Inhibiting Human Aversive Memory by Transcranial Theta-Burst Stimulation to the Primary Sensory Cortex

Karita E. Ojala, Matthias Staib, Samuel Gerster, Christian C. Ruff, and Dominik R. Bach

ABSTRACT

BACKGROUND: Predicting adverse events from past experience is fundamental for many biological organisms. However, some individuals suffer from maladaptive memories that impair behavioral control and well-being, e.g., after psychological trauma. Inhibiting the formation and maintenance of such memories would have high clinical relevance. Previous preclinical research has focused on systemically administered pharmacological interventions, which cannot be targeted to specific neural circuits in humans. Here, we investigated the potential of noninvasive neural stimulation on the human sensory cortex in inhibiting aversive memory in a laboratory threat conditioning model.

METHODS: We build on an emerging nonhuman literature suggesting that primary sensory cortices may be crucially required for threat memory formation and consolidation. Immediately before conditioning innocuous somatosensory stimuli (conditioned stimuli [CS]) to aversive electric stimulation, healthy human participants received continuous theta-burst transcranial magnetic stimulation (cTBS) to individually localized primary somatosensory cortex in either the CS-contralateral (experimental) or CS-ipsilateral (control) hemisphere. We measured fear-potentiated startle to infer threat memory retention on the next day, as well as skin conductance and pupil size during learning.

RESULTS: After overnight consolidation, threat memory was attenuated in the experimental group compared with the control cTBS group. There was no evidence that this differed between simple and complex CS or that CS identification or initial learning were affected by cTBS.

CONCLUSIONS: Our results suggest that cTBS to the primary sensory cortex inhibits threat memory, likely by an impact on postlearning consolidation. We propose that noninvasive targeted stimulation of the sensory cortex may provide a new avenue for interfering with aversive memories in humans.

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Memory for aversive events allows learning from past experience, adaptive behavior, and survival in ever-changing environments. However, in anxiety and stress-related disorders, such memories can become maladaptive and impairing (1,2). Because current treatments for these conditions leave room for improvement (3), preclinical research in healthy humans has sought to develop pharmacological interventions that could prevent or modify aversive memories (4). Drugs are administered systemically and cannot be targeted to specific brain circuits in humans. Transcranial magnetic stimulation (TMS), in contrast, could offer more focused interventions. Studies in rodents have shown that acquisition of threat memory depends fundamentally on synaptic plasticity in the basolateral and centromedial amygdala (5,6), a structure that is inaccessible to standard TMS. However, an emerging literature suggests an essential role of sensory cortices in learning from threat, and these areas are amenable to targeted TMS. Here, we sought to provide evidence that the primary sensory cortex is indeed causally required for human threat memory.

In rodents, the amygdala receives information about conditioned stimuli (CS) and unconditioned stimuli (US) directly via the sensory thalamus (7) and, in the case of auditory threat conditioning, via an additional indirect pathway through the auditory cortex (7,8). Similar cortico-amygdala projections exist for all sensory modalities across species (7,9), and secondary auditory, visual, and olfactory cortices are involved in rodent threat conditioning (10) and show postlearning plasticity (11). Yet, whether sensory cortices are necessary for formation and maintenance of threat memory remains controversial for some types of threat associations and may depend on the complexity of the CS. Acquisition of nondiscriminative threat conditioning with an artificial simple frequency tone as CS appears not to depend crucially on the auditory cortex ([10,12–18], but note [17,19]). The case is less clear for discriminative learning with two simple CS: optogenetic inactivation of the auditory cortex left learning unimpaired in one study (20), but muscimol inactivation of the auditory cortex (21) and electrolytic lesions of the cortex-projecting ventral division of the auditory medial geniculate nucleus (22) impaired learning in other studies. In contrast, the auditory cortex has an established key role for associating naturalistic or complex auditory CS (e.g., frequency sweeps) with threat US...
(20,23–25), but see (26). Specifically, disrupting neural transmission in the auditory cortex during learning impairs threat memory acquisition of complex stimuli (20,24), and blocking protein synthesis impairs postlearning consolidation but leaves acquisition unaffected (25). Finally, disrupting neural transmission in the auditory cortex during cue presentation in a postconditioning test impairs complex discriminative but not nondiscriminative threat memory retrieval (18).

