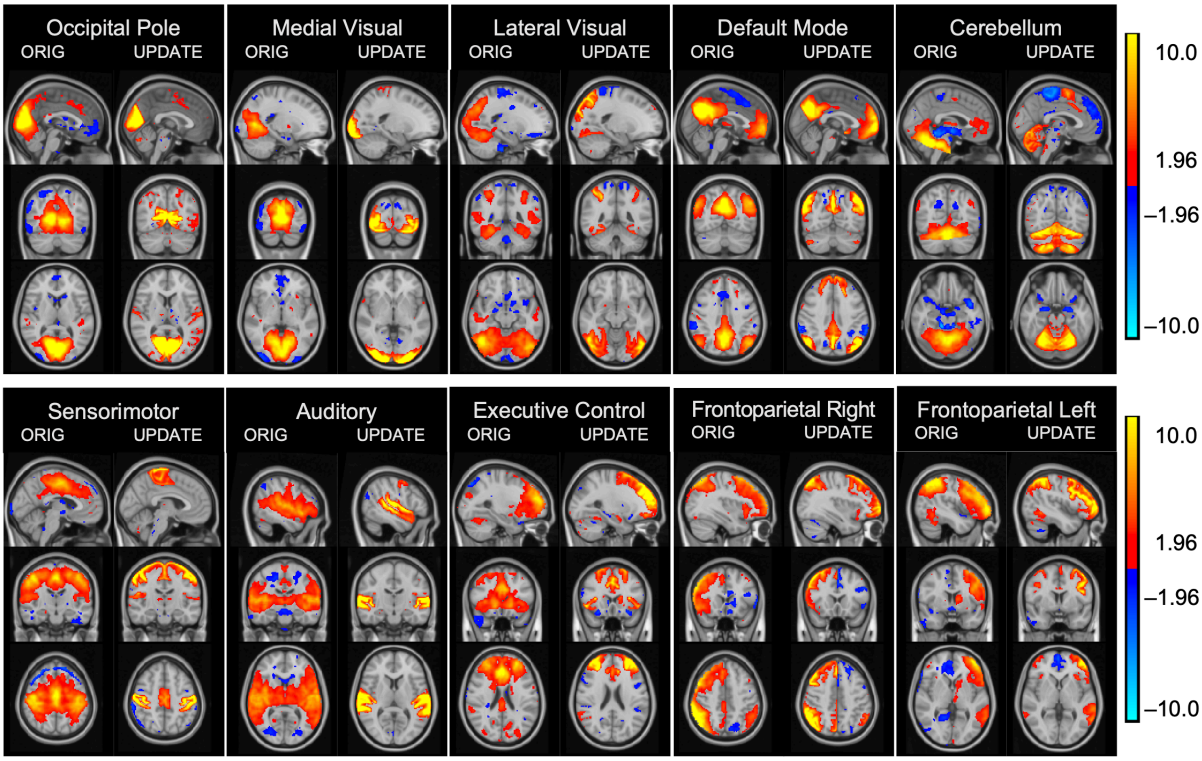

Figure 4. *The graphic shows a comparison between the ten original templates (ICA spatial maps) by S. M. Smith et al. (2009) (left column in each panel) and the updated templates by Tahedl & Schwarzbach (2023) (right column in each panel). The updated atlas version provides a better spatial alignment with the MNI152 brain template. Depicted are z-scored maps with a range from z = 1.96 to 10, positive and negative.*
Figure reproduced under a CC-BY-NC-ND 4.0 license (https://creativecommons.org/licenses/by-nc-nd/4.0/), for original see Figure 3 of Tahedl & Schwarzbach, 2023.

These template maps were used as spatial regressors to find the time courses associated with the voxels in these maps. In the second stage, we used the time courses obtained from the first stage as temporal regressors to find the voxels in each subject's preprocessed data that were associated with these time courses. This resulted in ten spatial maps for each subject and run. The dual regression was done separately for both part 1 and part 2.

Afterwards, we compared the spatial maps across the two groups of subjects in order to identify group differences for "pre1 - post1" and "pre2 - post2". The group-level analysis is a voxel wise procedure, so we computed t-statistics for each voxel. Since this resulted in a large number of statistical tests, we had to correct for multiple comparisons again using TFCE and permutation testing as explained in the previous chapter. The resulting TFCE corrected z-maps were thresholded at z = 1.96 which corresponds to an $\alpha = 0.05$.

3.9 Localizing the altered brain areas

We obtained a preliminary localization of the altered brain regions from a comparison with the Harvard-Oxford Cortical Structural Atlas (Desikan et al., 2006).

For a more detailed breakdown of the altered regions in the thalamus, we applied the In-vivo probabilistic atlas of human thalamic nuclei by Najdenovska et al. (2018), a probabilistic atlas of anatomical subparts of the thalamus. Based on a dataset of the Human Connectome Project (Van Essen et al., 2012) Najdenovska et al. define 14 thalamic nuclei, 7 per hemisphere, using an automatic diffusion-based clustering method (Battistella et al., 2017). We superimposed this atlas on our results and compared which thalamic nuclear areas our clusters overlapped with.

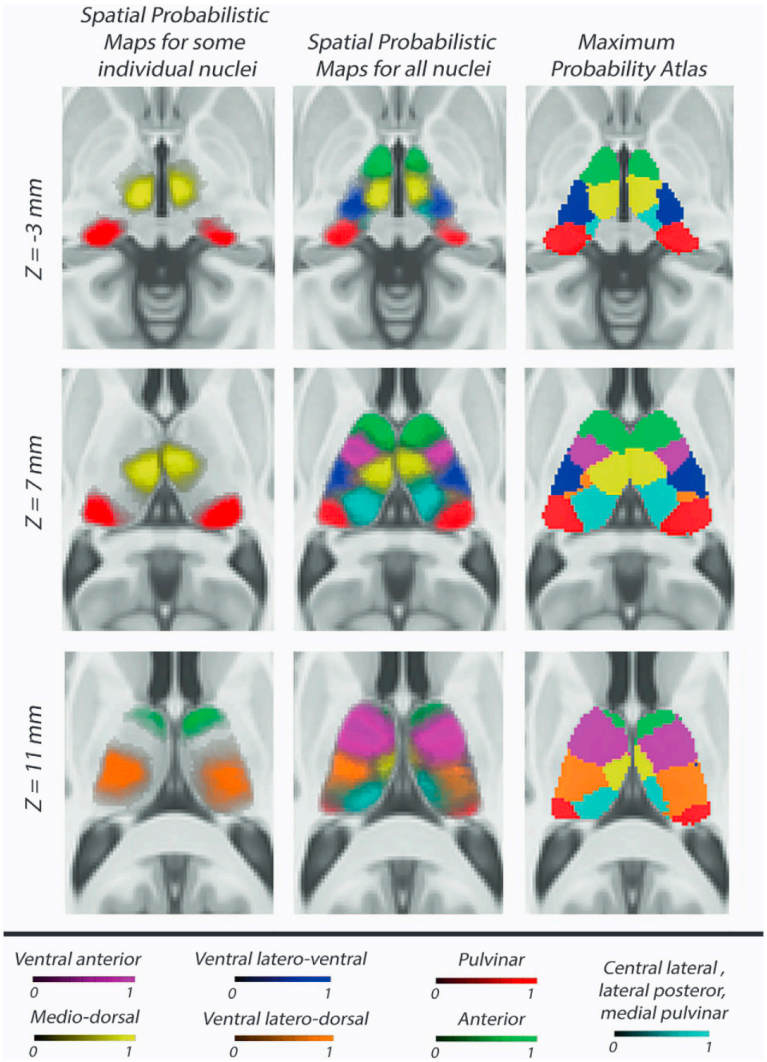

Figure 5. *The In-vivo probabilistic atlas of human thalamic nuclei by Najdenovska et al. (2018) provides a segmentation of human thalamus in 7 nuclear areas per hemisphere, based on diffusion-weighted MRI. Depicted are three exemplary slices, which show the overlay with the spatial probabilistic maps (first and second column) and the maximum probability atlas (third column).*
Figure reproduced under a CC-BY 4.0 license (http://creativecommons.org/licenses/by/4.0/), for original see Figure 2 of Najdenovska et al., 2018.

4 RESULTS

4.1 Seed-based correlation analysis: No change in FC through 1 Hz rTMS found

This analysis did not reveal any significant changes in FC between the seed region M1 and the rest of the brain. Without correcting for multiple comparisons, we observed differences between the pre- and post-session in both part 1 (paired t-test; max $t(13) = 5.1323$, $p < 0.0001$) and part 2 (paired t-test; max $t(13) = 6.2910$, $p < 0.0001$). However, after TFCE correction with 5000 resampling iterations each, the results vanished (part 1: z-score = 0.3120, $p = 0.3775$; part 2: z-score = -0.8382, $p = 0.2010$).

4.2 Dual regression analysis: 1 Hz rTMS decreases FC between cerebellum and left thalamus

Out of the 10 independent components from the updated Tahedl atlas (Tahedl & Schwarzbach, 2023) one component – the cerebellar component – showed a significant change of FC with some brain regions during the first part of the run (paired t-test; max $t(13) = 7.6527$, $p < 0.0001$ uncorrected; z-score = 2.2904, $p = 0.0110$ TFCE corrected, 5000 iterations).

Thresholding the TFCE corrected “pre1 - post1” z-score map at an alpha level = 0.05 (i.e., $z = 1.96$) yielded 8 voxel clusters that exhibited decreased FC with the cerebellum in the first part of the run, i.e., in the first 11 minutes following 1 Hz rTMS. Recalling the definition of FC, this means that the time courses of voxels within the cerebellar component and the time courses of voxels within the 8 clusters showed a higher statistical similarity before 1 Hz rTMS than after. In the 11 minutes following stimulation the correlation of these time courses was lower than before stimulation. In other words, these brain regions temporarily (for about 11 minutes) lost part of their functional relationship.

The 8 clusters were all located in the left hemisphere, primarily in thalamus and white matter according to the Harvard-Oxford Cortical Structural Atlas (Desikan et al., 2006). The table below gives an overview of their locations within the brain.

