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ORIGINAL ARTICLE

# Neuromodulation of Visual Cortex Reduces the Intensity of Intrusive Memories

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## Abstract

Aversive events can be reexperienced as involuntary and spontaneous mental images of the event. Given that the vividness of retrieved mental images is coupled with elevated visual activation, we tested whether neuromodulation of the visual cortex would reduce the frequency and negative emotional intensity of intrusive memories. Intrusive memories of a viewed trauma film and their accompanied emotional intensity were recorded throughout 5 days. Functional connectivity, measured with resting-state functional magnetic resonance imaging prior to film viewing, was used as predictive marker for intrusions-related negative emotional intensity. Results indicated that an interaction between the visual network and emotion processing areas predicted intrusions' emotional intensity. To test the causal influence of early visual cortex activity on intrusions' emotional intensity, participants' memory of the film was reactivated by brief reminders 1 day following film viewing, followed by inhibitory 1 Hz repetitive transcranial magnetic stimulation (rTMS) over early visual cortex. Results showed that visual cortex inhibitory stimulation reduced the emotional intensity of later intrusions, while leaving intrusion frequency and explicit visual memory intact. Current findings suggest that early visual areas constitute a central node influencing the emotional intensity of intrusive memories for negative events. Potential neuroscience-driven intervention targets designed to downregulate the emotional intensity of intrusive memories are discussed.

**Key words:** intrusive memory, memory, reactivation, TMS, visual cortex

## Introduction

Following traumatic and aversive events, people commonly experience spontaneous intrusive recollections of the distressing incident (intrusive memories) (Iyadurai et al. 2019). These memory intrusions are predominantly visual, experienced in the form of mental imagery of discrete moments from within the distressing event (Ehlers et al. 2004; Holmes et al. 2004, 2005). The early visual cortex has been implicated in such visual mental imagery (Pearson et al. 2015; Pearson 2019), and it has a causal role in the ability to hold vivid mental images in mind (Kosslyn 1999; Cattaneo et al. 2012). Here, we found that functional connectivity of the visual network with emotion processing and memory-related brain regions prior to exposure to an aversive event predicts the negative emotional intensity of to-be intruding memory images. In addition, we found that inhibiting early visual activity using noninvasive neuromodulation can reduce the emotional intensity of such memory intrusions.

Intrusive memories constitute a basic mode of remembering (Berntsen 2010). While the functional role of memory intrusions is still not clear, there are indications that memory intrusions function to maintain the visual memory of negative events

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across time (Herz et al. 2020). While memory persistence for stressful situations can adaptively guide behavior in similar future circumstances, pathological persistence can lead to post-traumatic stress disorder (PTSD), where intrusive memories from the trauma lead to extreme distress and functional impairment (Bryant et al. 2011; Bar-Haim et al. 2021).

According to dual representation theory (Brewin et al. 2010), intrusive memories arise from high sensory-bound representations that lack sufficient contextual representation during encoding of the traumatic event. Emergence of these sensory-bound memories, which are usually accompanied by a strong emotional reaction, involve projections of the dorsal visual stream to superior parietal areas as well as to the amygdala and insula (Brewin et al. 2010). Exposing patients with PTSD to reminders of their trauma while undergoing functional magnetic resonance imaging (fMRI) revealed that relative to ordinary episodic memories of the trauma, intrusive memories involved increased activation of the sensory and motor areas, corresponding with the affective and visual components of the sensory-bound representations predicted by the dual representation theory (Whalley et al. 2013).