In humans, CS+ associated with threat US and CS− associated with safety elicit differential evoked-potential amplitude, oscillatory synchrony, and univariate functional magnetic resonance imaging (fMRI) blood oxygen level–dependent amplitude in the visual cortex (27–29), multivariate blood oxygen level–dependent patterns in the olfactory cortex (30), and univariate blood oxygen level–dependent amplitude and multivariate patterns in the auditory cortex, with no difference between simple and complex CS (31–33). Recent evidence has also shown that the visual cortex is involved in long-term threat memory in humans (34). However, the precise function of these areas in the acquisition and retention of threat memories remains unresolved. In particular, it is unclear whether activity in these areas is in fact required for threat memories to be formed and/or consolidated.

To elucidate the role of the primary sensory cortex for discriminative conditioning to simple and complex CS in humans, we used continuous theta-burst TMS (cTBS) as a technique that can transiently downregulate cortical excitability and synaptic plasticity in the targeted area (35). We selected somatosensation as our model system because the primary somatosensory cortex (S1) is well accessible to cTBS and stimulus representation is strictly contralateral, unlike in the auditory system or in foveal vision (36). Somatosensory threat conditioning in humans has been demonstrated previously (37,38), including a study from our own laboratory with the same CS as in this work (39). To examine the role of complex stimulus features, we used simple CS defined by stimulus location (finger) and complex CS defined by a temporal pattern of alternating locations. S1 was localized individually with fMRI.

We expected reduced threat memory retention after overnight memory consolidation when cTBS had been applied to the stimulus–contralateral sensory cortex (experimental group) as compared with the stimulus–ipsilateral cortex (control group). We measured threat memory retention by potentiation of the startle eye-blink reflex to CS+ versus CS−. Studies in rodents suggest that cTBS exerts effects at multiple timescales: it can elicit action potentials immediately during stimulation, lead to a period of reduced cortical excitability in the direct aftermath of the stimulation, and induce longer-term changes in learning and memory at different timescales through synaptic long-term depression (LTD) and by modulating neurotransmitters, neural growth factors, and gene expression (40,41). In humans, there is evidence that the inhibitory LTD-like effect of cTBS (35) may be mediated by effects on both GABAergic (gamma-aminobutyric acidergic) interneurons and glutamate (NMDA) receptors that are involved in synaptic long-term potentiation (LTP) and LTD (42–44).

However, the timescales of these effects are not precisely known, and neither is the time course of memory consolidation, which starts immediately after a CS-US coupling. Synaptic plasticity independent of protein synthesis (early LTP) may last up to 1 to 3 hours, synaptic consolidation dependent on protein synthesis starts soon after the first instance of learning and may last up to 24 hours (late LTP), and systems consolidation takes place over days and weeks (45,46). To maximize the sensitivity of our study to answer whether S1 is causally involved in threat memory formation and/or retention, we conducted cTBS before learning and measured threat memory recall on the next day as the primary outcome. By analyzing conditioned responses during initial learning, we additionally sought to disentangle whether a possible effect on memory retention was primarily driven by learning deficits already measurable during conditioning or consolidation deficits only measurable during the recall test.

METHODS AND MATERIALS

Participants

A total of 68 participants (34 women and 34 men; mean ± SD age = 23.7 ± 4.2 years) recruited from the general and student population completed the cTBS and threat conditioning session on test day 1 according to protocol. After exclusions due to data collection and quality issues (detailed in Figure S1 in Supplement 1), the final sample for skin conductance analyses was 62 participants (28 experimental, 34 control) and 34 participants (18 experimental, 16 control) for pupil size analyses. A total of 52 participants were included in our analyses of startle eye-blink responses in the threat memory recall test (25 experimental, 27 control). All recruited participants stated no history of neurological and psychiatric disorders or contraindications for TMS and MRI and gave written informed consent. The study protocol, including the form of taking consent, was in accordance with the Declaration of Helsinki and approved by a governmental research ethics committee (Kantonale Ethikkommission Zürich, KEH-ZH 2013-0383).