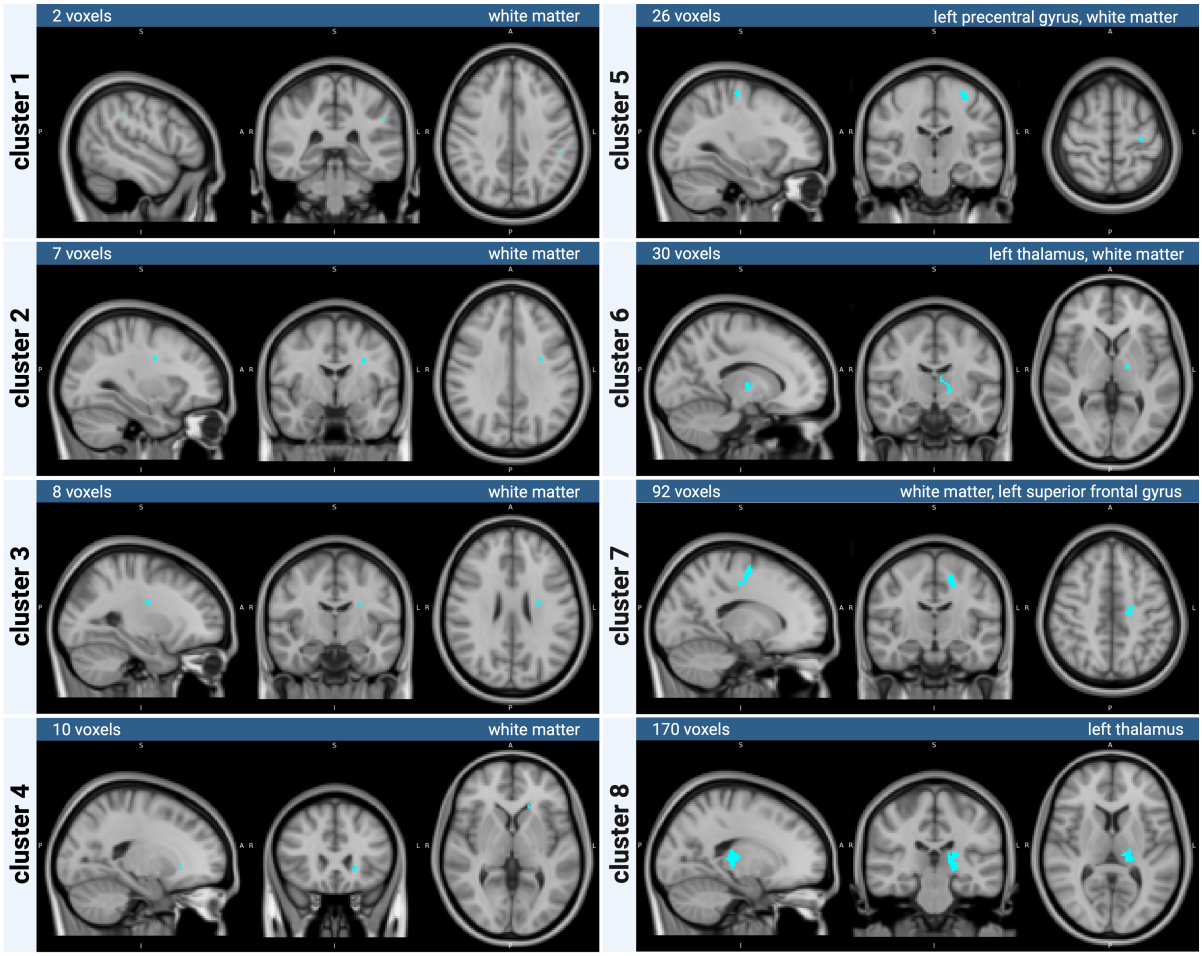

Figure 6. *The 8 clusters were mainly located in left cerebral white matter and left thalamus according to Harvard-Oxford Cortical Structural Atlas (Desikan et al., 2006).*
Figure created with BioRender.com.

Even though the location of clusters within white matter does not automatically mean that it is noise (see section 5.2.2), we focused on those clusters that we could clearly locate in subcortical or cortical gray matter. Special attention was paid to the 2 clusters that lay fully or partly in the left thalamus, cluster no. 6 and 8.

4.2.1 Localization of clusters located in the thalamus based on the thalamic nuclei atlas

The overlay with the thalamic nuclei atlas by Najdenovska et al. (2018) revealed that clusters no. 6 and 8 were predominantly located in the ventral nuclear group of thalamus. The ventral nuclei serve as a central relay station for sensorimotor functions, they are therefore also referred to as motor thalamus (Bosch-Bouju et al., 2013). According to the segmentation into 7 thalamic nuclear areas per hemisphere, the 2 clusters showed the following overlaps: cluster no. 6 was part of anterior, ventral anterior, and ventral latero-ventral nucleus, cluster no. 8 overlapped with pulvinar,

ventral latero-dorsal, central lateral/lateral posterior/medial pulvinar, and ventral latero-ventral nuclear areas. The following table provides an overview, extended by the best possible attribution of the thalamic nuclei areas to the internationally standardized nomenclature according to MeSH (Medical Subject Headings; Rogers, 1963).

	Thalamic nuclei atlas (Najdenovska)	MeSH (incl. abbreviation)
Cluster 6	Anterior Ventral anterior Ventral latero-ventral	Anterior Ventral anterior (VA) Ventral lateral (VL)
Cluster 8	Pulvinar Ventral latero-dorsal Central lateral, lateral posterior, medial pulvinar Ventral latero-ventral	Pulvinar Ventral posterolateral (VPL) Ventral posterolateral (VPL), ventral posteromedial (VPM), pulvinar Ventral lateral (VL)

Table 3. *After matching with the thalamic nuclei atlas, the 2 relevant thalamic clusters were shown to be located primarily in the ventral part of the thalamus. The table provides a comparison of the nomenclatures of the thalamic nuclei atlas (Najdenovska et al., 2018) and the internationally agreed MeSH (Medical Subject Headings; Rogers, 1963).*

The ventral thalamic nuclei are subdivided in ventral anterior, ventral lateral, ventral posterolateral and ventral posteromedial nucleus. They receive input from the basal ganglia, cerebellum, and different sensory pathways; their efferences largely lead to the sensory and motor cortex areas (Mai & Forutan, 2012). This is illustrated schematically in the following diagram.

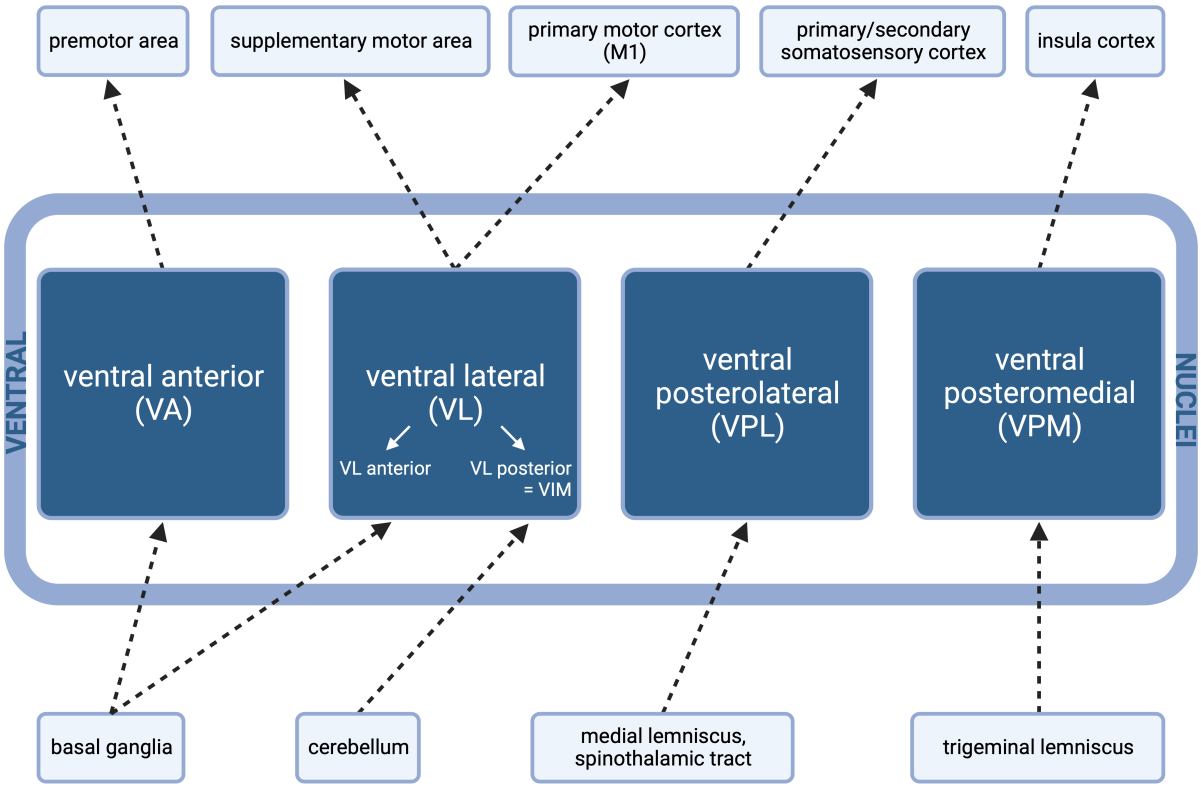

Figure 7. *This chart illustrates the subunits of the ventral nuclear group of human thalamus and their respective afferences and efferences. VIM = ventral intermediate nucleus.*
Figure created with BioRender.com.

5 DISCUSSION

In this work we investigated whether stimulating the left primary motor cortex (M1) with 1 Hz repetitive transcranial magnetic stimulation (rTMS) had an effect on resting-state functional connectivity (FC) as measured by functional magnetic resonance imaging (fMRI). To ensure that 1 Hz rTMS indeed induced a change in the excitability of M1, we used motor evoked potentials (MEPs) as objective readout to detect a potential relationship. The data from a pre-experiment (reference) showed that the number of MEPs was significantly reduced in the first 11 minutes after 1 Hz rTMS. We concluded that 1 Hz rTMS reduces the excitability of primary motor cortex.

Our 14 participants underwent 30 minutes of 1 Hz rTMS, framed by a 22-minute resting-state fMRI session before and after.

For the imaging data, we first performed a seed-based correlation analysis. Here, we extracted and correlated an average time course, before and after rTMS, of a region of interest within left M1 with all other voxels of the brain. This analysis did not yield any effects of 1 Hz rTMS.

Shifting the focus from left M1 to the entire brain, we then performed a dual regression analysis (Beckmann et al., 2009; Nickerson et al., 2017), which helped us to identify underlying functional networks in our data. In this two-step regression using the Tahedl atlas (Tahedl & Schwarzbach, 2023) as a spatial regressor we obtained 10 spatial maps per run and subject. The subsequent group statistics revealed a decrease of FC between the cerebellar component and 8 clusters in the left hemisphere in the first 11 minutes following 1 Hz rTMS. Because of their clear affiliation, we focused on the 2 clusters located in left thalamus, more specifically in the ventral nuclear group of thalamus.