Studies have used the trauma film paradigm to study intrusive memories in a more controlled laboratory environment (James et al. 2016). Using fMRI during encoding of aversive material, it was found that subsequently intrusive scenes, relative to neutral scenes, involved elevated activation of the amygdala and the ventral occipital cortex. Relative to aversive material that did not intrude, an elevated activation of the inferior frontal gyrus and bilateral middle temporal gyrus was observed for the material that did intrude (Bourne et al. 2013). A subsequent study found a similar pattern of results and also used machine learning on fMRI data acquired during encoding to predict scenes that would subsequently become intrusive. The classifier indicated a number of brain networks predictive of intrusions, including areas involved in emotional processing and a perception-vision-shape network involving visual brain regions (Clark et al. 2014, 2016). These results are consistent with the highly emotional and visual nature of intrusive memories. Together with enhanced visual priming for subsequently intrusive material (Ehlers et al. 2006), findings appear to generally support the involvement of emotion-related and visual brain areas in the formation of intrusive memories.

Various ways have been considered to modify negative intrusive memories. Key approaches have drawn on reconsolidation theory (Haubrich and Nader 2016) and relied on reminder stimuli, intended to reactivate the memory trace, to enable its modification and downregulation (Kindt and van Emmerik 2016; Monfils and Holmes 2018). For example, administration of Propranolol in proximity to memory reactivation stimuli was found to reduce behavioral expressions of fear (Kindt and van Emmerik 2016) and subjective feelings of anxiety (Soeter and Kindt 2012). In a similar vein, trauma-focused cognitive behavior therapy relies on the systematic recall of trauma memories and their elaboration in the safe and supportive context of psychotherapy (McLean and Foa 2011). Such interventions aim to reduce the involuntary nature of memory retrieval and the emotional intensity associated with it, while leaving voluntary memory of the trauma intact (Visser et al. 2018; Lau-Zhu et al. 2019). Visuospatial cognitive tasks delivered following a memory reminder procedure were shown to reduce the amount of intrusions experienced in the week following an aversive event, presumably by taxing visual working memory resources necessary for the reformation of perceptual memory intrusions (Kessler et al. 2018, 2020). Given the relevance of sensory-visual elements to the intrusion formation, direct inhibition of visual brain regions may function as a mechanistically specific target for intervention. Indeed, inhibitory 1 Hz repetitive transcranial magnetic stimulation (rTMS) over the early visual cortex has been shown to effectively interfere with a previously consolidated perceptual memory (Shmuel et al. 2021), suggesting that this protocol may also prove effective for interfering with perceptual memory intrusions.

Here, using an experimental analog of trauma, we used rTMS to determine whether inhibitory stimulation of early visual cortex following memory reactivation can reduce the frequency and negative emotional intensity of intrusive memories of traumatic material. In addition, we investigated whether baseline functional connectivity, measured by resting-state fMRI, can predict the frequency and emotional intensity of intrusive memories. Previous studies indicated that baseline brain activity can predict participants' behavioral responses to external stimuli (Fox and Raichle 2007) and that resting-state functional connectivity of the visual network predicts evoked blood oxygen level–dependent (BOLD) responses to visual stimuli (Liu et al. 2011). High variability in intracranial electroencephalography (iEEG) fluctuations within visual areas during resting state also predicts performance in a visual memory task, even when the resting state data are acquired 1 day or more apart from the behavioral task (Grossman et al. 2019). We therefore expected that interindividual variability in the frequency and emotional intensity of intrusions would be predicted from the baseline functional connectivity of the visual network with memory- and emotion-related brain regions, such as the hippocampus and the amygdala.

## Materials and Methods

### Participants

Participants were 44 individuals (24 females, $M_{age}$ = 24.8 years, standard deviation [SD] = 2.6, range = 20–30) recruited through online and printed advertisements. Exclusion criteria were current self-reported neurological, physical, or mental disorders, or the use of any medication that can affect the central nervous system. Individuals with a score $\geq$ 33 (the suggested clinical cutoff) in the PTSD checklist for DSM-5 were excluded (PCL-5; $M_{PCL}$ = 7.0, SD = 5.9, range = 2–15) (Blevins et al. 2015). Presence of a metal object within or near the head that precluded magnetic resonance imaging (MRI) or transcranial magnetic stimulation (TMS) also served as exclusion criteria. All participants had normal or corrected-to-normal vision.

