The Effect of TMS on Emotional Valence Evaluation of Aversive Pictures

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorization:	Risk category A according to ClinO, Art. 61
Study Registration:	NCT07191275 (clinicaltrials.gov) 67295 (HumRes)
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Investigated Intervention:	Transcranial magnetic stimulation (TMS)
Study ID	SAME_M 2025
Version and Date:	Version 3 (20.10.2025)

Change History

Version Nr	Version date	Modified without version change	Description, comments	Control
1.0	05.08.2025		Initial version	EA
2.0	15.09.2025		Randomisation process added.	
3.0	20.10.2025		• Changes in stimulation protocol for active control group • Adding 5 seconds of stimulation habituation in each session • Change in initiation date	

PROTOCOL SIGNATURE FORM

Study Title	The Effect of TMS on Emotional Valence Evaluation of Aversive Pictures
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The Sponsor- and the Principal-Investigator have approved the protocol version 3 (dated 10.10.2025) and confirm hereby to conduct the study according to the protocol, the current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor-Investigator:

Prof. Dominique de Quervain, MD

Date: 20.10.2025 Signature: 

Principlal Investigator:

Ehssan Amini, MD

Date: 20.10.2025 Signature: 

TABLE OF CONTENTS

GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR	*Annual Safety Repot*
BASEC	*Business Administration System for Ethical Committees*
BMI	*Body Mass Index*
BP	*Blood Pressure*
Bpm	*Beats per minute*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
cTBS	*continuous theta burst stimulation*
CTCAE	*Common Terminology Criteria for Adverse Events*
EHI	*Edinburgh Handedness Inventory*
EKNZ	*Ethikkommission Nordwest- und Zentralschweiz*
EMG	*Electromyography*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
fMRI	*functional Magnetic Resonance Imaging*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
Hz	*Hertz*
IAPS	*International Affective Picture System*
ICH	*International Conference on Harmonisation*
Ms	*Millisecond*
MEP	*Motor Evoked Potential*
MNI	*Montreal Neurological Institute*
MSO	*Maximum System Output*
TOC	*Temporo-occipital cortex*
PI	*Principal Investigator*
rMT	*resting Motor Threshold*
rTMS	*repetitive Transcranial Magnetic Stimulation*
SAE	*Serious Adverse Event*
TMS	*Transcranial Magnetic Stimulation*
VAS	*Visual Analog Scale*

1 STUDY SYNOPSIS

Sponsor-Investigator	Prof. Dominique de Quervain, MD University of Basel Co-Director Research Cluster Molecular and Cognitive Neurosciences Director Division of Cognitive Neuroscience Birmannsgasse 8, 4055 Basel E-Mail: dominique.dequervain@unibas.ch Phone: +41 61 207 02 37
Study Title	The Effect of TMS on Emotional Valence Evaluation of Aversive Pictures
Short Title / Study ID	SAME_M 2025
Protocol Version and Date	Version 3 (20.10.2025)
Study Registration	Clinicaltrials.gov / HumRes
Study Category and Rationale	Risk category A according to ClinO, Art. 61 TMS protocols are considered to be safe and impose minimal risk when following TMS safety guidelines (Rossi et al., 2021).
Background and Rationale	Based on results from a large-scale brain imaging study, we found that the bilateral temporo-occipital cortex is specifically involved in the encoding of aversive memories. Although these imaging findings are robust, they are correlational and do not imply causality. To investigate a causal relationship, we conducted a follow-up pilot TMS study (unpublished results, BASEC number: 2023-00392) using a 30 Hz cTBS protocol. In that study, we observed a small effect size for aversive memory performance (number of freely recalled pictures) and a medium-to-large effect size (Cohen's d = 0.77) for valence ratings of aversive stimuli: participants in the experimental group rated aversive pictures less negatively compared to those in the control group. Given the well-established link between emotional evaluation and memory performance, we hypothesised that the temporo-occipital cortex contributes to aversive memory performance through a mediating effect on the emotional perception of these stimuli. In the present study, we aim to test this hypothesis by comparing valence ratings of aversive stimuli between a group receiving cTBS to the temporo-occipital cortex and an active control group receiving similar stimulation to a brain region not involved in the encoding/processing of aversive memories.
Risk / Benefit Assessment	TMS has been used for many years in scientific studies and has proved to be useful in investigating the causal relationship of different brain regions' activity and behavioral phenotypes. The most serious risk of applying rTMS is seizure incidence, which has been reported very rarely. In order to minimize the risk, we will not include any participant with history of seizure events in his/hers or their family medical history. Neurocardiogenic syncope is a more common but still rare side effect of rTMS. We will exclude participants with repetitive syncope history to minimize the risk of its happening in our study. In general, the risk of applying rTMS for participants are minimal when following TMS safety guidelines that have been established for 30 years and have been updated at a consensus conference in year 2018 (Rossi et al., 2021). The main benefit of this study lies in the gain of knowledge regarding finding a causal relationship between neural activity in the temporo-occipital cortex and aversive emotional evaluation. Such a knowledge may have clinical implication concerning disorders such as post-traumatic stress disorder (PTSD) and depressive disorders.
Primary objective	To investigate whether cTBS of the temporo-occipital cortex alters the valence rating of aversive stimuli.
Primary outcome	Primary outcome: The mean valence rating of aversive pictures as assessed by a visual analogue scale
Study Design	Randomised, cross-over, single blind, controlled trial

Inclusion- / Exclusion Criteria	Inclusion criteria: • Generally healthy • Normotensive (BP 90/60mmHg - 140/90mmHg) • BMI: 18 - 30 kg/m^2 • Age: 18 - 30 years • Fluent in speaking German Exclusion Criteria: • Metal in the head area (e.g., splinters, fragments, clips, etc.) • Implanted neurostimulator (e.g., DBS, epidural/subdural, VNS) • Cardiac pacemaker or intracardiac lines • Medication infusion device • Non removable metal piercings in the head area, pivot teeth (retainers are no exclusion criterion) • Tattoos (head area) less than 3 months old or older than 20 years • Condition after neurosurgery • Hearing problems or tinnitus • Not able to sit still due to tremor, tics, itching • History of repeated syncope • Head trauma diagnosed as concussion or associated with loss of consciousness • diagnosis of epilepsy, or a convulsion or a seizure in the past of the participant or his/her close family (parents and siblings) • TMS in the past showing problems • Spinal or ventricular derivations • Positive pregnancy test • Alcohol intake 12 hours before TMS visits • Regular intake of any medication (excluding oral contraceptives) • CNS-active medication or illegal drugs 48h before TMS visits • Individual's rMT above the limits of rTMS device • Suicidal tendency as measured by Montgomery–Åsberg Depression Rating Scale (MADRS), item 10 > 0
Number of Participants with Rationale	Results from the pilot study showed a difference for valence ratings of aversive pictures between the experimental and active control groups, with a Cohen's *d* of 0.77. To increase statistical efficiency and reduce between-subject variability, we now opt for a cross-over, within-subject design in which each participant completes both conditions (experimental and active control). To account for potential noise introduced by repeated cognitive testing (e.g., practice effects), we conservatively assume a slightly reduced effect size of d = 0.6. Based on a two-tailed test with α = 0.05 and a desired power of 0.85, a total sample size of 27 participants is estimated. To account for potential data loss due to technical issues or late drop-outs, we plan to recruit 33 participants.
Study Intervention	Bilateral continuous theta burst stimulation (cTBS) 30 Hz to the temporo-occipital cortex • Frequency: trains of 30 Hz (3 pulses) every 167 ms (frequency of 6 Hz, in the range of theta band) • Intensity: 100% of resting motor threshold (rMT) • Location: consecutively on left and right temporo-occipital cortex (MNI: -47, -77, 4; 50, -69, -4) • Duration: 33.3 seconds for each side • Timing: Immediately before showing IAPS pictures (off-line)
Control Intervention	Active control condition using bilateral continuous theta burst stimulation (cTBS) 30 Hz to the superior parietal cortex • Frequency: trains of 30 Hz (3 pulses) every 167 ms (frequency of 6 Hz, in the range of theta band) • Intensity: 85% of resting motor threshold (rMT)