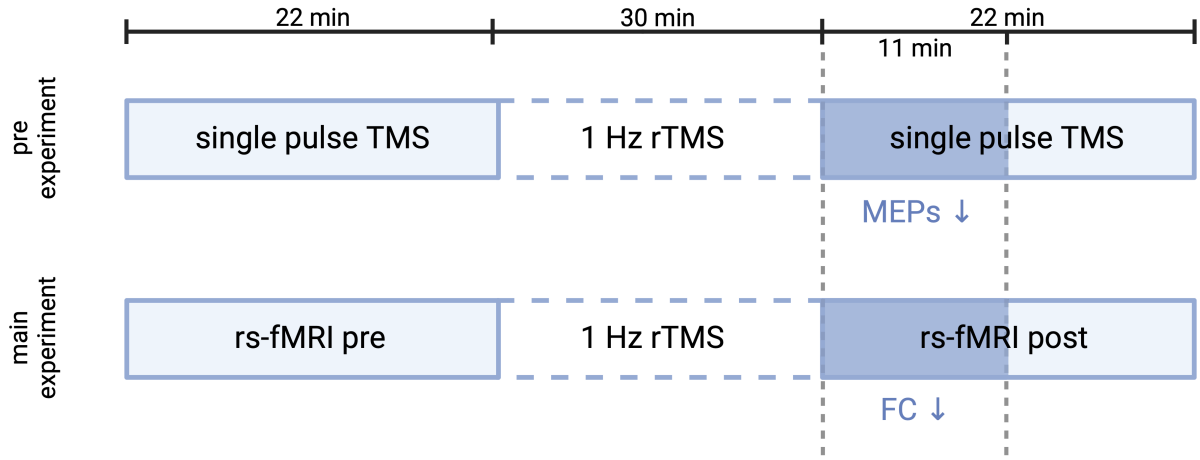

Figure 8. *This schematic diagram shows the experimental protocol of the pre and the main experiment as well as the main results. Noticeable is the observed parallel of decreased number of MEPs and decreased FC between cerebellum and 8 clusters in left hemisphere in the first 11 minutes following 1 Hz rTMS.*
Figure created with BioRender.com.

In the following, we will address the structural and functional relationship of the cerebellum, left thalamus, and left motor cortex, as well as provide an interpretation of the observed reduction of FC as a result of 1 Hz rTMS.

5.1 Tremor(network) as the linking element: an interpretive approach

5.1.1 Structural connection between cerebellum, thalamus, and motor cortex

Invasive fiber trajectory tracing studies in nonhuman primates (Asanuma et al., 1983; Yamamoto et al., 1983) and diffusion tensor imaging (DTI) studies in humans (Behrens et al., 2003; Kwon et al., 2011) have shown, that the motor thalamus shows strong structural connection with the ipsilateral motor cortex and contralateral cerebellum. The cerebello-thalamic tract as the largest cerebellar efference travels from cerebellum – essentially from the dentate nucleus – to the contralateral posterior ventrolateral nucleus (VL) of the thalamus. This posterior part of VL is also called ventral intermediate nucleus (VIM) following the Hassler nomenclature (Hassler, 1982) and is the most targeted structure for interventions in drug-refractory tremor. From there, the nerve cord projects to the premotor area and primary motor cortex commonly referred to as the *cerebello-thalamo-cortical pathway* (Allen & Tsukahara, 1974).

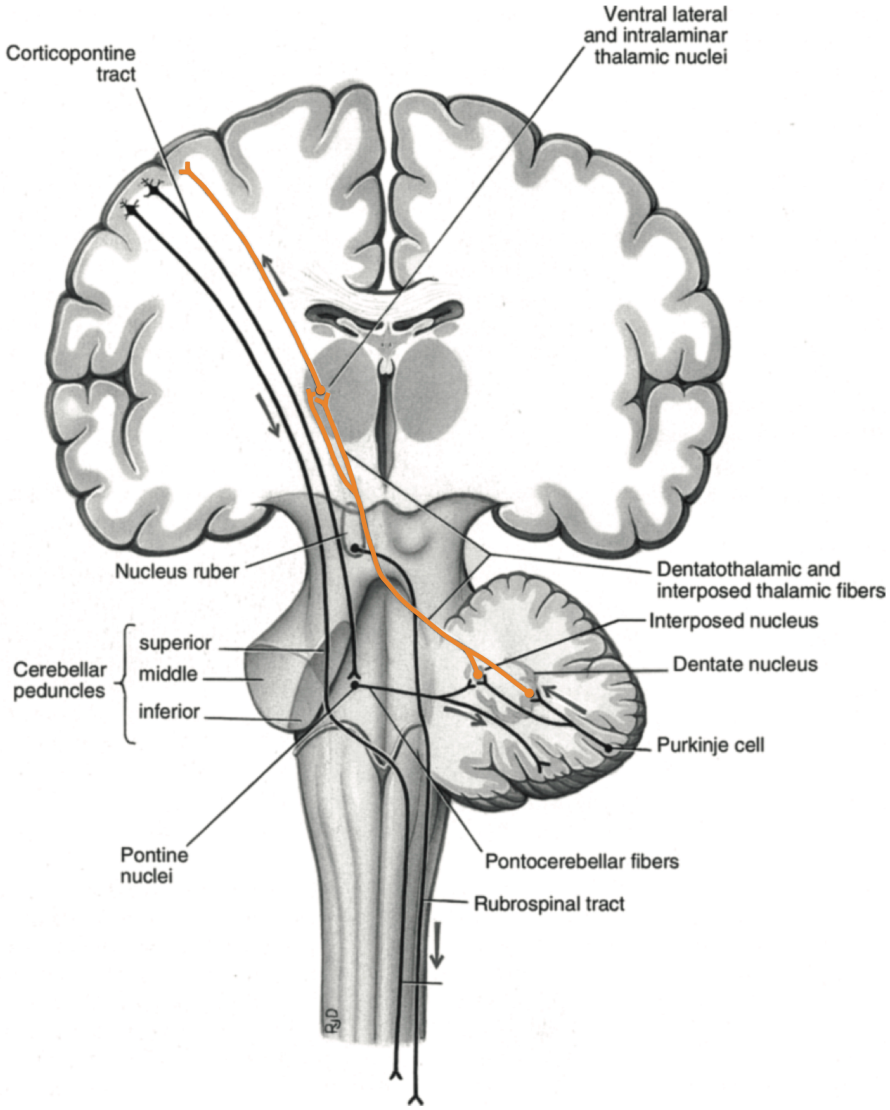

Figure 9. *The cerebello-thalamic tract as largest cerebellar efference is switched in the contralateral posterior ventrolateral nucleus of thalamus, to subsequently move on to the motor cortex. The entire cerebello-thalamo-cortical pathway is highlighted in orange.*
Figure reproduced and adapted with permission from Springer Nature (license number 5581430141144), for original see figure 18.4 of Noback, 2005.

5.1.2 Cerebello-thalamo-cortical pathway as main actor in generation of tremor

The cerebello-thalamo-cortical network is thought to play a key role in the pathophysiology as well as in the therapy of tremor-associated diseases – most notably essential tremor (ET) and tremor-dominant Parkinson's disease (PD) (Helmich et al., 2013). It is therefore also referred to as tremor network. ET is characterized by involuntary rhythmic trembling mostly of the upper extremities. It is an action/intention tremor or a postural tremor, it usually does not occur at rest. On the contrary, the tremor in Parkinson's disease is typically present at rest and decreases when performing activities. There is still little known about the tremor generation in these diseases and contradictory hypotheses are circulating.

For ET, the most widely supported theory is the gamma-aminobutyric acid (GABA) hypothesis, which assumes a dysregulation of the GABAergic neurotransmitter system. It involves a loss of cerebellar Purkinje cells, which results in lower release of inhibitory GABA and therefore leads to a disinhibition of deep cerebellar neurons, in particular the dentate nucleus. Due to their intrinsic spontaneous activity, the cells in dentate nucleus are considered pacemakers, which output neural activity to the contralateral ventrolateral thalamic nucleus. The missing suppression, in turn, leads to higher thalamo-cortical activity, which then manifests in tremors. This hypothesis is supported by several pathologic (Louis & Vonsattel, 2008; Paris-Robidas et al., 2012), electrophysiological (Mouginot & Gahwiler, 1996; Pinault & Deschênes, 1992; Uusisaari & Knöpfel, 2008) and neuroimaging studies (Bagepally et al., 2012; Boecker et al., 2010; Klein et al., 2011). A good overview of the GABA hypothesis can be found in Gironell's review (2014). At the same time, however, several post-mortem studies could not reveal a loss of Purkinje cells (Rajput et al., 2012; Symanski et al., 2014). In addition, most pharmacological studies have failed to show any benefit of GABA-influencing drugs in ET patients (Frima & Grünewald, 2006; Pahwa et al., 1998; Zesiewicz et al., 2013).

The pathophysiology of tremor in PD is even less well understood. Unlike the other two cardinal symptoms of PD, bradykinesia and rigor, tremor is in many cases not associated with dopamine deficiency due to degeneration of dopaminergic cells within substantia nigra (Hallett, 2012; Zach et al., 2020); this is especially true for the tremor at rest. It rather seems to originate from oscillating neural activity within the basal ganglia network and the cerebello-thalamo-cortical network. The globus pallidus, subthalamic nucleus and ventrolateral thalamus are discussed as possible pacemakers (Cagnan et al., 2014; Magnin et al., 2000; Pessiglione, 2005; Plenz & Kital, 1999) but, when considered individually, do not offer a conclusive explanation. The dimmer-switch-hypothesis (Helmich et al., 2011) tries to integrate the different concepts by proposing the basal ganglia as generator of tremor (“switch”) and the cerebello-thalamo-cortical circuit as modulator of tremor amplitude (“dimmer”).

Summarizing, ET and PD tremor are both related to impaired oscillatory activity in the cerebello-thalamo-cortical pathway, which might help explain the results in our experiment.

5.1.3 Cerebello-thalamo-cortical pathway as main target for therapeutic interventions in tremor

Despite many unresolved questions regarding tremor generation, the evidenced tremor reduction after various therapeutic interventions suggests a crucial involvement of the cerebello-thalamo-cortical network. The thalamic VIM, acting as a relay station connecting the contralateral cerebellum to ipsilateral motor cortex, proves to be an efficient and well-established target in the treatment of both ET and tremor in PD (Benabid et al., 1991). The posterior subthalamic area and the cerebello-thalamic tract are also suitable target structures (Blomstedt et al., 2009; Fenoy & Schiess, 2017; Groppa et al., 2014). Based on the respective pathophysiology, the subthalamic nucleus is primarily targeted in PD patients (Krack et al., 1997; Limousin et al., 1995). The different treatment methods include thalamotomy (Hassler & Riechert, 1954; Narabayashi, 1989; Ohye et al., 1982), deep-brain stimulation (DBS; Benabid et al., 1991), gamma-knife radiosurgery (Duma et al., 1998; Kondziolka et al., 2008) and transcranial MRI-guided focused ultrasound (Elias et al., 2013; Martin et al., 2009). DBS is the only one of these methods that works by stimulation rather than ablation, still the underlying mechanism is unknown. DBS appears to have multiple effects, including electrical, neurochemical, and neuroplastic. However, all above-mentioned treatments have a disruption of pathological oscillatory activity in common.

5.1.4 Tremor patients exhibit altered cerebello-thalamo-cortical FC

Several studies demonstrate alterations of FC within the cerebello-thalamo-cortical network for tremor patients. For example, Buijink (2015), Lenka (2017) and Nicoletti (2020) find increased FC between cerebellum and thalamus in ET patients compared to healthy controls, which may be an expression of overactivity in the cerebello-thalamic tract due to a disinhibition of cerebellar output activity. Fang (2016) and Tikoo (2020), on the other hand, observe decreased cerebello-thalamic FC. The degree of FC change correlates with tremor severity in each of the studies mentioned. Altered FC in ET patients is also identified between cerebellum and motor cortex (Neely et al., 2015; Tikoo et al., 2020). Changes in the tremor network are found both in resting-state as well as in task-based fMRI. In addition, Benito-León et al. (2015) even detected FC changes in resting-state networks in ET patients. Since ET usually occurs only when performing activities, these observations (even at rest) underscore the fundamental nature of the changes in the cerebello-thalamo-cortical network.