Due to technical failures, four participants did not receive the rTMS intervention. The remaining 40 participants were allocated to a visual-rTMS ($n$ = 19, 11 females) or a vertex-rTMS ($n$ = 21, 11 females) as a control stimulation site (Jung et al. 2016). Allocation to groups was made on day 2 of the study immediately prior to the rTMS procedure, alternately matching participants between groups on the sum of intrusions on day 1 of the study. Participants provided their written and informed consent prior to testing and were compensated $125 for their participation. The Tel Aviv Sourasky Medical Center (reference number: 0561-14) and the Tel-Aviv University Institutional

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Review Boards (reference number: 0000912-1) approved the study.

## Tasks and Measures

*MRI Data Acquisition*

Participants underwent an MRI session which included anatomical sequences and resting-state fMRI. Scans were acquired using a 3 Tesla scanner (Siemens) with a 64-channel head coil at the Alfredo Federico Strauss Center for Computational Neuro-Imaging, Tel Aviv University. For structural data, T1w high-resolution (1 $mm^3$) whole brain images were acquired with an MPRAGE sequence (time repetition/time echo [TR/TE] = 1750/2.62 ms; flip angle = 8°; in-plane acquisition matrix [AM] = 224 × 224; field of view [FOV] = 256 × 256 mm; slice thickness = 1 mm; 176 axial slices). Additional anatomical sequences (T2w and fluid-attenuated inversion recovery [FLAIR]) were acquired for radiological screening. Functional imaging data were acquired with a CMRR multiband accelerated echo planar imaging pulse sequence of functional T2∗-weighted images (TR/TE = 2000/30 ms; flip angle = 82°; AM = 104 × 104; FOV = 208 × 208 mm; slice thickness = 2 mm; 66 interleaved axial slices per volume). All images were acquired at a 30° angle off the anterior–posterior commissures (AC–PC) line. The resting-state functional scans comprised a total of 240 volumes (acquisition duration = 8 min). The first five volumes were discarded to account for T1-equilibrium effects.

*Trauma Film*

The trauma film consisted of eight different scenes displaying distressing content, including: self-injury, eye surgery, animal cruelty, car accident, knee surgery, a scene of humans attacked by an animal, tooth extraction, and a man stabbed with a knife. These scenes were taken from a previous study (Herz et al. 2020). Average scene duration was 80.12 s (SD = 25.35). The presentation of each scene was followed by a 2-min break during which participants were requested to remain seated with their eyes closed until a sound signaled the beginning of the next scene. Author N.H. received training from author E.A.H. on administration of the trauma film paradigm, including a lab exchange visit to learn and practice methods.

*Trauma Film Mood Manipulation Check*

Before and after the trauma film, participants rated how sad, scared, angry, and happy they felt "at this very moment" on an analog scale ranging from (0) "not at all" to (10) "extremely." A composite mood score (ranging 0–40) was computed by summing all scale scores after inverting the happy scale score (Holmes et al. 2010). Further manipulation checks, conducted immediately following film watching, included ratings of attention paid to the film and distress experienced in response to the film ranging from not at all (0) to extremely (10).

*Memory Reactivation Procedure*

A procedure intended to facilitate memory reactivation was applied 1 day following film viewing and consisted of presentation of one neutral still image from each of the eight scenes of the trauma film. The images served as reminder cues for scenes from the trauma film without reexposing participants to its aversive content (James et al. 2015). The cues were presented on the same computer in the same room as used for the trauma film viewing. Following the participants' key-press, images were presented one at a time against a black background for 3 s each, with 3-s interstimulus interval (ISI). The same eight reactivation images were presented to all participants, which were different from the images used in the recognition memory tests.

Subsequent to the memory reactivation procedure, participants were provided with a 10-min standardized filler task that consisted of pleasantness ratings of 15 classical music pieces (James et al. 2015).