	• Location: consecutively on left and right superior parietal cortex (MNI: 64, -2 ,-22; -64, -2, 22) • Duration: 33.3 seconds • Timing: Immediately before showing IAPS pictures (off-line)
Study procedures	Participants will be tested on two different days, 7-21 days apart. They will be randomly assigned to the experimental condition on one day and the active control condition on the other. The procedure for both days is identical and detailed below: After getting informed consent and screening consisting of checking the in- and exclusion criteria, eligible participants will complete mood and affect questionnaires and then will be guided to TMS lab. Participants will be provided by the instructions and trained for the N-back and IAPS encoding tasks. Afterwards, resting motor threshold (rMT) of participants will be measured, participants receive 5 seconds of habituation stimulation, and rTMS protocols will be applied. After the stimulation, participants will watch a standard picture set categorized by valence (i.e., negative (i.e. aversive), neutral, positive) and are asked to rate each picture based on valence and arousal level. Afterwards, participants will perform an n-back working memory task. After this task, participants are asked to remember as many pictures as they can. At this stage participants are asked to complete the IAPS encoding task for the second time without the influence of TMS. After 7-21 days, participants will be invited to the study site again for the TMS condition they have not received the first time (experimental or active control).
Study Duration and Schedule	The study duration is estimated to be 12 months. First-Participant-In: 11/2025 Last-Participant-Out: 11/2026
Investigators	• Dr. Ehssan Amini, MD Division of Cognitive Neuroscience, University of Basel ehssan.amini@unibas.ch • Dr. Nathalie Schicktanz, PhD Division of Cognitive Neuroscience, University of Basel nathalie.schicktanz @unibas.ch • MSc. Christian Wollmann Division of Cognitive Neuroscience, University of Basel Christian.wollmann@unibas.ch
Study Center(s)	University of Basel Division of Cognitive Neuroscience Birmannsgasse 8, 4055 Basel
Statistical considerations	To test for differences in valence ratings between the experimental and active control conditions in the cross-over design, we will use a linear mixed-effects model.
Data privacy	Trial and participant data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the study. On the study documents and electronically captured data, participants are only identified by a unique participant number.
Ethical consideration	Only through experimental modulation of brain activation it is possible to test the causal relationship between brain activation and behaviour. This is not possible with imaging studies that only allow correlational observations which brain regions are activated during a particular task or process. Because contraindications to TMS and conservative safety guidelines are followed, the requirements for a "Class 3 study" (indirect benefit & low risk; healthy subjects; no immediate relevance to clinical problems, but exceptional scientific utility for understanding brain physiology) apply (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). The three key requirements for studying healthy subjects are also met: First, participation is voluntary and based on the subject being fully informed of the risks. Second, the risk-benefit ratio justifies conducting this study because the risks of personal harm are minimal and no

	other means exists to obtain the data without this risk. Third, there is an equitable distribution of burdens and benefits, as only healthy subjects are studied and not patients who are particularly vulnerable due to their individual economic, social, or physical condition.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

There is a strong bias in episodic memory formation to retain emotionally arousing events rather than neutral ones. Although this quality is essential in daily life adaptation and survival as it plays a key role in fear learning and threat avoidance, in some extreme cases, it can lead to fear-related disorders such as post-traumatic stress disorder (PTSD) or mood disorders. To develop an efficient approach toward such disorders, we need to gain a better understanding of the mechanisms of emotional memory encoding, consolidation, and retrieval. In this regard, numerous studies have focused on finding neural correlates of emotional memory and introduced brain regions involved in the process, such as medial temporal lobe structures (Dahlgren, Ferris, & Hamann, 2020; Murty, Ritchey, Adcock, & LaBar, 2010). Although these studies have provided us with valuable knowledge about emotional memory in general, most of them did not differentiate positive and negative memories, and there is a lack of knowledge about valence-specific memory mechanisms (Dahlgren et al., 2020). Considering this, in a recent large-scale (1600 subjects) functional magnetic resonance imaging (fMRI) study performed in our division (EKBB 190/08), we could find four main brain regions (i.e., bilateral fusiform gyrus and bilateral temporo-occipital cortex) significantly (after correction for multiple comparisons) associated specifically with aversive memory encoding (unpublished data). Despite robustness, these results are merely on an associative level and do not imply a causal relationship. To be able to make causal interpretations, we need to rely on other methods such as transcranial magnetic brain stimulation (TMS).

TMS is a non-invasive method in which electrical currents are induced in cortical areas by a magnetic field generated around a stimulation coil (Robertson, Theoret, & Pascual-Leone, 2003). When this stimulation is applied over several minutes using repetitive TMS (rTMS), neural activity in the stimulated region can be temporarily modulated. Depending on the stimulation protocol, inhibitory or facilitatory effects on brain activation can be observed. TMS protocols such as 1Hz rTMS or continuous TBS (cTBS) can be used to specifically induce a temporally limited and reversible perturbation of a specific brain region also known as “virtual lesions”. If effects in behaviour accompany this virtual lesion, a causal relationship between the stimulated brain region and the corresponding task or behaviour can be inferred (Sandrini, Umilta, & Rusconi, 2011). In a recent meta-analysis comparing the effectiveness of different protocols, it was declared that no strong conclusion can be made due to the numerous differences in the specific rTMS parameters and experimental designs that were used (Yeh & Rose, 2019). Considering this, we conducted a pilot study to compare different TMS protocols and find the one with the highest effect on aversive memory encoding performance.

None of the protocols used in the pilot study showed a statistically significant effect on aversive memory performance. However, participants in the active 30 Hz cTBS group (over the bilateral temporo-occipital cortex) rated aversive pictures significantly less negatively compared to their respective sham and active control groups (Cohen’s d = 0.77). Moreover, the active group recalled fewer aversive pictures, although the difference in memory performance was not statistically significant and was at a small effect size.