Besides, FC changes between cerebellum and thalamic VIM are also reported in tremor-dominant PD (J.-R. Zhang et al., 2016).

Although the direction of change is not consistent, the studies mentioned clearly show alterations of FC in tremor patients. Predominantly, the magnitude of FC change correlates with tremor severity. However, there is still uncertainty as to whether the FC changes are cause or consequence of the tremor.

5.1.5 Similarities between tremor patients and our experiment: an attempt at interpretation

After these preliminary considerations, in the following we will try to integrate and interpret the results of our experiment. It should be noted that all considerations and conclusions have a highly speculative character.

There are notable parallels between the neuronal characteristics of tremor patients and the findings in our healthy subjects. First, in both cases we observe involuntary muscle twitching of the extremities. Second, in both cases we find associated changes in FC within the cerebello-thalamo-cortical network. We therefore postulate that the muscle twitches of the right hand – elicited by rTMS on left M1 – simulate a temporary “artificial” tremor. Just as FC is permanently altered in tremor patients, FC changes temporarily in our healthy subjects.

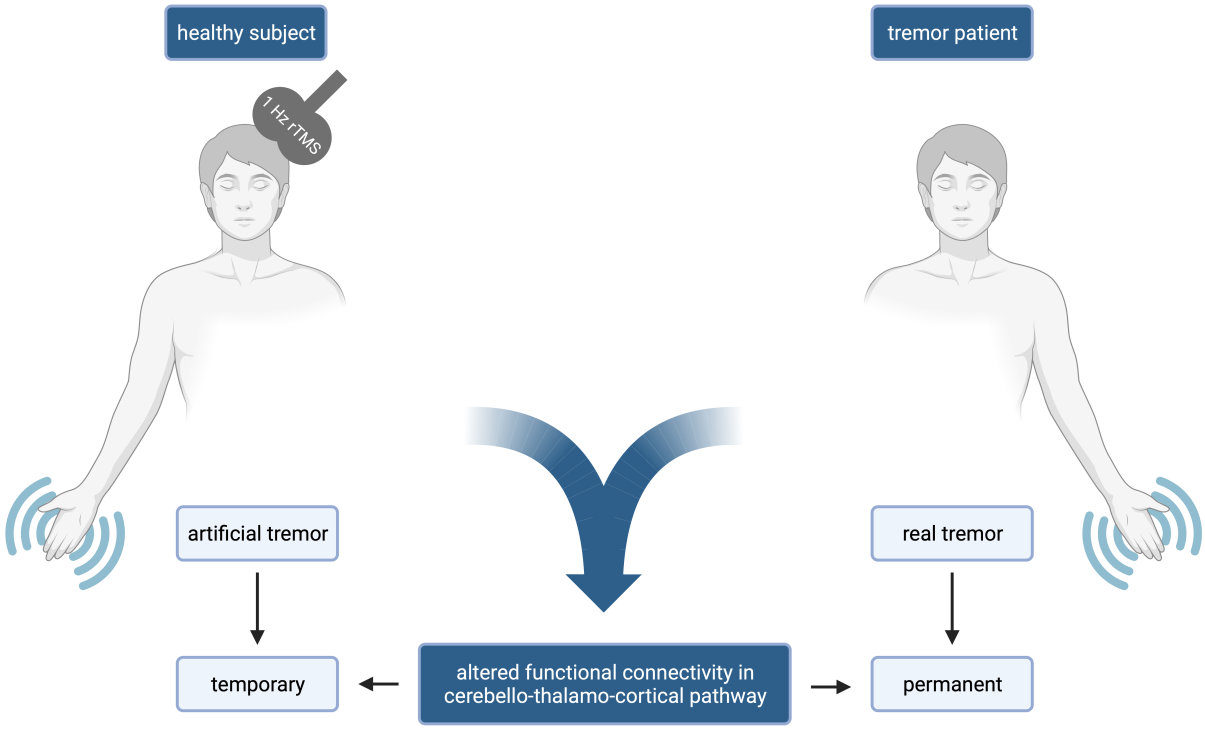

Figure 10. *Parallels between involuntary muscle twitching induced by 1 Hz rTMS in healthy subjects and tremor patients: Both "artificial" and "real" tremor exhibit alterations of FC within the cerebello-thalamo-cortical network, either temporarily or permanently.*
Figure created with BioRender.com.

To the extent that this comparison is permissible, so are the conclusions discussed below.

With regard to the GABA hypothesis as an explanation for the generation of ET, one could argue that the reduction of FC between cerebellum and left thalamus represents a compensatory mechanism towards the tremor artificially induced by rTMS. The impaired connectivity within the tremor network might be an expression of the brain's own counter regulation. Fittingly, the reduced number of MEPs might reflect subsequent tremor suppression. Since the literature has not yet settled on the direction of FC change in tremor diseases, we should not overstate the decrease in FC in our case, the important aspect is that a change was observed at all.

At the same time, rTMS might not only act as a trigger of the artificial tremor but might also modulate the tremor itself. As described in the introduction section, rTMS is thought to have the ability to alter cortical excitability as well as FC to remote brain areas. In our study, both cortical excitability and connectivity in the tremor network experienced a 11-minute modulation as a result of 1 Hz rTMS: the number of elicited MEPs as a possible measure of tremor severity as well as the FC between cerebellum and left thalamus were significantly reduced. Could this be indicative of 1 Hz rTMS

over M1 improving tremor symptoms in tremor patients through modulating FC in the cerebello-thalamo-cortical network?

A look at the literature once again reveals a heterogenous picture. Due to their favorable superficial location within the tremor circuit, the cerebellum and motor cortex (M1, premotor cortex, supplementary motor area) are the most common targets for TMS application in tremor patients. Like us, putative inhibitory protocols (≤1 Hz rTMS, continuous theta-burst stimulation) are mostly applied. Most authors use clinical tremor rating scales to evaluate tremor, other methods include accelerometry or MEP assessment. The effects found are rather inconclusive (Frey et al., 2021). Even under similar stimulation conditions – 1 Hz rTMS over the cerebellum for 5 days – some studies demonstrated improvement of tremor symptoms (Popa et al., 2013) and others did not (Olfati et al., 2020; Shin et al., 2019). One study, that applied 1 Hz rTMS over the pre-supplementary motor area for 15 days, found significant tremor suppression in ET patients compared to sham rTMS (Badran et al., 2016). The effect was detectable even after 8 weeks. In contrast, other studies were only able to demonstrate weak to no effects of inhibitory TMS on motor cortex areas (Chuang et al., 2014; Fricke et al., 2019; Hellriegel et al., 2012). However, a meta-analysis including 8 studies provides moderate evidence that non-invasive brain stimulation temporarily reduces tremor in ET patients (Kang & Cauraugh, 2017).

A large body of research studies the effect of rTMS on resting-state FC in general, but few studies address changes in the cerebello-thalamo-cortical circuit. Two studies applying inhibitory rTMS on left M1 observed an increase of FC involving cerebellum or thalamus (Bharath et al., 2015; Watanabe et al., 2014). The study by Popa already mentioned in the previous paragraph found a nearly restored FC between cerebellum and the cerebello-thalamo-cortical network after cerebellar 1 Hz rTMS in ET patients (Popa et al., 2013). To our knowledge, this is the first and so far only study that simultaneously investigated the effect of rTMS on tremor severity as well as FC changes within the tremor network in ET patients. The study design is therefore quite similar to ours.

In summary, there is some evidence that rTMS impacts tremor severity as well as FC in the cerebello-thalamo-cortical pathway. Our study provides further evidence of 1 Hz rTMS causing a reduction of MEPs, meaning an attenuation of the artificially produced tremor.

Importantly, our interpretation builds on the assumption that MEPs can be considered a valid measure of tremor severity. As outlined in the introduction section, MEPs are a measure of cortical excitability. A majority of studies have shown no significant difference in baseline excitability between ET patients and healthy individuals (e.g., Pinto et al., 2003; Romeo et al., 1998). Bologna et al. (2015) and Hellriegel et al. (2012) compared the effect of inhibitory continuous theta-burst stimulation (cTBS) on the excitability of M1 between ET patients and matched healthy controls. cTBS was applied on cerebellum or M1. Both studies found decreased cortical excitability – in terms of reduced MEP (amplitude) – in healthy subjects, though not in ET patients. At the same time, Hellriegel et al. (2012) observed a subclinical reduction of tremor severity (only in accelerometric recordings, not in clinical tremor rating scale) after cTBS on M1. This suggests that the effect on tremor severity may not be mediated by reduced cortical excitability. Thus, a reduction of MEPs probably cannot simply be equated with a reduction of tremor.

Beyond that, the effect of rTMS on the directionality of cortical excitability is also not entirely homogenous in literature. An extensive review by Fitzgerald et al. (2006) shows a wide range of partly even contradictory effects on cortical excitability depending on the use of rTMS parameters (frequency, pulse intensity, number of pulses). Moreover, it should be noted again that the majority of these studies use the amplitude of MEPs as a measure, not the number of MEPs as we do.

5.1.6 Future experiments

As described above, study results on non-invasive brain stimulation and associated FC changes in tremor patients as well as in healthy subjects are heterogeneous. To draw better conclusions in the future more systematic studies with larger sample sizes are required. Therefore, in the following we will point out possible suitable study designs.

In order to validate the postulation of an artificially produced tremor through 1 Hz rTMS in our participants, we would add a second group of subjects to our experiment. This group would consist of people with “real” tremor symptoms (e.g., ET patients), which would be compared to the already existing group of healthy subjects with induced “artificial” tremor. Can the reduced FC between cerebellum and left thalamus also be detected in tremor patients? Or do we find other FC abnormalities within the tremor network which could indicate a disturbed counter-regulation? How does the tremor

behave? Even better insight could be gained if the tremor patients also underwent the pre-experiment to find out how cortical excitability is changed in them by 1 Hz rTMS.

Further experiments could also involve possible modulation of tremor in respective patients. What influence do different frequencies have on tremor severity (measured by accelerometry or clinical tremor rating scale)? If inhibitory protocols seem to attenuate tremor as in several studies mentioned, do excitatory protocols (e.g., 20 Hz rTMS) lead to tremor enhancement? Would this induce a counter-regulation in the tremor network in terms of altered FC with consequent tremor attenuation (as a kind of desensitization)? The same experiment could also allow to study the effect of different frequencies on cortical excitability (measured by MEPs). Can the results of Hellriegel et al. (2012) – decreased cortical excitability in healthy subjects but not in ET patients following inhibitory protocol of rTMS – be replicated?