Primary Sensory Cortex Localization and Transcranial Stimulation Protocol

Participants took part in an fMRI experiment to individually localize the S1 representation of the index and middle fingers of both hands for later targeting with cTBS. After the fMRI localization, participants were invited to the laboratory on 2 consecutive days (Figure 1). On the first day, cTBS was administered before the experimental task. We used a protocol that has been shown to decrease cortical excitability for up to an hour (35). For the experimental group, cTBS was applied to the left hemisphere S1, and for the control group, it was applied to the right hemisphere S1. The protocol consisted of 600 pulses administered continuously for 40 seconds in bursts of three pulses at 50 Hz (every 20 ms) at 5-Hz intervals (every 200 ms) (35), applied with a figure-of-eight coil. Immediately after cTBS, participants underwent 20 minutes of classical threat conditioning, which is well within the estimated duration of the cTBS effect (55). Details of the localizer and cTBS protocols are described in Supplement 1.
CS and US of the Threat Conditioning Protocol

There were four different CS in the experiment: 1) simple CS+ paired with an electric shock US in 50% of trials, 2) simple CS− never paired with the US, 3) complex CS+ paired with an electric shock US in 50% of trials, and 4) complex CS− never paired with the shock. Simple and complex CS trials were presented in separate, alternating conditioning blocks in all conditioning and recall sessions. The intensity for the CS was set for each finger separately and to a subjectively clear but not unpleasant level by incremental increases of the current. CS were 4-second electric pulses to the middle and index fingers of the left hand delivered with a Digitimer DS7A stimulator through a pin-cathode/ring-anode electrode. Simple CS were short pulses either on the middle or index finger whereas complex stimuli alternated between the two fingers. Aversive US was an electric shock of 500-ms duration delivered with a Digitimer DS7A stimulator to the top of the foot. The US was delivered ipsilateral to the cTBS site to exclude possible cTBS effects on sensory processing of the US. Intensity of the US was individually calibrated for each participant.

Day 1: Training, cTBS, and Threat Conditioning

Participants trained the experimental task without US before cTBS. They received each of the four somatosensory CS three times in random order (i.e., 12 trials) and were asked to indicate which CS pattern they perceived by pressing the left/right arrow button. The training block was repeated until 75% accuracy was achieved for both simple and complex stimuli and served also as habituation to the CS alone. After cTBS, the threat conditioning protocol followed, consisting of eight blocks of 12 trials each, for a total of 96 trials. The intertrial interval was between 7 and 11 seconds. The order of simple and complex blocks (simple first or complex first) was randomized.

Day 2: Threat Memory Retention and Relearning

The next day, participants returned for a recall and relearning session to assess memory savings from the conditioning session of the previous day. Recall was measured in the absence of US in four blocks of six trials each, i.e., two blocks of simple and two blocks of complex stimuli, for a total of 24 trials (12 CS+, 12 CS−). Before the recall session, the experiment was set up the same way as the previous day, including the US electrode on the foot. To retain expectation of US, participants were instructed that they may experience US during the session, including the possibility of only one US at the very end. During the recall session, participants were exposed to auditory startle probes (50 ms, 100-dB white noise via headphones) on every trial at CS offset. The relearning session was identical to the learning session of the previous day, except for the cTBS.

Dependent Variables

Our primary index of memory retention was fear-potentiated startle, which has been suggested as the most sensitive conditioned response across various psychophysiological indices (47) as well as in a head-to-head comparison with skin conductance responses (SCRs) (48). Different from other conditioned responses, it is also assumed to unambiguously relate to US expectation (49). We did not use fear-potentiated startle during acquisition, because this has been shown to alter and delay the learning process (50) and might therefore reduce...
the sensitivity of the paradigm. To index acquisition of conditioning, we used SCRs and pupil size responses (PSRs) estimated with a model-based approach (39,51). These were not analyzed in the recall session because the presence of startle probes produces artefacts and makes the responses difficult to interpret. Details of the psychophysiological methods are found in Supplement 1.