Based on these findings, we hypothesised that bilateral temporo-occipital cortex is primarily involved in the perception of aversive valence and plays a mediatory role in aversive memory performance. In the current study, we aim to test this hypothesis by applying 30 Hz cTBS to the bilateral temporo-occipital cortex and measuring valence ratings of aversive pictures as the primary outcome.

TMS has been used for many years in scientific studies and has proved to be useful in investigating the causal relationship between different brain regions' activity and behavioural phenotypes. The risk of applying rTMS for participants is minimal when following TMS safety guidelines that have been established for 30 years and have been updated at a consensus conference in the year 2018 (Rossi et al., 2021). TMS protocols, which will be used in this study, will follow safety guidelines and will be in risk category A according to ClinO, Art. 61.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

The primary objective of this study is to investigate the effect of bilateral temporo-occipital 30 Hz continuous theta burst stimulation (cTBS) on valence ratings of aversive pictures, in comparison to an active control condition (30 Hz cTBS applied to a bilateral region not involved in the processing of aversive stimuli). We hypothesise that aversive pictures will be rated as less emotionally aversive in the experimental condition compared to the control condition.

3.2 Primary and secondary outcomes

Primary outcome:

The mean valence rating of aversive pictures as assessed by a visual analogue scale assessed directly after TMS.

Secondary outcomes:

- Mean arousal rating for aversive pictures as assessed by a visual analogue scale assessed directly after TMS
- Mean arousal rating for aversive pictures as assessed by a visual analogue scale assessed after free recall (without direct influence of TMS)
- Mean valence rating for aversive pictures as assessed by a visual analogue scale assessed after free recall (without direct influence of TMS)
- Memory performance (i.e. the number of freely recalled aversive pictures)

Control outcomes:

Here, we assume no effect of bilateral temporo-occipital 30 Hz cTBS on valence and arousal ratings:

- Mean valence rating for neutral and positive stimuli (assessed directly after TMS and after free recall)
- Mean arousal rating for neutral and positive stimuli (assessed directly after TMS and after free recall)
- Memory performance for neutral and positive stimuli
- Working memory performance (0-back, 2-back)

Safety endpoint variables:

- Adverse events (AEs)

3.3 Study design

We plan a monocentric study investigating the effect of temporo-occipital 30 Hz cTBS on emotional valence evaluation of aversive pictures using the following design:

- Cross-over
- Controlled
- Single blinded
- Counter-balanced (order of condition)

3.4 Study intervention

This crossover study consists of one experimental and one active control intervention.

3.4.1 Experimental Intervention:

Continuous theta burst stimulation (cTBS) 30 Hz:

This protocol has been shown to transiently result in reduced motor corticospinal output. Therefore, this protocol is used to temporarily disrupt neuronal processing in a specific region (Goldsworthy, Pitcher, & Ridding, 2012).

- Frequency: trains of 30 Hz (3 pulses) every 167 ms (frequency of 6 Hz, in the range of theta band)
- Intensity: 100% of resting motor threshold (rMT)
- Location (based on the aforementioned fMRI study): consecutively on left and right temporo-occipital cortex (MNI coordinates: left hemisphere: -47, -77, 4; right hemisphere: 50, -69, -4)
- Duration: 33.3 seconds for each hemisphere, 66.6 seconds in total.
- Timing: Immediately before viewing and rating pictures in the pictorial memory task (off-line)

3.4.2 Control conditions:

Active rTMS control group:

The frequency, intensity, duration and timing of this protocol will be the same as the experimental protocol. For this condition, the stimulation will be applied to a region which is not involved in the processing of aversive pictures. Based on the results from our aforementioned fMRI study, such a region was found in the superior parietal cortex, which will be used as the stimulation location in this group.

- Frequency: trains of 30 Hz (3 pulses) every 167 ms (frequency of 6 Hz, in the range of theta band)
- Intensity: 85% of resting motor threshold (rMT)
- Location: consecutively on the left and right superior parietal cortex (MNI coordinates: left hemisphere: -64, -2, 22; right hemisphere: 64, -2, 22)
- Duration: 33.3 seconds for each hemisphere, 66.6 seconds in total.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Generally healthy
- Normotensive (BP 90/60mmHg - 140/90mmHg)
- BMI: 18 - 30 kg/m2
- Age: 18 - 30 years
- Fluent in speaking German

The presence of any one of the following exclusion criteria will lead to the exclusion of the participant:

- Metal in the head area (e.g., splinters, fragments, clips, etc.)
- Implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)
- Cardiac pacemaker or intracardiac lines
- Medication infusion device
- Non-removable metal piercings in the head area, pivot teeth (retainers are no exclusion criterion)
- Tattoos (head area) less than 3 months old or older than 20 years old
- Condition after neurosurgery
- Hearing problems or tinnitus
- Not able to sit still due to tremors, tics, and itching
- History of repeated syncope
- Head trauma diagnosed as a concussion or associated with loss of consciousness

- diagnosis of epilepsy, or a convulsion or a seizure in the past of the participant or his/her close family (parents and siblings)
- TMS in the past showed problems
- MRI in the past showed problems
- Spinal or ventricular derivations
- Positive pregnancy test
- Alcohol or drug intake 12 hours before TMS visits
- Regular intake of any medication (excluding oral contraceptives)
- CNS-active medication or illegal drugs 48 hours before TMS visits
- The individual's rMT is above the limits of the rTMS device.
- Suicidal tendency as measured by Montgomery–Åsberg Depression Rating Scale (MADRS), item 10 > 0

4.2 Recruitment, screening and informed consent procedure

4.2.1 Recruitment and pre-screening

Study participants will be searched in the German-speaking part of Switzerland using the websites mcn.unibas.ch and markt.unibas.ch, posts in social media like LinkedIn, ads in print media or public transportation.

The study takes place at the Division of Cognitive Neuroscience, University of Basel, Birmannsgasse 8.

Interested persons will be redirected to the study website on mcn.unibas.ch, where they can read the "Participant information and consent form" describing the study and providing sufficient information for participants to make an informed decision about their participation in the study. Together with the participant information, they get some administrative information. If the interested person remains interested in participating, they can continue on the website by completing the prescreening questionnaire via a SoSci-survey link. These questionnaires consist of:

- TMS safety screening questionnaire (Rossi, Hallett, Rossini, & Pascual-Leone, 2011) and study in- and exclusion criteria.
- Self-assessment questionnaire covering some sociodemographic information and health declaration.

To gather as little data as possible in the pre-screening steps, questions related to in/exclusion criteria and TMS safety will be asked one by one with SoSci-Survey, and as soon as the answer provided does not fulfil the criteria, the survey will end and all data already acquired will be permanently deleted.

If the person is interested in participating and meets all inclusion criteria and none of the exclusion criteria, they will provide us with their contact details, which will be saved separately from their pre-screening data on SoSci-survey. A study team member will contact the interested person to set the schedule for the visit.