A further possible experiment relates to the effects of physiological shivering (e.g., during freezing) on FC in the tremor network. To trigger the tremor, the subjects would only have to lie lightly clothed in the MRI scanner. Would these likewise involuntary muscle twitches cause FC changes similar to those in our study?

5.2 Various further aspects

In addition to the above interpretation of our results, we would like to mention several other aspects that have not been addressed so far.

5.2.1 FC alterations in the cerebellum as a possible expression of neuroplasticity

There seems to be evidence that changes of FC might be an expression of the brain's capability to learn and adapt, also known as neuroplasticity. One example gives the study of Tahedl et al. (2022), where they investigated functional brain networks in patients with multiple sclerosis, using an analogous approach to ours (rs-fMRI, dual regression with the same template networks from Tahedl & Schwarzbach (2023)). The authors found alterations of FC (increasing and decreasing) between the cerebellar network and a set of other brain networks between the first clinical episode and remission. These changes were irrespective of severity of clinical symptoms and of the patients' lesion load in white matter. They suggest that the altered FC might be a compensatory mechanism of the cerebellar network to make up for the structural lesions in white matter caused by multiple sclerosis.

There is now a noticeable relation between Tahedl's results and ours: in both studies, it is the cerebellum to change its FC with other brain areas (in our study thalamus), in their case in the range of weeks, in ours in the range of minutes. This observed association now raises the idea of interpreting the FC changes we found triggered by rTMS in terms of neuroplastic changes. In that case, altered FC would be a compensatory mechanism to counteract the neuronal disturbances caused by rTMS. Interestingly, Tahedl's results do not show a directionality of the altered FC, just as the FC in the cerebello-thalamo-cortical network in tremor patients can be either increased or decreased (see chapter 5.1.4).

5.2.2 FC changes located in white matter

Several clusters that had reduced their FC with the cerebellar component were located in white matter. Previously, FC researchers assumed that neural activation in white matter did not exist or could not be detected with fMRI (Logothetis & Wandell, 2004). BOLD signal in white matter was labeled as noise or artifact; it had no relevance for brain connectivity analysis. More recent studies provide some evidence for measurable BOLD signals in white matter (Ding et al., 2018; Gore et al., 2019; Grajauskas et al., 2019). As described in the introduction section, the BOLD signal is an indirect measure for neuronal activity. Since an active brain region has a higher oxygen demand, the resulting altered concentration of oxygenated and deoxygenated hemoglobin in the blood modifies the BOLD signal. This also applies to the metabolically active tissue of white matter, containing mitochondria in all length of the axon. White matter also has a vasculature independent of the cortex through the medullary artery (Akashi et al., 2017; Nonaka et al., 2003), hence the oxygen demand of gray matter does not affect the oxygenation of white matter. Even though BOLD signal in white matter is weaker and harder to detect, it could provide valuable information and should therefore be considered in future studies.

5.2.3 Possible limitations concerning data analysis

An ever-present challenge in the analysis of fMRI data is noise removal. It involves finding a balance between sufficient noise reduction and preserving the true signal. For this reason, we have placed great emphasis on cleaning our data properly. In addition to conventional preprocessing steps, our protocol involved the use of ICA-AROMA (Pruim et al., 2015) in a non-aggressive manner to reduce the risk of missing actual rTMS effects. Since ICA-AROMA only removes motion artifacts, it is worth

considering using the more complex classifier FIX (FMRIB's ICA-based Xnoiseifier; Salimi-Khorshidi et al., 2014) instead in the future. FIX does not exclusively focus on motion components, but automatically removes multiple types of noise components, e.g., physiological noise as breathing and heartbeat.

So far, we have limited our attention to FC as a static concept. There is evidence, that brain connectivity is a dynamic process changing over time (Hutchison et al., 2013). Future work could benefit from adding functional connectivity dynamics to the analysis.

For the dual regression analysis we used the template maps from the Smith atlas (S. M. Smith et al., 2009) respectively from the Tahedl atlas (Tahedl & Schwarzbach, 2023) as spatial regressors in the first stage of dual regression. One advantage of these external template maps is that splitting the networks happens in a way that is consistent with literature and therefore allows good comparability. Disadvantageous, however, is that they do not reflect the structure of the own specific dataset. For example, there might be differences in the fMRI acquisition parameters or in the amount of removed noise. One alternative is to use the group-level ICA maps estimated from the own data as input for dual regression. Because the own data represents the structure of components (including noise components) best, this approach is very sensitive to find any results. Maybe this would have yielded an even greater effect of 1 Hz rTMS on FC in the brain.

5.3 Conclusion

Using MEPs as an objective readout parameter, we succeeded in simultaneously detecting changes in cortical excitability and changes in FC. We found that inhibitory 1 Hz rTMS reduced the number of MEPs for about 11 minutes, which we interpreted as reduced excitability. At the same time, using dual regression analysis, we found an 11-minute change of FC as a response to 1 Hz rTMS, primarily reduced FC between cerebellum and ventral left thalamus. The cerebello-thalamo-cortical pathway as a strong structural connection of cerebellum and contralateral motor cortex, with a relay station in the contralateral motor thalamus, plays a key role in the development and therapy of tremor disorders (Helmich et al., 2013). Within this also called tremor network, FC changes can be detected in tremor patients depending on tremor severity (Nicoletti et al., 2020; Tikoo et al., 2020). These parallel observations between our healthy subjects and tremor patients led us to consider that the reduced FC between

the cerebellum and left thalamus could be a compensatory response to an artificial tremor induced by rTMS. Based on the evidence that non-invasive brain stimulation temporarily ameliorates tremor symptoms (Kang & Cauraugh, 2017), the reduced number of MEPs could be interpreted as attenuated artificial tremor resulting from inhibitory 1 Hz rTMS. However, the extent to which MEPs reflect tremor severity requires further research; there are some studies casting doubt that the effect of non-invasive brain stimulation on tremor symptoms is mediated via reduced cortical excitability (Bologna et al., 2015; Hellriegel et al., 2012).

In conclusion, this study provides an indication of how 1 Hz rTMS on the primary motor cortex might affect the tremor network, based on the FC reduction found between the cerebellum and thalamus. Still, the results and the respective interpretation are uncharted territory and should therefore be evaluated with reservations. Further research is needed to assess which role rTMS can play in treating tremor patients.

6 BIBLIOGRAPHY

Akashi, T., Takahashi, S., Mugikura, S., Sato, S., Murata, T., Umetsu, A., & Takase, K. (2017). Ischemic White Matter Lesions Associated With Medullary Arteries: Classification of MRI Findings Based on the Anatomic Arterial Distributions. *American Journal of Roentgenology*, *209*(3), W160–W168. https://doi.org/10.2214/AJR.16.17231

Allen, G. I., & Tsukahara, N. (1974). Cerebrocerebellar communication systems. *Physiological Reviews*, *54*(4), 957–1006. https://doi.org/10.1152/physrev.1974.54.4.957

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007). *Non-linear registration aka Spatial normalisation, FMRIB Technial Report TR07JA2*. https://www.fmrib.ox.ac.uk/datasets/techrep/tr07ja2/tr07ja2.pdf

Asanuma, C., Thach, W. T., & Jones, E. G. (1983). Distribution of cerebellar terminations and their relation to other afferent terminations in the ventral lateral thalamic region of the monkey. *Brain Research Reviews*, *5*(3), 237–265. https://doi.org/10.1016/0165-0173(83)90015-2

Auerbach, E. J., Xu, J., Yacoub, E., Moeller, S., & Uğurbil, K. (2013). Multiband accelerated spin-echo echo planar imaging with reduced peak RF power using time-shifted RF pulses. *Magnetic Resonance in Medicine*, *69*(5), 1261–1267. https://doi.org/10.1002/mrm.24719

Azevedo, F. A. C., Carvalho, L. R. B., Grinberg, L. T., Farfel, J. M., Ferretti, R. E. L., Leite, R. E. P., Filho, W. J., Lent, R., & Herculano-Houzel, S. (2009). Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *The Journal of Comparative Neurology*, *513*(5), 532–541. https://doi.org/10.1002/cne.21974

Badran, B. W., Glusman, C. E., Austelle, C. W., Jenkins, S., DeVries, W. H., Galbraith, V., Thomas, T., Adams, T. G., George, M. S., & Revuelta, G. J. (2016). A Double-Blind, Sham-Controlled Pilot Trial of Pre-Supplementary Motor Area (Pre-SMA) 1 Hz rTMS to Treat Essential Tremor. *Brain Stimulation*, *9*(6), 945–947. https://doi.org/10.1016/j.brs.2016.08.003

Bagepally, B. S., Bhatt, M. D., Chandran, V., Saini, J., Bharath, R. D., Vasudev, M., Prasad, C., Yadav, R., & Pal, P. K. (2012). Decrease in Cerebral and Cerebellar Gray Matter in Essential Tremor: A Voxel-Based Morphometric Analysis under 3T MRI. *Journal of Neuroimaging*, *22*(3), 275–278. https://doi.org/10.1111/j.1552-6569.2011.00598.x

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). *Non-invasive magnetic stimulation of human motor cortex. Lancet 1: 1106–1107.*

Battistella, G., Najdenovska, E., Maeder, P., Ghazaleh, N., Daducci, A., Thiran, J.-P., Jacquemont, S., Tuleasca, C., Levivier, M., Bach Cuadra, M., & Fornari, E. (2017). Robust thalamic nuclei segmentation method based on local diffusion magnetic resonance properties. *Brain Structure and Function*, *222*(5), 2203–2216. https://doi.org/10.1007/s00429-016-1336-4

Beckmann, C. F., & Smith, S. M. (2004). Probabilistic Independent Component Analysis for Functional Magnetic Resonance Imaging. *IEEE Transactions on Medical Imaging*, *23*(2), 137–152. https://doi.org/10.1109/TMI.2003.822821

Beckmann, C., Mackay, C., Filippini, N., & Smith, S. (2009). Group comparison of resting-state FMRI data using multi-subject ICA and dual regression. *NeuroImage*, *47*, S148. https://doi.org/10.1016/S1053-8119(09)71511-3

Behrens, T. E. J., Johansen-Berg, H., Woolrich, M. W., Smith, S. M., Wheeler-Kingshott, C. A. M., Boulby, P. A., Barker, G. J., Sillery, E. L., Sheehan, K., Ciccarelli, O., Thompson, A. J., Brady, J. M., & Matthews, P. M. (2003). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *NATURE NEUROSCIENCE*, *6*(7), 8.