*Digitized Intrusive Memories Diary*

Participants recorded their intrusive memories about the film in a digitized online diary that was accessible through their mobile phones (Qualtrics—version November 2017–July 2018, Provo, UT), which was developed in a previous study (Herz et al. 2020). It was explained that intrusive memories come to mind unbidden (rather than deliberately recalled) in the form of sensory mental images. A distinction was made between intrusive memories versus pure verbal thoughts, which were defined as words/verbal language relating to the film, without remembering any specific perceptual details from it. Participants were requested to record any involuntary memories of the film immediately following its occurrence, to indicate its type (mental image, verbal thought, or both) and describe its content in a way that would allow identifying the intrusion as related to a specific scene of the film. Verbal thoughts, if they occurred alone, were not included in the intrusion analysis.

The emotional intensity of each of the recorded intrusive memories was rated as the amount of distress elicited by the recorded intrusion on a scale ranging from 0 (not at all) to 10 (extremely). Ratings were completed in the diary immediately after recording the occurrence of a given intrusion.

Separate diary entries were requested for each intrusive memory even if the same memory intruded more than once or if several memories intruded in succession. Participants were asked to provide diary entries for at least three times per day (morning, afternoon, and evening) even if they did not experience any intrusive memories in which case a "no intrusive memory" option could be selected. An experimenter checked whether each diary entry was matched to one of the eight scenes viewed and that participants completed the diary for each of the study days. Detailed description of data extracted from the digital diary can be found in the Supplementary Material.

*Visual Recognition Memory Test*

The visual recognition memory test was a two-alternative forced-choice test. The test consisted of three trials per scene, yielding a total of 24 trials. On each trial, two images were presented serially: One image was taken from the original viewed film, and the other depicted a similar content taken from another unviewed film. Each image was presented for 1000 ms with 1000 ms ISI. The order of presentation of the two pictures was random, as well as the order of the trials. After watching the two images, participants had to indicate as fast and accurate as possible which of the two images was taken from the film. Pictures were presented on a 19.6-inch screen, with 1600 × 1200 resolution. Viewing distance was 80 cm. No time limit was imposed on responses. The next trial began following participants' response.

*Noninvasive Brain Stimulation*

rTMS was delivered using a cooled figure-of-eight coil. Stimulation was given at 115% of resting motor threshold, which was measured over the contralateral hemisphere of the participant's

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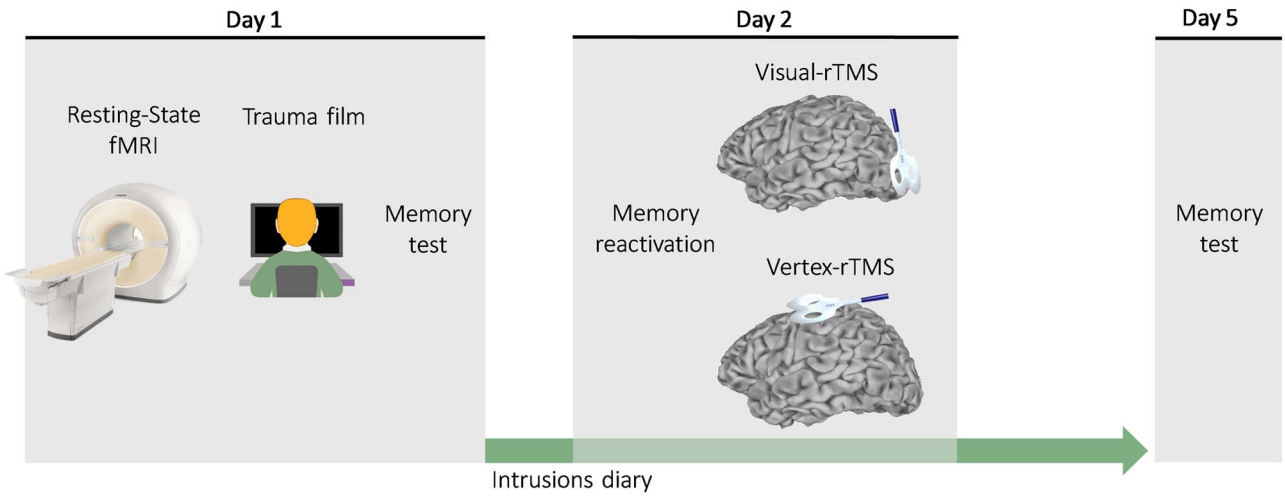