Interested persons can contact our study team at any time if they still have questions.

4.2.2 Informed consent procedure and screening

At the beginning of the visit, one of the study team members will explain to the participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. The participant will be informed that participation in the study is voluntary and that his or her participant file may be examined by authorised individuals other than study team members. At this point, participants will decide whether they wish to take part in the study. There is no time limit for this decision, and in case they need more time to consider, they may leave the study site and return at a later scheduled time if they choose to participate.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure.

The consent form will be signed by the participant and by the principal investigator or their designee (responsible investigator on site). A copy (or second original) of the signed informed consent will be given

to the study participant. The consent form will be retained as part of the study records. The informed consent process will be documented in the participant's file, and any discrepancy from the process described in the protocol will be explained.
The screening procedure consists of checking the inclusion and exclusion criteria. As part of the screening, all participants of childbearing potential will be requested to perform a pregnancy test before administration of the study intervention. In case of a positive pregnancy test, the participant will be excluded from the study.
At the end of the screening, the investigator or sponsor-investigator decides whether a participant can be included. Screening failures occur when participants do not meet all inclusion criteria or meet one or more of the exclusion criteria. Excluded participants will be listed on a screening failure log as part of the subject master list.
The screening documents will be filed as part of the Source Data (SD) in the participant's file. All steps will be documented, and we will assess the number of participants who were not eligible during screening.
A study compensation of CHF 150, including travel expenses, will be paid at the end of the second visit. In case of a dropout after the screening or first visit completion, a compensation of 30 CHF or 75 CHF will be paid, respectively.
The principal investigator or the sponsor notifies the Ethics Committee of the first study participant, in accordance with art 62 lit. c ClinO, resp. art 38 ClinO. If the first participating person is not included in the trial within two years following the issuance of the authorisation, the trial is considered interrupted (art. 23a ClinO). The clinical trial may not be commenced until an application for an extension of the time limit has been approved. The application for the extension is submitted to the CEC as a substantial amendment.

4.2.3 Randomisation process

To randomise participants, we employ the maximum tolerated imbalance (MTI) and the asymptotic maximal procedure, as implemented in the NIH clinical randomisation tool (https://ctrandomization.cancer.gov). Randomisation will be carried out across four arms defined by stimulation condition and picture set:

1. Experimental_Set1
2. Experimental_Set2
3. Control_Set1
4. Control_Set2

Stratification by sex will be applied, resulting in two strata. As the tool permits only a single fixed number of participants per stratum, 17 participants will be randomised to each group, yielding a total of 34 subjects. One of the final randomisation slots will be excluded according to the order of enrolment. In case of drop-outs, we will replace the next participant with the dropped-out one.

4.3 Study procedures

The duration of the study from the first participant in, to the last participant out is approximately twelve months. After the screening, participants will fill in mood, affect, and anxiety questionnaires. The maximum duration for each participant will be 5 hours for the two visits.

4.3.1 Assessing the mood and affect intensity of the participants

Anxiety state and depression severity of participants will be assessed using the state-trait anxiety inventory (STAI) and a modified version for use as a self-rating questionnaire of the Montgomery–Åsberg Depression Rating Scale (MADRS, Schmidtke et al.; German version), respectively. Moreover, to control for the differences in the affective response of different participants, we ask them to complete the Affect Intensity Measurement (Larsen, Diener, & Emmons, 1986) questionnaire.

4.3.1.1 The State-Trait Anxiety Inventory (STAI):

STAI is a widely used measure of both trait and state anxiety (Laux, Glanzmann, Schaffner, & Spielberger, 1981). It consists of 20 questions for trait anxiety, asking respondents how they feel "generally," and 20 questions for state anxiety, asking them how they feel "right now". All items are rated on a 4-point scale (e.g., from "Rarely" to "Almost Always"), with higher scores indicating greater anxiety. Internal consistency coefficients for the scale have ranged from .86 to .95, while test-retest reliability coefficients have ranged from .65 to .75 over a 2-month interval (Laux et al., 1981). In the present study, only the state part of the questionnaire will be used.

4.3.1.2 Montgomery–Åsberg Depression Rating Scale (MADRS):

MADRS is a clinician-rated scale designed to measure depression severity (Montgomery & Asberg, 1979). The scale consists of items evaluating apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item is scored based on a 7-point Likert scale (0-6; range: 0-60), with higher scores representing more severe symptoms of depression.

MADRS psychometric properties have been studied extensively in adults (Mulder, Joyce, & Frampton, 2003). It has an inter-rater reliability as high as 0.97 between a psychiatrist and a general practitioner (Montgomery & Asberg, 1979). In the current study, participants will be asked to fill out the German version of the MADRS questionnaire (Schmidtke, Fleckenstein, Moises, & Beckmann, 1988), and its total score will be used as a depression score.

4.3.1.3 Affect Intensity Measurement (AIM)

We will use a version of AIM with 29 items. AIM is a self-administered questionnaire, measuring the individual's intensity in experiencing and responding to negative and positive emotional stimuli (Larsen et al., 1986). Respondents rate on a 6-point Likert scale how they react to events and experiences in their lives. Individuals who score higher on this scale tend to experience emotions more intensely compared to ones with lower scores. AIM total score and three sub-factors (score for negative emotions, score for positive emotions, score for calmness and excitability relating to positive and negative affects) will be extracted and used as covariates in the analysis.

4.3.2 Intervention

As the study follows a crossover design, participants will be tested on two different days, 7-21 days apart. Participants will be assigned to receive either the experimental or the control condition during their first session, with the alternate condition administered during the second session. The assignment will be stratified by sex and counterbalanced for condition order using a computer-generated randomisation list. The main procedure for both days is identical and only differs in the intervention protocol. The sessions will consist of:

4.3.2.1 Resting motor threshold (rMT) measurement:

The resting motor threshold (rMT) will be measured with a biphasic Magstim Rapid2 stimulator (The MAGSTIM® Company Ltd, Whitland, UK) and a 70 mm figure-of-eight coil.

rMT will be determined by measuring the motor-evoked potential (MEP) from the abductor digiti minimi muscle. rMT will be defined as the lowest stimulation intensity by stimulating the primary motor cortex of the left or right hemisphere required to induce an MEP in the abductor digiti minimi of the dominant hand (as assessed by Edinburgh Handedness Inventory) in at least 5 out of 10 trials. In the case of a relaxed target muscle, a positive MEP is defined as an MEP with $\geqslant$ 50 µV peak-to-peak amplitude. If the abductor digiti minimi hotspot cannot be reliably located, but a consistent visible muscle contraction of another hand muscle can be observed, the visual motor threshold will be assessed instead, defined as the lowest stimulation intensity that produces a visible muscle twitch in the hand at minimal intensity in at least 5 out of 10 trials.