Benabid, A. L., Pollak, P., Hoffmann, D., Gervason, C., Hommel, M., Perret, J. E., de Rougemont, J., & Gao, D. M. (1991). Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *The Lancet*, *337*(8738), 403–406. https://doi.org/10.1016/0140-6736(91)91175-T

Benito-León, J., Louis, E. D., Romero, J. P., Hernández-Tamames, J. A., Manzanedo, E., Álvarez-Linera, J., Bermejo-Pareja, F., Posada, I., & Rocon, E. (2015). Altered Functional Connectivity in Essential Tremor: A Resting-State fMRI Study. *Medicine*, *94*(49), e1936. https://doi.org/10.1097/MD.0000000000001936

Bennett, C. M., Wolford, G. L., & Miller, M. B. (2009). The principled control of false positives in neuroimaging. *Social Cognitive and Affective Neuroscience*, *4*(4), 417–422. https://doi.org/10.1093/scan/nsp053

Bharath, R. D., Biswal, B. B., Bhaskar, M. V., Gohel, S., Jhunjhunwala, K., Panda, R., George, L., Gupta, A. K., & Pal, P. K. (2015). Repetitive transcranial magnetic stimulation induced modulations of resting state motor connectivity in writer's cramp. *European Journal of Neurology*, *22*(5), 796-e54. https://doi.org/10.1111/ene.12653

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine*, *34*(4), 537–541. https://doi.org/10.1002/mrm.1910340409

Blomstedt, P., Sandvik, U., Fytagoridis, A., & Tisch, S. (2009). THE POSTERIOR SUBTHALAMIC AREA IN THE TREATMENT OF MOVEMENT DISORDERS: PAST, PRESENT, AND FUTURE. *Neurosurgery*, *64*(6), 1029–1042. https://doi.org/10.1227/01.NEU.0000345643.69486.BC

Boecker, H., Weindl, A., Brooks, D. J., Ceballos-Baumann, A. O., Liedtke, C., Miederer, M., Sprenger, T., Wagner, K. J., & Miederer, I. (2010). GABAergic Dysfunction in Essential Tremor: An ^{11}C-Flumazenil PET Study. *Journal of Nuclear Medicine*, *51*(7), 1030–1035. https://doi.org/10.2967/jnumed.109.074120

Bologna, M., Rocchi, L., Leodori, G., Paparella, G., Conte, A., Kahn, N., Fabbrini, G., & Berardelli, A. (2015). Cerebellar Continuous Theta Burst Stimulation in Essential Tremor. *The Cerebellum*, *14*(2), 133–141. https://doi.org/10.1007/s12311-014-0621-0

Bosch-Bouju, C., Hyland, B. I., & Parr-Brownlie, L. C. (2013). Motor thalamus integration of cortical, cerebellar and basal ganglia information: Implications for normal and parkinsonian conditions. *Frontiers in Computational Neuroscience*, *7*. https://doi.org/10.3389/fncom.2013.00163

Brainard, D. H. (1997). The Psychophysics Toolbox. *Spatial Vision*, *10*(4), 433–436. https://doi.org/10.1163/156856897X00357

Broca, P. (1865). *Sur le siège de la faculté du langage articulé. Bulletins de La Société d'anthropologie de Paris, 6(1), 377–393. Https://doi.org/10.3406/bmsap.1865.9495*.

Buijink, A. W. G., van der Stouwe, A. M. M., Broersma, M., Sharifi, S., Groot, P. F. C., Speelman, J. D., Maurits, N. M., & van Rootselaar, A.-F. (2015). Motor network disruption in essential tremor: A functional and effective connectivity study. *Brain*, *138*(10), 2934–2947. https://doi.org/10.1093/brain/awv225

Cagnan, H., Little, S., Foltynie, T., Limousin, P., Zrinzo, L., Hariz, M., Cheeran, B., Fitzgerald, J., Green, A. L., Aziz, T., & Brown, P. (2014). The nature of tremor circuits in parkinsonian and essential tremor. *Brain*, *137*(12), 3223–3234. https://doi.org/10.1093/brain/awu250

Chen, A. C., Oathes, D. J., Chang, C., Bradley, T., Zhou, Z.-W., Williams, L. M., Glover, G. H., Deisseroth, K., & Etkin, A. (2013). Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proceedings of the National Academy of Sciences*, *110*(49), 19944–19949. https://doi.org/10.1073/pnas.1311772110

Chuang, W.-L., Huang, Y.-Z., Lu, C.-S., & Chen, R.-S. (2014). Reduced cortical plasticity and GABAergic modulation in essential tremor: Cortical Plasticity in Essential Tremor. *Movement Disorders*, *29*(4), 501–507. https://doi.org/10.1002/mds.25809

Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences*, *103*(37), 13848–13853. https://doi.org/10.1073/pnas.0601417103

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Ding, Z., Huang, Y., Bailey, S. K., Gao, Y., Cutting, L. E., Rogers, B. P., Newton, A. T., & Gore, J. C. (2018). Detection of synchronous brain activity in white matter tracts at rest and under functional loading. *Proceedings of the National Academy of Sciences*, *115*(3), 595–600. https://doi.org/10.1073/pnas.1711567115

Duma, C. M., Jacques, D. B., Kopyov, O. V., Mark, R. J., Copcutt, B., & Farokhi, H. K. (1998). Gamma knife radiosurgery for thalamotomy in parkinsonian tremor: A five-year experience. *Journal of Neurosurgery*, *88*(6), 1044–1049. https://doi.org/10.3171/jns.1998.88.6.1044

Eldaief, M. C., Halko, M. A., Buckner, R. L., & Pascual-Leone, A. (2011). Transcranial magnetic stimulation modulates the brain's intrinsic activity in a frequency-dependent manner. *Proceedings of the National Academy of Sciences*, *108*(52), 21229–21234. https://doi.org/10.1073/pnas.1113103109

Elias, W. J., Huss, D., Voss, T., Loomba, J., Khaled, M., Zadicario, E., Frysinger, R. C., Sperling, S. A., Wylie, S., Monteith, S. J., Druzgal, J., Shah, B. B., Harrison, M., & Wintermark, M. (2013). A Pilot Study of Focused Ultrasound Thalamotomy for Essential Tremor. *New England Journal of Medicine*, *369*(7), 640–648. https://doi.org/10.1056/NEJMoa1300962

Fang, W., Chen, H., Wang, H., Zhang, H., Puneet, M., Liu, M., Lv, F., Luo, T., Cheng, O., Wang, X., & Lu, X. (2016). Essential tremor is associated with disruption of functional connectivity in the ventral intermediate Nucleus-Motor Cortex-Cerebellum circuit: ET Is Associated With Disruption of FC in the VIM. *Human Brain Mapping*, *37*(1), 165–178. https://doi.org/10.1002/hbm.23024

Fenoy, A. J., & Schiess, M. C. (2017). Deep Brain Stimulation of the Dentato-Rubro-Thalamic Tract: Outcomes of Direct Targeting for Tremor. *Neuromodulation: Technology at the Neural Interface*, *20*(5), 429–436. https://doi.org/10.1111/ner.12585

Fitzgerald, P., Fountain, S., & Daskalakis, Z. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology*, *117*(12), 2584–2596. https://doi.org/10.1016/j.clinph.2006.06.712

Frey, J., Hess, C. W., Kugler, L., Wajid, M., & Wagle Shukla, A. (2021). Transcranial Magnetic Stimulation in Tremor Syndromes: Pathophysiologic Insights and Therapeutic Role. *Frontiers in Neurology*, *12*, 700026. https://doi.org/10.3389/fneur.2021.700026

Fricke, C., Duesmann, C., Woost, T. B., von Hofen-Hohloch, J., Rumpf, J.-J., Weise, D., & Classen, J. (2019). Dual-Site Transcranial Magnetic Stimulation for the Treatment of Parkinson's Disease. *Frontiers in Neurology*, *10*, 174. https://doi.org/10.3389/fneur.2019.00174

Frima, N., & Grünewald, R. A. (2006). A Double-blind, Placebo-controlled, Crossover Trial of Topiramate in Essential Tremor: *Clinical Neuropharmacology*, *29*(2), 94–96. https://doi.org/10.1097/00002826-200603000-00007

Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. J. (1993). Functional Connectivity: The Principal-Component Analysis of Large (PET) Data Sets. *Journal of Cerebral Blood Flow & Metabolism*, *13*(1), 5–14. https://doi.org/10.1038/jcbfm.1993.4

Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., & Evans, A. C. (1994). Assessing the significance of focal activations using their spatial extent: Assessing Focal Activations by Spatial Extent. *Human Brain Mapping*, *1*(3), 210–220. https://doi.org/10.1002/hbm.460010306

Fritsch, G., & Hitzig, E. (1870). *Über die elektrische Erregbarkeit des Grosshirns. Archiv Anat Physiol Wiss Med 37: 300–332*.

Fukunaga, M., Horovitz, S. G., van Gelderen, P., de Zwart, J. A., Jansma, J. M., Ikonomidou, V. N., Chu, R., Deckers, R. H. R., Leopold, D. A., & Duyn, J. H. (2006). Large-amplitude, spatially correlated fluctuations in BOLD fMRI signals during extended rest and early sleep stages. *Magnetic Resonance Imaging*, *24*(8), 979–992. https://doi.org/10.1016/j.mri.2006.04.018

Gironell, A. (2014). The GABA Hypothesis in Essential Tremor: Lights and Shadows. *Tremor and Other Hyperkinetic Movements*, *4*(0), 254. https://doi.org/10.5334/tohm.229

Gore, J. C., Li, M., Gao, Y., Wu, T.-L., Schilling, K. G., Huang, Y., Mishra, A., Newton, A. T., Rogers, B. P., Chen, L. M., Anderson, A. W., & Ding, Z. (2019). Functional MRI and resting state connectivity in white matter—A mini-review. *Magnetic Resonance Imaging*, *63*, 1–11. https://doi.org/10.1016/j.mri.2019.07.017

Grajauskas, L. A., Frizzell, T., Song, X., & D'Arcy, R. C. N. (2019). White Matter fMRI Activation Cannot Be Treated as a Nuisance Regressor: Overcoming a Historical Blind Spot. *Frontiers in Neuroscience*, *13*, 1024. https://doi.org/10.3389/fnins.2019.01024

Greicius, M. (2008). Resting-state functional connectivity in neuropsychiatric disorders. *Current Opinion in Neurology*, *21*(4), 424–430. https://doi.org/10.1097/WCO.0b013e328306f2c5

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., Reiss, A. L., & Schatzberg, A. F. (2007). Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. *Biological Psychiatry*, *62*(5), 429–437. https://doi.org/10.1016/j.biopsych.2006.09.020

Griffanti, L., Salimi-Khorshidi, G., Beckmann, C. F., Auerbach, E. J., Douaud, G., Sexton, C. E., Zsoldos, E., Ebmeier, K. P., Filippini, N., Mackay, C. E., Moeller, S., Xu, J., Yacoub, E., Baselli, G., Ugurbil, K., Miller, K. L., & Smith, S. M. (2014). ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. *NeuroImage*, *95*, 232–247. https://doi.org/10.1016/j.neuroimage.2014.03.034

Groppa, S., Herzog, J., Falk, D., Riedel, C., Deuschl, G., & Volkmann, J. (2014). Physiological and anatomical decomposition of subthalamic neurostimulation effects in essential tremor. *Brain*, *137*(1), 109–121. https://doi.org/10.1093/brain/awt304

Hallett, M. (2012). Parkinson's disease tremor: Pathophysiology. *Parkinsonism & Related Disorders*, *18*, S85–S86. https://doi.org/10.1016/S1353-8020(11)70027-X

Hassler, R. (1982). Architectonic organization of the thalamic nuclei. *A.E. Walker (Ed.), Georg Thieme Verlag, New York, 140*.