**CS-US Contingency Ratings.** Immediately after the conditioning and relearning sessions, participants were presented with each CS alone without US. Participants were asked to indicate what they thought was the probability of the US occurring together with this CS, from a choice of 0%, 25%, 50%, 75%, or 100%.

**Statistical Analysis**

The estimated startle eye-blink, SCRs and PSRs, and post-experiment contingency ratings, accuracies, and reaction times for each participant were analyzed in R (62). For SCRs and PSRs in both learning and relearning sessions, only trials without US were included in the analyses to avoid confounding of the conditioned responses with unconditioned responses. Psychophysiological response estimates, CS-US contingency ratings, reaction times, and accuracy percentages were entered into three-way repeated-measures analyses of variance of the form $DV \sim group \times CS$ type $\times CS$ complexity + error (subject/CS type $\times CS$ complexity). Post hoc tests were conducted with emmeans R package (53) and effect sizes were approximated with the $t_{to\_d}$ function of effect size package (54). Further specific tests were conducted with Student’s paired $t$ tests for within-subject effects and Welch’s two-sample $t$ tests for comparing groups with unequal sample sizes. One-tailed $p$ values were used for a priori hypotheses for $CS+ > CS-$ and control > experimental group; two-tailed tests were used for all other comparisons.

**RESULTS**

**Threat Memory Retention: Startle Eye-Blink Responses**

The primary focus of our study was to investigate the cTBS effect on memory retention on test day 2. Consistent with a cTBS-induced reduction of threat memory retention, we found a significant group $\times CS$ type interaction (Table 1 and Figure 2), with an overall smaller $CS+/CS-$ difference in the experimental group compared with the control group. There was no evidence that this effect depended on CS complexity (Table 1). Post hoc $t$ tests suggested a difference in fear-potentiated startle elicited by $CS+$ versus $CS-$ (collapsing across CS complexity) in the control group ($t_{50} = 3.76$, $p = .0002$, Cohen’s $d = 0.53$) but not in the experimental group ($t_{50} = 0.25$, $p = .60$, $d = 0.04$).

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Startle eye-blink responses (SEBRs) during threat memory recall test on test day 2. (A) Trial-by-trial responses for each condition show the time course of the responses, with little differentiation of $CS+$ and $CS-$ for the control group and overall quick decline in amplitude across trials (habituation). (B) The $CS+/CS-$ difference was smaller for the experimental group than for the control group across simple and complex conditioned stimuli (CS), indicating that the fear-potentiated startle was inhibited by continuous theta-burst transcranial magnetic stimulation as measured in the threat memory recall test the next day. Error bars are 95% within-subject standard errors of the mean reflecting paired, one-tailed $CS+ > CS-$ comparison (59). a.u., arbitrary units.

| Table 1. Statistical Test Results for Conditionwise Startle Eye-Blink Responses During Threat Memory Recall Test on Test Day 2 |
|-----------------|----------------|------------------|
| Repeated-Measures ANOVA | $F_{1,50}$ | $p$ | $\eta^2$ |
| Group | 7.71 | .008 | 0.024 |
| CS Type | 6.39 | .015 | 0.020 |
| CS Complexity | 5.48 | .023 | 0.049 |
| Group $\times$ CS Type | 7.71 | .008 | 0.024 |
| Group $\times$ CS Complexity | 0.00 | .99 | <0.001 |
| CS Type $\times$ CS Complexity | 0.30 | .59 | <0.001 |
| Group $\times$ CS Type $\times$ CS Complexity | 2.56 | .12 | 0.006 |

$\eta^2$ represents the explained variance. ANOVA, analysis of variance; CS, conditioned stimulus.
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group difference in CS+/CS− discrimination was already present during the first six trials of the recall test (t_{30,71} = 2.16, p = .036, d = 0.598). Moreover, the size of the group difference in CS+/CS− discrimination did not differ between the first and last half of the recall test (t_{47,17} = 1.58, p = .12, d = 0.435).