The coil will be held tangentially to the skull over M1, approximately 4 cm lateral and 1 cm anterior to the Vertex. Additionally, the coil-handle points backwards at an angle of 45° to the corresponding parasagittal

line. Then the coil will be shifted systematically in steps of approximately one cm in anterior, posterior, lateral and medial directions. Stimulation will be performed at an initial output intensity of 30% of the maximum stimulator's output (MSO) and will be increased in steps of 10% until a twitch is detected. Thereafter, 10 pulses will be applied. If fewer than five MEPs are observed, stimulator output intensity will be increased by 5 %. Depending on the result, the intensity will be further decreased or again increased by steps of two and then one per cent until the lowest stimulator intensity is found. Otherwise, stimulator output intensity is first decreased by 5% and thereafter increased or decreased by steps of two and then one per cent until rMT is found. At the end, the intensity will be decreased again by 1% to confirm the found rMT, and again decreased if required. The participant is always allowed to stop the measuring if he/she feel ill at ease.

4.3.2.2 Administration of Intervention

After measuring the rMT, participants will receive 5 seconds of stimulation on the target site according to their group allocation. This brief stimulation serves as a habituation procedure to reduce participant stress and increase compliance with the study protocol. Afterwards, participants will be given time to reflect and decide whether they wish to continue with the study procedures. After measuring rMT, we will administer one of the experimental or control protocols (see section 3.4). Both protocols will be applied with a biphasic MAGSTIM Rapid2 stimulator (The MAGSTIM® Company Ltd, Whitland, UK) and 70 mm figure-of-eight or D70 Air Film Coil (AFC) coils. The stimulation protocol for the experimental group will consist of 30 Hz cTBS applied to the occipitotemporal region at 100% of the individual resting motor threshold (rMT). For the active control group, the same protocol will be applied to the right superior parietal cortex; however, to maintain a comparable level of comfort between the experimental and control conditions, stimulation intensity will be set to 85% of the rMT.

4.3.2.3 Safety Issues

We will use the MAGSTIM Rapid2 stimulator (The MAGSTIM® Company Ltd, Whitland, UK) in this study. This device has a CE 0086 certificate, meaning that it meets the requirements of the European directives, and conformity assessment has been carried out. Therefore, it may be freely sold and used within the European Economic Area (EEA). We will follow the latest version of the user operating manual (dated December 2020) provided by the MAGSTIM company. We also perform a recommended yearly maintenance service of the device (Last maintenance was done on 24.09.2024, the document uploaded in BASEC)

4.3.3 Outcome measurements

4.3.3.1 Valence rating, arousal rating, and episodic memory task

To measure valence and arousal rating, and memory performance, we will use a picture rating and recall memory task. We will use an adapted version of the task used in a large-scale study (Spalek et al., 2015), which will take only about 7.6 minutes.

Participants will be shown a set of 76 pictures selected from the International Affective Picture System (IAPS)(Lang, Bradley, & Cuthbert, 2005). These pictures consist of three sets of 24 with different emotional valences (positive, neutral, or negative (i.e. aversive)) presented in a sequential randomised manner so that a maximum of four pictures of the same category will be shown consecutively. At the beginning and end of the task 2 primacy and recency pictures will be added that will not enter the analysis. A fixation cross will appear on the screen for 500 ms before each picture presentation. Participants will see each picture for one second and afterwards have 5 seconds to rate the picture for emotional valence and arousal on a continuous visual analogue scale (Valence: -100: highly aversive, 0: neutral, +100: highly positive; Arousal: 0: not arousing at all to +100: highly arousing).

We will use two parallel versions of the picture set, each using different images, but matched for arousal and valence ratings. However, to ensure comparability across sessions and allow for meaningful modelling

of trial number as a proxy for time, the sequence of emotional categories and emotional normative scores will be matched across versions.

Ten minutes after this picture viewing and valence rating phase in a previously announced free recall task, participants will be asked to freely recall the pictures. Participants will be instructed to describe the pictures with short keywords, to note as much as they can remember related to the remembered pictures and to describe as many of the pictures as possible. There will be no time limit for completion of this task. Then, participants have to rate the 76 pictures again without the influence of TMS. In the next step, participants are requested to match their provided descriptions with the corresponding pictures.

As for the main behavioural variables, we will consider the mean valence rating, mean arousal rating, and number of correctly recalled pictures for each valence category as valence-specific emotional valence evaluation, emotional arousal evaluation, and episodic memory performance score, respectively.

4.3.3.2 N-back working memory task:

To maintain a comparable cognitive load for all participants in the 10-minute time window between the end of the intervention and the recall phase of the episodic memory task, participants will be asked to perform a working memory task. We will use a letter n-back task (Gevins & Cutillo, 1993) , which includes a 2-back task, to assess working memory. The 2-back task requires participants to respond to a letter repeated with two intervening letters (for example, S−m−s−g…). Performance will be quantified with the d' measure, controlling for false positives (Stanislaw & Todorov, 1999).

4.3.3.3 Assessment of the stimulation discomfort

At the end of each TMS visit, we will asses the level of discomfort and pain of the stimulation condition retrospectively using a visual analog scale (VAS) ranging from no discomfort (0) to maximal discomfort (100).

4.3.4 Methods for minimising bias

To ensure high standardisation across all test days, investigators will undergo comprehensive training and adhere to detailed working instructions.

A crossover design has been implemented to mitigate interindividual variability, with each participant acting as their own control. The order of experimental and control interventions will be counterbalanced. All testing will be conducted at the University of Basel's Division of Cognitive Neuroscience, utilising the same facility and consistent daily timing for each participant to minimise the impact of diurnal fluctuations on cognitive performance.

4.4 Withdrawal and Discontinuation

Participants have the right to withdraw from the study at any time for any reason without being obliged to give a reason. The investigator also has the right to withdraw participants from the study if it is in the best interest of the participant.

The following reasons result in withdrawal:

- Adverse events challenging the health of the participant if continuing the study
- Adverse events prohibiting cognitive testing, e.g., headache, dizziness, syncope.
- The participant is ill at ease during TMS sessions.
- Severe administrative or technical troubles
- Non-compliance
- Severe protocol violations

Withdrawal date and reason will be listed in the participant enrolment log.

5 STATISTICS AND METHODOLOGY

5.1 Statistical analysis plan and sample size calculation

5.1.1 Hypothesis

We hypothesise that aversive pictures will be rated as less emotionally aversive in the experimental condition compared to the control condition.

5.1.2 Determination of sample size

Results from the pilot study showed a difference between the experimental and active control groups, with a Cohen's d of 0.77. To increase statistical efficiency and reduce between-subject variability, we now opt for a cross-over, within-subject design in which each participant completes both conditions (experimental and active control). To account for potential noise introduced by repeated cognitive testing (e.g., practice effects), we conservatively assume a slightly reduced effect size of d = 0.6. Based on a two-tailed test with $\alpha = 0.05$ and a desired power of 0.85, a total sample size of 27 participants is estimated. To account for potential data loss due to technical issues or late drop-outs, we plan to recruit 33 participants.