Hassler, R., & Riechert, T. (1954). [Indications and localization of stereotactic brain operations]. *Der Nervenarzt*, *25*(11), 441–447.

Hellriegel, H., Schulz, E. M., Siebner, H. R., Deuschl, G., & Raethjen, J. H. (2012). Continuous theta-burst stimulation of the primary motor cortex in essential tremor. *Clinical Neurophysiology*, *123*(5), 1010–1015. https://doi.org/10.1016/j.clinph.2011.08.033

Helmich, R. C., Janssen, M. J. R., Oyen, W. J. G., Bloem, B. R., & Toni, I. (2011). Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. *Annals of Neurology*, *69*(2), 269–281. https://doi.org/10.1002/ana.22361

Helmich, R. C., Toni, I., Deuschl, G., & Bloem, B. R. (2013). The Pathophysiology of Essential Tremor and Parkinson's Tremor. *Current Neurology and Neuroscience Reports*, *13*(9), 378. https://doi.org/10.1007/s11910-013-0378-8

Hutchison, R. M., Womelsdorf, T., Allen, E. A., Bandettini, P. A., Calhoun, V. D., Corbetta, M., Della Penna, S., Duyn, J. H., Glover, G. H., Gonzalez-Castillo, J., Handwerker, D. A., Keilholz, S., Kiviniemi, V., Leopold, D. A., de Pasquale, F., Sporns, O., Walter, M., & Chang, C. (2013). Dynamic functional connectivity: Promise, issues, and interpretations. *NeuroImage*, *80*, 360–378. https://doi.org/10.1016/j.neuroimage.2013.05.079

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain

Images. *NeuroImage*, *17*(2), 825–841. https://doi.org/10.1006/nimg.2002.1132

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*(2), 143–156. https://doi.org/10.1016/S1361-8415(01)00036-6

Kang, N., & Cauraugh, J. H. (2017). Does non-invasive brain stimulation reduce essential tremor? A systematic review and meta-analysis. *PLOS ONE*, *12*(9), e0185462. https://doi.org/10.1371/journal.pone.0185462

Klein, J. C., Lorenz, B., Kang, J.-S., Baudrexel, S., Seifried, C., van de Loo, S., Steinmetz, H., Deichmann, R., & Hilker, R. (2011). Diffusion tensor imaging of white matter involvement in essential tremor. *Human Brain Mapping*, *32*(6), 896–904. https://doi.org/10.1002/hbm.21077

Kondziolka, D., Ong, J. G., Lee, J. Y. K., Moore, R. Y., Flickinger, J. C., & Lunsford, L. D. (2008). Gamma Knife thalamotomy for essential tremor. *Journal of Neurosurgery*, *108*(1), 111–117. https://doi.org/10.3171/JNS/2008/108/01/0111

Krack, P., Pollak, P., Limousin, P., Benazzouz, A., & Benabid, A. (1997). Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease. *The Lancet*, *350*(9092), 1675. https://doi.org/10.1016/S0140-6736(97)24049-3

Kwon, H. G., Hong, J. H., Hong, C. P., Lee, D. H., Ahn, S. H., & Jang, S. H. (2011). Dentatorubrothalamic tract in human brain: Diffusion tensor tractography study. *Neuroradiology*, *53*(10), 787–791. https://doi.org/10.1007/s00234-011-0878-7

Lenka, A., Bhalsing, K. S., Panda, R., Jhunjhunwala, K., Naduthota, R. M., Saini, J., Bharath, R. D., Yadav, R., & Pal, P. K. (2017). Role of altered cerebello-thalamo-cortical network in the neurobiology of essential tremor. *Neuroradiology*, *59*(2), 157–168. https://doi.org/10.1007/s00234-016-1771-1

Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Le Bas, J.-F., Perret, J. E., Benabid, A.-L., & Broussolle, E. (1995). Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *The Lancet*, *345*(8942), 91–95. https://doi.org/10.1016/S0140-6736(95)90062-4

Logothetis, N. K., & Wandell, B. A. (2004). Interpreting the BOLD Signal. *Annual Review of Physiology*, *66*(1), 735–769. https://doi.org/10.1146/annurev.physiol.66.082602.092845

Louis, E. D., & Vonsattel, J. P. G. (2008). The emerging neuropathology of essential tremor: Pathology of Essential Tremor. *Movement Disorders*, *23*(2), 174–182. https://doi.org/10.1002/mds.21731

Lynall, M.-E., Bassett, D. S., Kerwin, R., McKenna, P. J., Kitzbichler, M., Muller, U., & Bullmore, E. (2010). Functional Connectivity and Brain Networks in Schizophrenia. *Journal of Neuroscience*, *30*(28), 9477–9487. https://doi.org/10.1523/JNEUROSCI.0333-10.2010

Magnin, M., Morel, A., & Jeanmonod, D. (2000). Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. *Neuroscience*, *96*(3), 549–564. https://doi.org/10.1016/S0306-4522(99)00583-7

Mai, J. K., & Forutan, F. (2012). Thalamus. In *The Human Nervous System* (pp. 618–677). Elsevier. https://doi.org/10.1016/B978-0-12-374236-0.10019-7

Martin, E., Jeanmonod, D., Morel, A., Zadicario, E., & Werner, B. (2009). High-intensity focused ultrasound for noninvasive functional neurosurgery. *Annals of Neurology*,

66(6), 858–861. https://doi.org/10.1002/ana.21801

Merton, P. A., & Morton, H. B. (1980). *Stimulation of the cerebral cortex in the intact human subject. Nature 285: 227.*

Mouginot, D., & Gahwiler, B. H. (1996). Presynaptic GABAB receptors modulate IPSPs evoked in neurons of deep cerebellar nuclei in vitro. *Journal of Neurophysiology*, *75*(2), 894–901. https://doi.org/10.1152/jn.1996.75.2.894

Najdenovska, E., Alemán-Gómez, Y., Battistella, G., Descoteaux, M., Hagmann, P., Jacquemont, S., Maeder, P., Thiran, J.-P., Fornari, E., & Bach Cuadra, M. (2018). In-vivo probabilistic atlas of human thalamic nuclei based on diffusion- weighted magnetic resonance imaging. *Scientific Data*, *5*(1), 180270. https://doi.org/10.1038/sdata.2018.270

Narabayashi, H. (1989). Stereotaxic Vim Thalamotomy for Treatment of Tremor. *European Neurology*, *29*(1), 29–32. https://doi.org/10.1159/000116450

Neely, K. A., Kurani, A. S., Shukla, P., Planetta, P. J., Wagle Shukla, A., Goldman, J. G., Corcos, D. M., Okun, M. S., & Vaillancourt, D. E. (2015). Functional Brain Activity Relates to 0–3 and 3–8 Hz Force Oscillations in Essential Tremor. *Cerebral Cortex*, *25*(11), 4191–4202. https://doi.org/10.1093/cercor/bhu142

Nickerson, L. D., Smith, S. M., Öngür, D., & Beckmann, C. F. (2017). Using Dual Regression to Investigate Network Shape and Amplitude in Functional Connectivity Analyses. *Frontiers in Neuroscience*, *11*. https://doi.org/10.3389/fnins.2017.00115

Nicoletti, V., Cecchi, P., Pesaresi, I., Frosini, D., Cosottini, M., & Ceravolo, R. (2020). Cerebello-thalamo-cortical network is intrinsically altered in essential tremor: Evidence from a resting state functional MRI study. *Scientific Reports*, *10*(1), 16661. https://doi.org/10.1038/s41598-020-73714-9

Noback, C. R. (Ed.). (2005). *The human nervous system: Structure and function* (6th ed). Humana Press.

Nonaka, H., Akima, M., Hatori, T., Nagayama, T., Zhang, Z., & Ihara, F. (2003). Microvasculature of the human cerebral white matter: Arteries of the deep white matter. *Neuropathology*, *23*(2), 111–118. https://doi.org/10.1046/j.1440-1789.2003.00486.x

Ogawa, S., Lee, T.-M., Nayak, A. S., & Glynn, P. (1990). Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magnetic Resonance in Medicine*, *14*(1), 68–78. https://doi.org/10.1002/mrm.1910140108

Ohye, C., Hirai, T., Miyazaki, M., Shibazaki, T., & Nakajima, H. (1982). Vim Thalamotomy for the Treatment of Various Kinds of Tremor. *Stereotactic and Functional Neurosurgery*, *45*(3), 275–280. https://doi.org/10.1159/000101611

Olfati, N., Shoeibi, A., Abdollahian, E., Ahmadi, H., Hoseini, A., Akhlaghi, S., Vakili, V., Foroughipour, M., Rezaeitalab, F., Farzadfard, M.-T., Layegh, P., & Naseri, S. (2020). Cerebellar repetitive transcranial magnetic stimulation (rTMS) for essential tremor: A double-blind, sham-controlled, crossover, add-on clinical trial. *Brain Stimulation*, *13*(1), 190–196. https://doi.org/10.1016/j.brs.2019.10.003

Oosterhof, N. N., Connolly, A. C., & Haxby, J. V. (2016). CoSMoMVPA: Multi-Modal Multivariate Pattern Analysis of Neuroimaging Data in Matlab/GNU Octave. *Frontiers in Neuroinformatics*, *10*. https://doi.org/10.3389/fninf.2016.00027

Pahwa, R., Lyons, K., Hubble, J. P., Busenbark, K., Dierkes Rienerth, J., Pahwa, A., & Koller, W. C. (1998). Double-blind controlled trial of gabapentin in essential tremor: GABAPENTIN IN ET. *Movement Disorders*, *13*(3), 465–467. https://doi.org/10.1002/mds.870130315

Paris-Robidas, S., Brochu, E., Sintes, M., Emond, V., Bousquet, M., Vandal, M., Pilote, M., Tremblay, C., Di Paolo, T., Rajput, A. H., Rajput, A., & Calon, F. (2012). Defective dentate nucleus GABA receptors in essential tremor. *Brain*, *135*(1), 105–116. https://doi.org/10.1093/brain/awr301

Pascual-Leone, A., Valls-Solé, J., Wassermann, E. M., & Hallett, M. (1994). Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain*, *117*(4), 847–858. https://doi.org/10.1093/brain/117.4.847

Pauling, L., & Coryell, C. D. (1936). The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin. *Proceedings of the National Academy of Sciences of the United States of America*, *22*(4), 210–216. PubMed. https://doi.org/10.1073/pnas.22.4.210

Pessiglione, M. (2005). Thalamic Neuronal Activity in Dopamine-Depleted Primates: Evidence for a Loss of Functional Segregation within Basal Ganglia Circuits. *Journal of Neuroscience*, *25*(6), 1523–1531. https://doi.org/10.1523/JNEUROSCI.4056-04.2005

Pinault, D., & Deschênes, M. (1992). The origin of rhythmic fast subthreshold depolarizations in thalamic relay cells of rats under urethane anaesthesia. *Brain Research*, *595*(2), 295–300. https://doi.org/10.1016/0006-8993(92)91063-K

Pinto, A. D., Lang, A. E., & Chen, R. (2003). The cerebellothalamocortical pathway in essential tremor. *Neurology*, *60*(12), 1985–1987. https://doi.org/10.1212/01.WNL.0000065890.75790.29

Plenz, D., & Kital, S. T. (1999). A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. *Nature*, *400*(6745), 677–682. https://doi.org/10.1038/23281

Popa, T., Russo, M., Vidailhet, M., Roze, E., Lehéricy, S., Bonnet, C., Apartis, E., Legrand, A. P., Marais, L., Meunier, S., & Gallea, C. (2013). Cerebellar rTMS stimulation may induce prolonged clinical benefits in essential tremor, and subjacent changes in functional connectivity: An open label trial. *Brain Stimulation*, *6*(2), 175–179. https://doi.org/10.1016/j.brs.2012.04.009

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

Pruim, R. H. R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J. K., & Beckmann, C. F. (2015). ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *NeuroImage*, *112*, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*(2), 676–682. https://doi.org/10.1073/pnas.98.2.676

Rajput, A. H., Robinson, C. A., Rajput, M. L., Robinson, S. L., & Rajput, A. (2012).