Threat Conditioning on the Day Before Recall Test: SCRs and PSRs

Our finding of reduced memory retention after cTBS could be due to impairments in synaptic consolidation after the threat conditioning or due to impairments in neural processing and synaptic transmission during acquisition of conditioning. To assess the latter possibility, we analyzed SCRs and PSRs to CS during conditioning on test day 1. In line with our previous somatosensory threat conditioning data (39), participants learned to discriminate CS+ and CS− as evidenced by SCRs (Table 2 and Figure 3A, C) and PSRs (Table 2 and Figure 3B, D). There was no evidence that learning differed between control or experimental cTBS groups. Pairwise comparisons within the groups showed a different constellation of results for SCRs and PSRs, with stronger learning in the control group than in the experimental group for SCRs but the opposite pattern for PSRs (Figure 3C, D; Table S3 in Supplement 1). There was no evidence that learning differed between groups was not close to significant for either SCR or PSR (Table 2).

Threat Relearning After Recall Test: SCRs and PCRs

To assess memory savings carried over from the conditioning session of the previous day, we conducted a second learning session directly after the threat memory recall test. PSRs discriminated between CS+ and CS− overall, with no difference between experimental and control cTBS groups (Figure S3 and Table S5 in Supplement 1). No significant differences in CS+/CS− responses were found in condition-wise SCRs (Figure S3 and Table S5 in Supplement 1) while a small difference was found in trialwise responses (F_{1,3886} = 5.83, p = .02) but no group × CS type interaction (Table S6 in Supplement 1).

CS-US Contingency Learning

Participants learned to explicitly distinguish CS+/CS− (F_{1,50} = 18.1, p < .001, η^2 = 0.121) (Figure S4A in Supplement 1) after day 1 and on day 2 after relearning (F_{1,50} = 83.3, p < .001, η^2 = 0.356) (Figure S4B in Supplement 1). There was no difference between ratings for simple and complex stimuli on either test day or between cTBS groups on test day 1 (all p values > .30). Further results can be found in Supplement 1.

DISCUSSION

Growing evidence from rodent studies suggests that sensory cortices are important for processing complex stimuli during auditory threat conditioning, but their role for simple CS, and for human threat conditioning in general, remains unclear. We addressed this question in a TMS study with the goal of inducing temporary inhibition of neural processing in the sensory cortex. We applied cTBS in healthy human participants over S1, either ipsilateral (control) or contralateral (experimental) to somatosensory stimuli, immediately prior to a threat conditioning protocol where the somatosensory stimuli were paired with painful shocks (CS+) or not (CS−). We found that after overnight consolidation, differential fear-potentiated startle to CS+/CS− was smaller in the experimental (contralateral cTBS) group compared with the control (ipsilateral cTBS) group. Detailed analyses confirmed the robustness of this finding and showed that it was not due to group differences in extinction learning or in the random trial sequence.

Table 2. Statistical Test Results for Conditionwise SCRs and PSRs During Threat Learning on Test Day 1

|                   | F      | p      | η^2 |
|-------------------|--------|--------|-----|
| SCRs              |        |        |     |
| Group             | F_{1,80} = 0.45 | .51    | 0.001 |
| CS type           | F_{1,80} = 7.82 | .007   | 0.02 |
| CS complexity     | F_{1,80} = 1.25 | .27    | 0.1  |
| Group × CS type   | F_{1,80} = 0.39 | .53    | <0.001 |
| Group × CS complexity | F_{1,80} = 0.06 | .82    | <0.001 |
| CS type × CS complexity | F_{1,80} = 1.68 | .20    | 0.004 |
| Group × CS type × CS complexity | F_{1,80} = 0.19 | .67    | <0.001 |
| PSRs              |        |        |     |
| Group             | F_{1,35} = 1.36 | .25    | 0.021 |
| CS type           | F_{1,35} = 5.33 | .027   | 0.015 |
| CS complexity     | F_{1,35} = 33.2 | <.001  | 0.002 |
| Group × CS type   | F_{1,35} = 0.85 | .36    | 0.119 |
| Group × CS complexity | F_{1,35} = 2.29 | .14    | 0.008 |
| CS type × CS complexity | F_{1,35} = 1.53 | .23    | 0.003 |
| Group × CS type × CS complexity | F_{1,35} = 0.05 | .82    | <0.001 |