5.1.3 Planned analysis

To test for differences in valence ratings for aversive pictures between the experimental and active control conditions, we will use a linear mixed-effects model appropriate for the cross-over, within-subject design. The model will include the following fixed effects: condition (experimental vs. control), order (first vs. second session), sex (male/female), and age (continuous). A random intercept for each participant will be included to account for repeated measurements. This approach allows us to model within-subject dependencies, control for potential order effects, and adjust for demographic covariates that may influence valence ratings.

To examine whether the effect of cTBS decays over time, we will include trial number as a proxy for elapsed time and test for an interaction between condition and trial number (included as a fixed effect). A significant interaction would indicate a time-dependent attenuation of the stimulation effect. Post-hoc test for each trial number separately will be applied to describe the interaction effect.

In secondary analyses, we will include resting motor threshold (rMT), depression, anxiety scores, affective intensity, and level of discomfort as additional fixed effects to assess their potential influence on baseline valence ratings and the strength of the stimulation effect. Where appropriate, we will explore interactions between these covariates and the condition to test for possible moderation effects.

Exploratory analyses will examine whether the reduction in negative valence ratings potentially observed after TMS persists at recall, relative to the placebo condition.

Significance testing will be conducted using two-tailed tests with an alpha level of 0.05. Effect sizes and 95% confidence intervals will be reported alongside p-values. Model assumptions (e.g., normality of residuals, homoscedasticity) will be checked, and appropriate data transformations or robust estimation techniques will be applied if necessary. If model convergence permits, we will also explore including a random slope for condition to account for inter-individual differences in responsiveness to stimulation.

Secondary and control outcomes will be analysed in the same way as the primary outcome.

Additional exploratory analyses might be performed.

5.1.4 Deviation(s) from the original statistical plan

Deviations from the original statistical plan will be justified and reported to the ethical committee and regulatory authorities.

Deviation from the original statistical plan will be performed if reviewers demand specific analyses. If, in the meantime, other studies find important effects or confounding effects related to our study, we will include these found confounders (if we have assessed those) as an additional analysis in our statistical plan, besides our planned analyses.

5.2 Handling of missing data and drop-outs

Missing data will be recorded as NA.
There will be a replacement of Drop-Outs until the data of 30 participants is completed. Drop-outs will be thoroughly described to assess the reason(s) for dropping out.

6 REGULATORY ASPECTS AND SAFETY

6.1 Local Regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA, as well as other locally relevant legal and regulatory requirements.

6.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Principal Investigator and Sponsor make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor- of the study.

If it cannot be excluded that the SAE occurring is attributable to the intervention under investigation, the Principal Investigator reports it to the Ethics Committee via BASEC within 15 days.

Follow-up of (Serious) Adverse Events

In case of minor health problems, the participant will have to stay under the control of an investigator in our division.
In case of major health problems, the participant will be transferred to the emergency department at the University Hospital of Basel (USB). The responsible investigator will inform the healthcare provider about the participation in the study.
Information about the outcome in all the above-mentioned cases will be collected until resolution or stabilisation.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the principal investigator notifies the Ethics Committee of these measures and of the circumstances necessitating them, within 7 days.

6.3 Periodic safety reporting and general progress of the clinical trial

Once a year, the principal investigator submits to the Ethics Committee a list of the safety events, including the severity of the events, their causality to the intervention and the safety of the study participants. The investigator also informs the Ethics Committee about the general progress of the clinical trial (ClinO, Art. 43).

The safety report and the general study progress report can be merged into one single report.

6.4 Radiation

Not applicable.

6.5 Pregnancy

All participants of childbearing potential will be requested to perform a pregnancy test before the administration of the study intervention. In case of a positive test, the participant will be excluded from the study.

6.6 Amendments

Substantial changes to the study setup and study organisation, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or

of investigator and sponsor (ClinO, Art. 29). A list of substantial changes is also available on www.swissethics.ch.

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the safety report / general study progress report.

6.7 Notification and reporting upon completion, discontinuation or interruption and resumption of the study

Upon regular study completion, the Ethics Committee is notified via BASEC within 30 days (ClinO, Art. 38).

The last visit of the last study participant (LPLV) is defined as the end of the trial.

The Sponsor may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

The principal investigator reports the premature termination, interruption or resumption of the study, including reasons thereof, to the Ethics Committee within 15 days. An interruption lasting more than two years is considered a premature termination (Article 38, ClinO).

A final report is submitted to the Ethics Committee via BASEC within a year after the completion or discontinuation of the study (ClinO, Art. 38).

A template for reporting upon completion, discontinuation or interruption of the study is available at www.swissethics.ch.

6.8 Insurance

In the event of study-related damage or injuries, the liability of University of Basel provides compensation.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

Neuroimaging only offers correlational information with regard to the involvement of a brain region in a certain behaviour. Only through experimental modulation of brain activation is it possible to test the causal relationship between brain activity in a certain brain region and behaviour. With this TMS study, we hope to gain insights into the causal role of the temporo-occipital cortex in emotional valence evaluation and subsequently memory encoding of aversive pictures. Because participants with contraindications for TMS will be excluded and conservative safety guidelines are followed, the requirements for a "Class 3 study" (indirect benefit & low risk; healthy subjects; no immediate relevance to clinical problems, but exceptional scientific utility for understanding brain physiology) apply (Rossi et al., 2009).

As this study is a basic study in pursuit of finding physiologic mechanisms, participants will be selected from a healthy and young population. The three key requirements for studying healthy subjects are also met: First, participation is voluntary and based on the subject being fully informed of the risks. Second, the risk-benefit ratio justifies conducting this study because the risks of personal harm are minimal and no other means exist to obtain the data without this risk. Third, there is an equitable distribution of burdens and benefits, as only healthy subjects are studied and not patients who are particularly vulnerable due to their individual economic, social, or physical condition.

7.2 Risk-benefit assessment

TMS has been used for many years in scientific studies and has proved to be useful in investigating the causal relationship between different brain regions' activity and behavioural phenotypes. The risk of applying rTMS for participants is minimal when following TMS safety guidelines that have been established for 30 years and have been updated at a consensus conference in the year 2018 (Rossi et al., 2021).