Essential tremor is not dependent upon cerebellar Purkinje cell loss. *Parkinsonism & Related Disorders*, *18*(5), 626–628. https://doi.org/10.1016/j.parkreldis.2012.01.013

Rogers, F. B. (1963). Medical subject headings. *Bulletin of the Medical Library Association*, *51*(1), 114–116.

Romeo, S., Berardelli, A., Pedace, F., Inghilleri, M., Giovannelli, M., & Manfredi, M. (1998). Cortical excitability in patients with essential tremor. *Muscle & Nerve*, *21*(10), 1304–1308. https://doi.org/10.1002/(SICI)1097-4598(199810)21:10<1304::AID-MUS9>3.0.CO;2-F

Romero, J. R., Anschel, D., Sparing, R., Gangitano, M., & Pascual-Leone, A. (2002). Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. *Clinical Neurophysiology*, *113*(1), 101–107. https://doi.org/10.1016/S1388-2457(01)00693-9

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*(12), 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016

Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., Dimitrijević, M. R., Hallett, M., Katayama, Y., Lücking, C. H., Maertens de Noordhout, A. L., Marsden, C. D., Murray, N. M. F., Rothwell, J. C., Swash, M., & Tomberg, C. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: Basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology*, *91*(2), 79–92. https://doi.org/10.1016/0013-4694(94)90029-9

Sack, A. T., Cohen Kadosh, R., Schuhmann, T., Moerel, M., Walsh, V., & Goebel, R. (2009). Optimizing Functional Accuracy of TMS in Cognitive Studies: A Comparison of Methods. *Journal of Cognitive Neuroscience*, *21*(2), 207–221. https://doi.org/10.1162/jocn.2009.21126

Salimi-Khorshidi, G., Douaud, G., Beckmann, C. F., Glasser, M. F., Griffanti, L., & Smith, S. M. (2014). Automatic denoising of functional MRI data: Combining independent component analysis and hierarchical fusion of classifiers. *NeuroImage*, *90*, 449–468. https://doi.org/10.1016/j.neuroimage.2013.11.046

Schwarzbach, J. (2011). A simple framework (ASF) for behavioral and neuroimaging experiments based on the psychophysics toolbox for MATLAB. *Behavior Research Methods*, *43*(4), 1194–1201. https://doi.org/10.3758/s13428-011-0106-8

Seidel, P. (2019). *Modulation of functional connectivity dynamics by means of repetitive transcranial magnetic stimulation*. Unpublished master thesis. Universität Regensburg.

Shin, H.-W., Hallett, M., & Sohn, Y. H. (2019). Cerebellar repetitive transcranial magnetic stimulation for patients with essential tremor. *Parkinsonism & Related Disorders*, *64*, 304–307. https://doi.org/10.1016/j.parkreldis.2019.03.019

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., Watkins, K. E., Toro, R., Laird, A. R., & Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest.

Proceedings of the National Academy of Sciences, *106*(31), 13040–13045. https://doi.org/10.1073/pnas.0905267106

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*, S208–S219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Smith, S., & Nichols, T. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, *44*(1), 83–98. https://doi.org/10.1016/j.neuroimage.2008.03.061

Stam, C., Jones, B., Nolte, G., Breakspear, M., & Scheltens, P. (2006). Small-World Networks and Functional Connectivity in Alzheimer's Disease. *Cerebral Cortex*, *17*(1), 92–99. https://doi.org/10.1093/cercor/bhj127

Symanski, C., Shill, H. A., Dugger, B., Hentz, J. G., Adler, C. H., Jacobson, S. A., Driver-Dunckley, E., & Beach, T. G. (2014). Essential tremor is not associated with cerebellar Purkinje cell loss: ET not Associated with Cerebellar PC Loss. *Movement Disorders*, *29*(4), 496–500. https://doi.org/10.1002/mds.25845

Tahedl, M., Levine, S. M., Weissert, R., Kohl, Z., Lee, D.-H., Linker, R. A., & Schwarzbach, J. V. (2022). Early remission in multiple sclerosis is linked to altered coherence of the Cerebellar Network. *Journal of Translational Medicine*, *20*(1), 488. https://doi.org/10.1186/s12967-022-03576-4

Tahedl, M., & Schwarzbach, J. V. (2023). An automated pipeline for obtaining labeled ICA -templates corresponding to functional brain systems. *Human Brain Mapping*, hbm.26435. https://doi.org/10.1002/hbm.26435

Tikoo, S., Pietracupa, S., Tommasin, S., Bologna, M., Petsas, N., Bharti, K., Berardelli, A., & Pantano, P. (2020). Functional disconnection of the dentate nucleus in essential tremor. *Journal of Neurology*, *267*(5), 1358–1367. https://doi.org/10.1007/s00415-020-09711-9

Uusisaari, M., & Knöpfel, T. (2008). GABAergic synaptic communication in the GABAergic and non-GABAergic cells in the deep cerebellar nuclei. *Neuroscience*, *156*(3), 537–549. https://doi.org/10.1016/j.neuroscience.2008.07.060

Van Essen, D. C., Ugurbil, K., Auerbach, E., Barch, D., Behrens, T. E. J., Bucholz, R., Chang, A., Chen, L., Corbetta, M., Curtiss, S. W., Della Penna, S., Feinberg, D., Glasser, M. F., Harel, N., Heath, A. C., Larson-Prior, L., Marcus, D., Michalareas, G., Moeller, S., … Yacoub, E. (2012). The Human Connectome Project: A data acquisition perspective. *NeuroImage*, *62*(4), 2222–2231. https://doi.org/10.1016/j.neuroimage.2012.02.018

Watanabe, T., Hanajima, R., Shirota, Y., Ohminami, S., Tsutsumi, R., Terao, Y., Ugawa, Y., Hirose, S., Miyashita, Y., Konishi, S., Kunimatsu, A., & Ohtomo, K. (2014). Bidirectional effects on interhemispheric resting-state functional connectivity induced by excitatory and inhibitory repetitive transcranial magnetic stimulation: Bidirectional Connectivity Change by rTMS. *Human Brain Mapping*, *35*(5), 1896–1905. https://doi.org/10.1002/hbm.22300

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal Autocorrelation in Univariate Linear Modeling of FMRI Data. *NeuroImage*, *14*(6),

1370–1386. https://doi.org/10.1006/nimg.2001.0931

Yamamoto, T., Wagner, A., Hassler, R., & Sasaki, K. (1983). Studies on the cerebellocerebral and thalamocortical projections in squirrel monkeys (Saimiri sciureus). *Experimental Neurology*, *79*(1), 27–37. https://doi.org/10.1016/0014-4886(83)90376-X

Zach, H., Dirkx, M. F., Roth, D., Pasman, J. W., Bloem, B. R., & Helmich, R. C. (2020). Dopamine-responsive and dopamine-resistant resting tremor in Parkinson disease. *Neurology*, *95*(11), e1461–e1470. https://doi.org/10.1212/WNL.0000000000010316

Zesiewicz, T. A., Sullivan, K. L., Hinson, V., Stover, N. P., Fang, J., Jahan, I., Miller, A., Carranza, M. A., & Elble, R. (2013). Multisite, double-blind, randomized, controlled study of pregabalin for essential tremor. *Movement Disorders*, *28*(2), 249–250. https://doi.org/10.1002/mds.25264

Zhang, J.-R., Feng, T., Hou, Y.-N., Chan, P., & Wu, T. (2016). Functional Connectivity of Vim Nucleus in Tremor- and Akinetic-/Rigid-Dominant Parkinson's Disease. *CNS Neuroscience & Therapeutics*, *22*(5), 378–386. https://doi.org/10.1111/cns.12512

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, *20*(1), 45–57. https://doi.org/10.1109/42.906424

7 TOOLS

DeepL Translate, DeepL SE (https://www.deepl.com/de/translator): Used for translation of text passages.

DECLARATION

I hereby declare that I have prepared this thesis without the unauthorized assistance of third parties and without the use of aids other than those specified. Data and concepts taken directly or indirectly from other sources are marked with the source. In particular, I have not made use of the paid assistance of placement or advisory services (doctoral advisors or other persons). No one has directly or indirectly received monetary benefits from me for work related to the content of this dissertation. The thesis has not been submitted in the same or a similar form to any other examination authority in Germany or abroad.

Ich erkläre hiermit, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet. Insbesondere habe ich nicht die entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten (Promotionsberater oder andere Personen) in Anspruch genommen. Niemand hat von mir unmittelbar oder mittelbar geldwerte Leistungen für Arbeit erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen. Die Arbeit wurde bisher weder im In- noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

ACKNOWLEDGMENTS

First of all, I want to give many thanks to my supervisor Prof. Dr. Jens Schwarzbach, who supported and encouraged me during the whole time of this work, both personally and professionally.

Secondly, I would like to express my special thanks to Philipp Seidel, who acquired the data with me and shared his data analysis skills with me. He was always on hand to provide advice and support with great commitment.

I also want to thank Prof. Dr. Ralf Linker, who agreed to be the second reviewer of my dissertation.

Thanks to all my lab colleagues in Regensburg, I look back on many cheerful memories with you in our office. Thank you for all the encouragement during this time.

Another thank you goes to PD Dr. Martin Schecklmann from the University of Regensburg for providing us with the TMS device and instructing us in the correct use of it. To him and his doctoral student Kilian Prei also thanks for collecting the MEP data.

Furthermore, I want to thank Alexander Sack and Rainer Goebel from the Maastricht University, who supplied us with one of their neuronavigation systems and a free license for using the respective software.

I would particularly like to thank my whole family and friends, who never gave up confidence that this work would come to an end. Special thanks to my husband Peter, who always helped me to get over my weaker self, gave me one or two statistical hints and knew how to keep me motivated.

And above all this, I want to say thank you to my God – Father, Son, and Holy Spirit – who safely led me through this challenging time.

Who is this King of glory? The Lord strong and mighty, the Lord mighty in battle.

Psalm 24:8