η^2 represents the explained variance.

ANOVA, analysis of variance; CS, conditioned stimulus; PSRs, pupil size responses; SCRs, skin conductance responses.
We found no evidence for an inhibitory cTBS effect during the initial learning session. Moreover, contralateral cTBS did not impair CS identification, excluding the possibility that our results merely reflect a cTBS-induced deficit in immediate somatosensory processing unrelated to the threat conditioning. Taken together, these results suggest that cTBS did not interfere with basic sensory processing and activity-dependent short-term plasticity, but rather with synaptic structural reconfiguration required for memory consolidation (45).

As a caveat, cTBS was conducted before threat conditioning. The lack of a significant effect of cTBS on learning cannot conclusively rule out that there was no impact on learning, particularly so because distinct and not directly comparable conditioned responses were assessed during learning and during recall. Future work could conduct cTBS after conditioning to conclusively confirm that cTBS impacts on consolidation. This could also be useful to explore the possibility of using cTBS clinically in a post-trauma prevention setting. Recently, it was shown that repetitive TMS over the dorsolateral prefrontal cortex administered after visual threat memory retrieval was successful in reducing physiological threat responses during the so-called reconsolidation period and preventing return of threat responding after reinstatement, while leaving declarative CS-US learning intact (56). The authors speculate that this effect may be due to the role of the dorsolateral prefrontal cortex in memory retrieval and potentially due to long-range connections to the amygdala (56).

Therefore, there may be several putative time windows and neural pathways through which to influence threat memories with TMS. Beyond TMS studies, there is very little data from clinical lesion samples to address the role of sensory cortices in threat conditioning. One lesion case study suggested that the visual cortex is not required for nondiscriminative visual conditioning in humans (57), in line with nondiscriminative auditory conditioning in rodents (10,12,14–16).

While we selected somatosensory threat conditioning as a model system for methodological reasons, somatosensation is an important sensory modality to investigate next to the more commonly investigated auditory and visual modalities. Clinically, somatosensation is affected in posttraumatic stress disorder (59), a psychiatric disorder that has been proposed to develop partly as a result of maladaptive conditioning mechanisms such as threat overgeneralization and impaired safety learning (1,2). In rodents, somatosensory threat conditioning with whisker touch as CS is suggested to induce increased neural response strength, sparse coding (59), dendritic spine plasticity (60), and inhibitory postsynaptic potentials (61) in the primary somatosensory barrel cortex, somewhat similar to postconsolidation changes in the auditory cortex (62). Our study adds to the scarce literature on somatosensory threat conditioning in humans (37,38). In line with our previous work (39), we have shown that somatosensory threat learning is possible from simple and complex patterned electric pulses on fingers, but now we additionally demonstrate that the associative memory is retained at least overnight.