- The most common **risks regarding rTMS protocols:**
    - Seizures are the most serious possible TMS-related adverse events. Only a few cases of TMS-induced seizures have been reported so far out of hundreds of thousands of examined subjects (Rossi et al., 2021). Studies investigating physiological mechanisms of corticocortical plasticity in healthy subjects, which did not require repeated sessions over several days to reach a clinical effect, did not show major AE, including seizure occurrence (Rossi et al., 2021). Thus, there should not be any special concern for the methods that we are using in this study. We will exclude all persons who have experienced a seizure in the past and/or with a positive family history (first-degree relatives) of seizures.
    - Several medications have been reported to increase the risk of seizure in clinical populations (Dahlgren et al., 2020), and it was previously assumed that their use in combination with repetitive TMS may confer a heightened risk for seizure induction (Rossi et al., 2009). However, empirical evidence for this risk is lacking, and the observed seizure rate even in repetitive TMS patients is extremely low overall, despite that the majority of them were on CNS-active medications (Rossi et al., 2021). In this study, we will exclude all persons who use CNS-active medications.
    - Compared to seizure, syncope is more likely to occur during a TMS investigation. Syncope is typically a benign, self-limiting event, especially in younger individuals without underlying conditions. No systematic studies addressed the relative incidence of the two phenomena during TMS, but this is a common experience in many labs (Groppa et al., 2012). Vasodepressor (neurocardiogenic) syncope is a common reaction to anxiety and physical discomfort, and it can take place following TMS, as with many other non-invasive or minimally invasive medical procedures. The cardinal feature that distinguishes syncope from seizure is the rapid recovery of full consciousness within a few seconds and not minutes (Lin, Ziegler, Lai, & Bayer, 1982). We will exclude individuals with a history of repeated syncope.
- Moreover, in terms of data safety, there is a very slight chance of illegal data access by third parties (e.g. system hacking of data repositories).

To minimise the occurrence:

- We carefully go through a detailed list of exclusion criteria concerning TMS in general (single-pulse, paired-pulse and repetitive TMS) with each participant during screening. The questionnaire for screening of subjects before TMS investigations has been developed at a consensus conference by considering the safety and ethical guidelines for the use of TMS in clinical practice and research(Groppa et al., 2012; Rossi et al., 2011)
- All TMS investigations will be performed by specially trained persons.
- The participant is always allowed to stop the TMS measuring if he/she feel ill at ease.
- All data will be saved anonymously and under the code assigned to each participant. For electronic data recordings, no IP address, identification information or contact details will be saved along with the data.

Benefits

The benefit of the study lies in the gain of knowledge regarding finding a causal relationship between neural activity in the temporo-occipital cortex and emotional valence evaluation. Such knowledge may have clinical

implications concerning disorders related to aversive events, such as post-traumatic stress disorder (PTSD) and depressive disorders.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

The study personnel will receive careful training on all aspects of the study. Support by experienced staff of the departments of Molecular and Cognitive Neuroscience will be provided, and we have a QM system in place to support the preparation and conduct of the study (respectively, preparation of TMF, reporting and reporting obligations, AE documentation).
To ensure highly reliable data acquisition, we minimise the data entry requirements. Only the data at the screening stage are collected on paper; all other data are captured electronically and entered by/recorded from the participant directly. There will be no double data entry in the process.

A monitoring procedure will be in place, as described in Chapter 9.

For quality assurance, the sponsor-investigator, the Ethics Committee and a trial monitor may visit the research site. Direct access to the source data and all study-related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

Specification of source documents
Source data in this trial will consist of the following documents (there is no routinely collected data during the daily practice).

Paper documentation:

- Informed Consent Form
- Checklist in- and exclusion criteria (The checklist is completed based on the screening interview).
- AE-log
- Certified pre-screening copy

Direct data entry with SoSci-survey (https://www.soscisurvey.de/):
Pre-screening data

- TMS safety screening
- Other study exclusion criteria
- Socio-demographic and health declaration

Visit day data

- Administrative documents: visit checklists, rMT-value, etc.
- Edinburgh Handedness Inventory
- STAI-S Questionnaire
- MADRS Questionnaire
- AIM Questionnaire

Direct data entry with Presentation® (https://www.neurobs.com/):

- Picture rating task
- N-back working memory task

Direct data entry with Unity-based, in-house-developed app:

- Picture recall task

Data recording with Brainsight® (TMS-software):

- Location of rMT assessment (MNI coordinates)
- Electromyography (EMG) during rMT (MEP information: peak-to-peak amplitude, EMG waveform information; accuracy specifications such as distance to the associated target, target error).

Data recording

The pre-screening documents of individuals who are eligible to participate in the study will be printed before the visit, and a certified copy will be made. The certified copies become part of the screening documentation in the subject dossier and will be archived in the investigator site file (ISF) after study termination.

During the data collection phase, SoSci-Survey data is collected on a server at sciCORE (Centre for Scientific Computing at the University of Basel) while data collected with Presentation® and Brainsight are recorded on the local computer and transferred to the MCN file share on the servers of the University of Basel.

For further processing, data integration and long-term data storage, we use our local secure electronic archive, Studiendatenbank-MCN. All log-files, i.e. the SoSci Survey log-files, Presentation® log-files and the TMS data, including MNI coordinates and electromyography during rMT assessment, will be transferred to Studiendatenbank-MCN. Studiendatenbank-MCN is implemented using LabKey®. LabKey® Server is a software suite for integrating and analysing biomedical research data. It provides a secure data repository, audit trail and access via a web browser. Studiendatenbank-MCN extends the LabKey® server platform with scripts and workflows for archiving and tracking study data and related log files, as well as performing the data transformation to provide data files in a format for statistical analysis, detailed in the statistical methods section.

The data manager of the Divisions of Molecular and Cognitive Neuroscience is responsible for the user administration and for the user training regarding the Studiendatenbank-MCN. Regular automatic backups are performed according to the processes of the IT department of the University of Basel. Studiendatenbank-MCN has a detailed audit trail so that every relevant change is traceable and assignable to the person who made it. An additional text-file-based database dump is stored within the file system provided by the University IT Department. These additional backups are performed at key points of the study, e.g., when the data collection is finished and the database lock is initiated.

The *source data (including Presentation®, SoSci-Survey, and TMS-logfiles*) will be stored after the last visit of each protocol on a file system with restricted user access (main file system). The meta-information of the source data (SHA-1 hashes as file ID, file modification time, path to the file on the file system, date and time information logged in the log file) is stored in Studiendatenbank-MCN in a study-specific folder (main study folder). The relevant content of the source data that is necessary for creating an analytical database is additionally uploaded to Studiendatenbank-MCN (main study folder). The analytical database is created as text files with time stamps based on the uploaded or manually entered raw data. These text files are stored and accessible within the Studiendatenbank-MCN file system in the main study folder.

For source data, we don't expect that any changes will be made. Therefore, we store the meta-information of the source data to be able to verify that the files are in the original state. All other information is documented and stored within Studiendatenbank-MCN.

For source data (including the Presentation®, SoSci-Survey, Unity®, and Brainsight®-logfiles) we use different levels of *validation*: As a first step, we evaluate for each subject, visit and computer if all expected files or entries are available and stored in the correct sequence (via the time-stamp). If these basis checks fail, we manually curate the source data, if possible; manual data curation is documented in text files stored together with the source data or in LabKey®. After performing these basic checks, the data is copied and stored in the final storage space of a study in the main file system (deployed by the Psychology IT department). At the same time, the meta-information of each file is stored in LabKey®. When uploading the relevant content of the raw data, we further validate if the file content corresponds to the expected design of a task or survey, if possible (this is data-dependent). Furthermore, within LabKey®, we track each subject and visit and ask if there are exclusion reasons (filter variables). While creating the final analytical database,

we apply these filter variables to the data. An audit trail system maintains a record of initial entries and changes (time and date of changes, user identification of entries and changes). Reasons for changes can be added in a commentary. The data entered or uploaded in the LabKey® study folder will be reviewed by the investigator.