**Figure 1.** Overview of study design. On day 1, participants underwent anatomical MRI and a resting-state fMRI scan. They then viewed the trauma film, completed a visual recognition memory test, and were asked to record any intrusions about the film in a digitized diary every day until day 5. On the following day (day 2), brief reminder cues were used to reactivate participants' memory of the film, and then rTMS was delivered either over the early visual cortex (visual rTMS) or a control site (vertex rTMS). On day 5, participants attended a final meeting in which they were retested using the visual recognition memory test.

dominant hand. Resting motor threshold was determined as the minimal stimulation intensity over the primary motor cortex (M1) inducing 5 out of 10 motor-evoked potentials that were greater than 0.05 mV in the left first dorsal interosseous (FDI) muscle (Rossini et al. 1994). rTMS was delivered over either the early visual cortex or the vertex as a control site by using the same stimulation parameters (Jung et al. 2016). rTMS was delivered at 1-Hz stimulation frequency for 15-min duration, which is a common protocol that is expected to decrease cortical excitability (Chen et al. 1997).

Early visual cortex was localized at the tip of the calcarine fissure (Brodmann's area 17) (Kosslyn 1999) based on each participant's anatomical MRI acquired on the previous day. A neuronavigation system (Brainsight) enabled identification of the stimulation target by marking the stimulation site on each participant's anatomical MRI and coregistering the participant's head to his or her MRI using four anatomical landmarks (nasion, tip of the nose, and the left and right crus of helix). During stimulation, the coil was held with the handle pointing directly upward. The target of stimulation was maintained online using the neuronavigation system. Mean Montreal Neurological Institute (MNI) coordinates of early visual cortex stimulation across participants were $x = 1.4$, $y = -84.3$, and $z = -6.8$. Mean MNI coordinates of vertex stimulation across participants were $x = 0$, $y = -12.5$, and $z = 84.1$.

## Procedure

As shown in Figure 1, the study consisted of three laboratory sessions.

On day 1, a detailed explanation about the study was given. Participants were informed that the study consisted of three laboratory sessions that included MRI and TMS and that they would be required to watch a film containing distressing content and were to fill a diary in between sessions. Participants were required to sleep at least 6 h before each of the experimental sessions and were informed that they could stop participation at any time. After providing their written and informed consents, participants underwent an anatomical MRI scan that was followed by a 8-min resting-state fMRI during which they were asked to remain awake with their eyes closed. Participants then completed a demographic questionnaire and the visual analog mood scales. Participants were next given specific viewing instructions for the trauma film. They watched the film alone, in a darkened room, using earphones that were set to a predefined volume intensity. Following film watching, the visual analog mood scales were completed again, as well as the ratings of attention paid to the film and the day 1 visual recognition memory test. To complete the diary, participants were then given detailed explanation about intrusive memories and were shown how to record intrusions of the film using a practice diary entry on their private mobile phones. A checklist ensured understanding of diary completion.

On day 2, participants completed the memory reactivation procedure in the same context as the film-viewing in day 1. Following a 10-min standardized filler task, rTMS was applied over either the early visual cortex, or over the vertex. Participants did not receive information about the purpose or the location of the stimulation. At the end of day 2, participants were reminded to continue filling in the digital diary until day 5.