We found that S1 is required at least for consolidation of associative somatosensory threat memories in humans, in line with previous findings in rodent auditory threat conditioning to complex cues. It has been suggested that primary sensory cortices are involved in stimulus identification and are specifically needed for processing complex stimuli, such as frequency sweeps and tone pips, which necessitate the binding together of different stimulus elements into a unitary representation (20,63). However, we did not find evidence that the role of S1 in threat conditioning and threat memory retention differed between simple and complex somatosensory stimuli (here differentiated by the temporal pattern of the stimulus across one or two fingers). Indeed, the role of the sensory cortex in rodent discriminant conditioning with simple cues has not been conclusively established or falsified. Our results are more in line with studies suggesting that primary sensory cortices are important for discriminant simple-cue conditioning as well (17,19). They are also in line with human neuroimaging studies that found equal CS+/CS− neural pattern discriminability for simple and complex CS in the auditory cortex (32,33) and that were able to cross-decode simple CS threat predictions from complex threat predictions and vice versa (32). However, it is possible that experiments with larger...
sample sizes may detect effects of complexity (64,65). Finally, as of yet, there is no direct evidence from neuroimaging studies that somatosensory cortices are associated with threat learning and memory processes in humans irrespective of stimulus complexity.

The neural effects of theta-burst TMS are multifaceted (40). They may reflect synaptic LTP and LTD at excitatory glutamatergic (42,66) and inhibitory GABAergic neurons (44,67), neurotrophic factors (68,69), and neurogenesis (70). It has been proposed that the LTD-like effect of continuous theta-burst TMS used here is based on an initial facilitatory LTP-like effect, as seen with intermittent theta-burst TMS, which reverses and becomes inhibitory with continuing stimulation (71). However, at this moment, it is not yet known whether these mechanisms truly underlie the observed inhibitory effect of continuous theta-burst TMS observed in humans. The best evidence comes from a study where an NMDA receptor antagonist blocked both the LTP-like excitatory and LTD-like inhibitory effects of theta-burst TMS in 6 healthy human participants (42). Finally, the efficacy of repetitive TMS is strongly influenced by baseline cortical excitability as well as individual and contextual factors (40,43,72). Crucially, rodent studies suggest also longer-lasting effects of cTBS via modulating neurotransmitters, neural growth factors, and gene expression (40,41). This may have contributed to the results we observe here, a hypothesis that could be tested by future extensions of our approach in rodents.

TMS is known to influence wide functional networks in the human brain, with potential effects on even distant brain regions through long-range connections (41,73). This has also been shown for cTBS of S1 at rest, which led to reductions in functional connectivity of S1 with a variety of distant brain regions, including regions important for threat conditioning such as the amygdala, striatum, and anterior cingulate cortex (74). Therefore, without concurrent fMRI measurement, we cannot confirm or exclude possible downstream influences of our cTBS protocol on other brain areas.

Taken together, we found that inhibitory cTBS over S1 led to reduced threat memory retention after overnight consolidation, with no clear influence of CS complexity. This finding extends the rodent and human literature on the function of primary sensory cortices in threat learning and memory by suggesting that primary sensory cortices are involved in stimulus representation for threat conditioning and play a role in consolidation of threat memories. Further studies may investigate the neurophysiological mechanisms underlying these effects with concurrent neuroimaging and TMS, examine whether cTBS on S1 could be used as a method to modify threat memories through a reconsolidation update mechanism (75), and attempt to establish whether intervening with (re)consolidation of threat memories may have clinical relevance for patients with fear and anxiety disorders.

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DRB, MS, and CCR designed the experiment; SG and CCR provided methodological expertise, training, and access to equipment; SG and MS piloted the experiment; KEO and MS acquired the data; KEO analyzed the data; KEO wrote the original draft of the article; MS, CCR and DRB contributed to the editing and revising of the paper; and DRB supervised work at all stages.

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ARTICLE INFORMATION

From the Computational Psychiatry Research (KEO, MS, SG, DRB), Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital; Neuroscience Centre Zurich (KEO, MS, CCR, DRB); Zurich Center for Neuroeconomics (CCR), Department of Economics, University of Zürich, Zürich, Switzerland; and the Wellcome Centre for Human Neuroimaging and Max-Planck UCL Centre for Computational Psychiatry and Ageing Research (DRB); University College London, London, United Kingdom.

KEO and MS contributed equally to this work.

Address correspondence to Karita E. Ojala, Ph.D., at k.ojala@uke.de, or Dominik R. Bach, Ph.D., at d.bach@ucl.ac.uk.

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