8.3 Confidentiality and coding

The principal investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, the anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

The investigator has appropriate knowledge and skills in the areas of data security and data protection or can ensure compliance by calling in appropriate expertise (Art. 6, ClinO).

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited.

Trial and participant data will be handled with the utmost discretion and are only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study-specific documents, participants are only identified by a unique participant number.

Only non-genetic data are used
SoSci-Survey data collected during pre-screening are stored on a server at sciCORE (Centre for Scientific Computing at the University of Basel) without identifying characteristics of the respective computer (IP address, timestamp). These data are pseudonymised, i.e. no identifying data such as name, date of birth, etc., is collected. Instead, a code is used. There is a list linking the SoSci-code (serial number) with the email address. Only study investigators have access to this list, and it will be deleted after LPLV as soon as the data is saved in the Studiendatenbank MCN. The SoSci-code will be entered in the SML.

Trial and participant data will be handled with utmost discretion and are only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. The participant number is used in the participant dossier, in Presentation, Unity, and Brainsight, i.e. in the logfiles (Presentation, SoSci-Survey, BrainSight), in study-specific documents and the Studiendatenbank-MCN; participants are only identified by a unique participant number.
Pre-screening is performed before the assignment of the participant number. The pre-screening questionnaire is anonymous and will be generated by SoSci-Survey. Participants who fulfil all criteria will be asked to provide their contact details, and their data will be recorded via SoSci-survey. Contact details will be saved separately from the survey data. The pre-screening questionnaire does NOT contain any other identifying information (i.e. name, date of birth). The pre-screening data (SoSci-Survey) is stored on a server at sciCORE (Centre for Scientific Computing at the University of Basel), without identifying characteristics of the respective computer (IP address, timestamp).
All codes are listed in the combined Screening, Enrolment and Identification Log. This Subject Master List (SML) will be kept under lock and key. Access to the participant identification list will be authorised only to study team members.
All Source Data is kept under lock and key. All electronic systems used in this study are password-protected, to ensure that only authorised persons can enter the system to view, add or modify data according to their permissions within the scope of the study. Software running on the servers of the University of Basel, especially Studiendatenbank-MCN, SoSci-Survey are additionally protected via the VPN (2-factor authentication) of the university. The servers are located in access-controlled computer rooms; only the administrators have physical access to the machines.

8.4 Retention and destruction of study data

The investigator retains all documents necessary for the identification and follow-up of trial participants, as well as all other original data, for at least twenty years after the completion or discontinuation of the clinical trial.
All study-related data will be archived for a minimum of 20 years after study termination or premature termination of the clinical trial in the archives of the Research Platform MCN. Electronically captured data with presentation® (Picture rating and recall episodic memory task and n-back working memory task) and Brainsight® (EMG) will be archived in a read-only status in the Studiendatenbank-MCN for at least 10 years (for further information on LabKey®, see chapter 8.5.2).

9 MONITORING AND REGISTRATION

An experienced staff member of the Molecular and Cognitive Neuroscience Departments monitors the following areas:

- Informed Consent Forms, 100%.
- Inclusion/exclusion criteria (pre-screening Q (certified copy, participant) compared to checklist at screening (completed by responsible investigator)): Initially, about 5 participants and then randomly at least 5 more (depending on the quality of documentation).
- Safety documentation, 100%

The source data/documents will be accessible to monitors, and questions will be answered during monitoring by the PI and the site staff. The study will be registered in the clinicaltrials.gov registry and the Swiss registry of Humanforschung Schweiz (HumRes) before the start of the recruitment.

10 FUNDING / PUBLICATION / DECLARATION OF INTEREST

10.1 Funding

This study is funded by the Research Platform Molecular and Cognitive Neurosciences of the University of Basel.

10.2 Publication and Dissemination Policy

The main publication will be created by Prof. Dominique de Quervain. Subsequent publications of subgroups can follow thereafter and will have to be approved by Prof. de Quervain.
No unpublished data given to the investigator may be transmitted to a third party without prior written approval by Prof. de Quervain. No publication or communication involving the results of the study is authorised without prior written consent from Prof. de Quervain. The investigator's name should not be used in any publication without the prior written permission of Prof. de Quervain.
The sponsor enters and publishes a summary of the trial results in a public register in accordance with ClinO Art. 65a within one year of completion or discontinuation of the trial. An interruption lasting more than two years is considered a discontinuation of the trial.
For the purpose of publication in the public register, the sponsor also ensures that a lay summary of the trial results is entered in BASEC within one year of completion or discontinuation of the trial. The entry is made at least in the national languages of Switzerland in which the study participants were recruited.
The investigator will provide each study participant with the lay summary of the trial results at the end of the study, directly. The investigator should ensure that study participants are adequately informed about this in the patient information document and that they are informed where the lay summary of the study results will be published online.

11 REFERENCES

11.1 Regulatory documents

1. Common Terminology Criteria for Adverse Events (CTCAE)
   https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
2. Declaration of Helsinki
   https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
3. Federal Act on Data Protection (FADP)
   https://www.admin.ch/opc/en/classified-compilation/19920153/index.html
4. Human Research Act (HRA)
   https://www.admin.ch/opc/de/classified-compilation/20061313/index.html
5. Gesetz über die Information und den Datenschutz des Kantons BS (Informations- und Datenschutzgesetz, IDG)
   https://www.gesetzessammlung.bs.ch/app/de/texts_of_law/153.260
6. International Conference on Harmonization (ICH) E6(R3) Guideline for Good Clinical Practice
   https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e6-r3-guideline-good-clinical-practice-gcp-step-5_en.pdf
7. International Conference on Harmonisation (ICH) E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
   http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf
8. Ordinance on Clinical Trials in Human Research (ClinO)
   https://www.admin.ch/opc/de/classified-compilation/20121176/index.html

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APPENDIX 1. Schedule of assessments

	Visit		
Task	**Duration**	**Screening**	**1 & 2**
Written informed consent, assignment of the subject number	15 min	+	-
Screening	20 min	+	-
Pregancy test for females	10 min	-	+
Questionnaires (EHI, MADRS, STAI-S, AIM)	30 min	-	+
Resting motor threshold (rMT) measurement	30 min	-	+
Intervention (experiment/control stimulation)	5 min	-	+
IAPS pictorial task – rating phase (1)	8 min	-	+
N-back (working memory task)	10 min	-	+
IAPS pictorial task - recall phase	30 min	-	+
IAPS pictorial task – rating phase (2)	8 min	-	+
Pain and discomfort ratings	1 min	-	+
Total (Screening and two internvetions)	~ 5 h		

Appendix 2. Study procedure