On day 5 (laboratory session 3), participants arrived for a final meeting and completed the visual recognition memory test for the second time. They also rated how accurately they thought they had completed the diary (diary compliance) from 1 ("not accurate at all") to 10 ("extremely accurate"). They were then thanked, debriefed, and compensated for their participation.

## fMRI Analysis

*MRI Preprocessing*

The anatomical data were skull-stripped using the FSL Brain Extraction Tool (BET) (Smith 2002). Preprocessing of the resting-state functional imaging data was performed using FMRIB software library (FSL version 6.0.0) (Smith et al. 2004), and it included high-pass filtering at 0.01 Hz, correction for motion artifacts, linear registration to the T1w anatomical scan, nonlinear registration to 152 MNI space, and smoothing with 5-mm Gaussian kernel. Residual noise was cleaned using FMRIB's ICA-based

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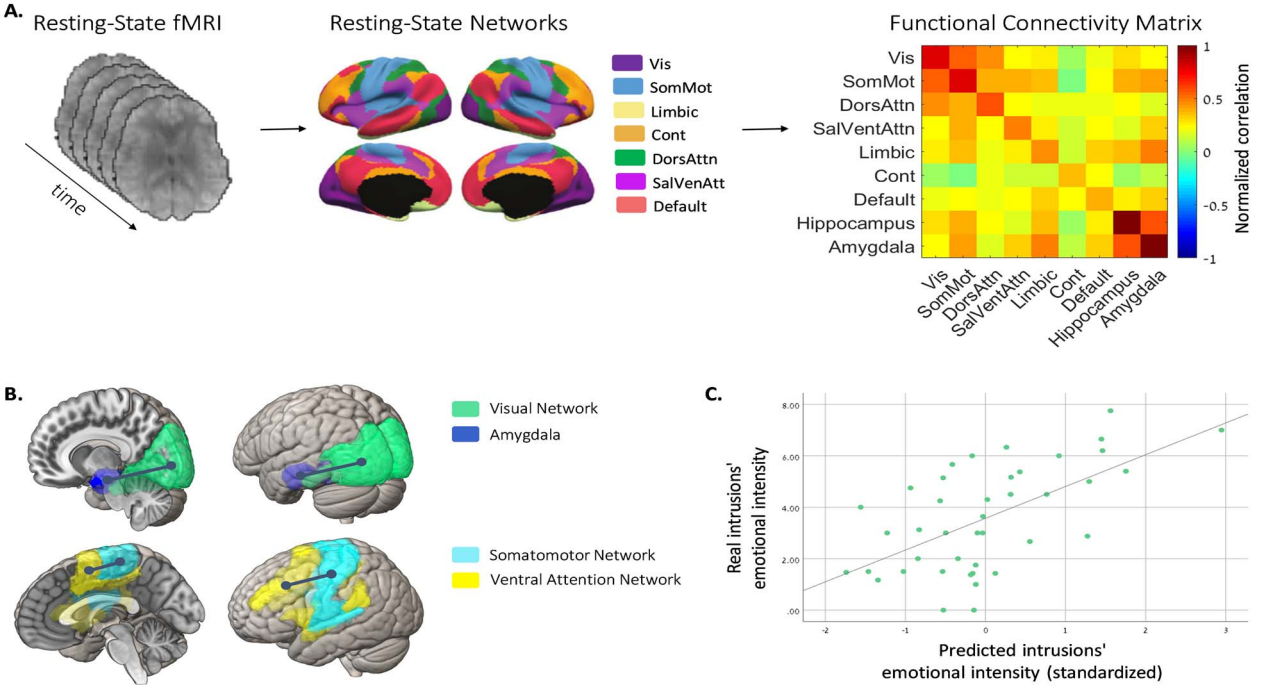


**Figure 2.** Predictive functional connectivity edges of the emotional intensity of intrusive memories. (*A*) Overview of the fMRI analysis on a single subject's data. Each individual resting-state fMRI data were parcellated to seven known resting-state networks based on Thomas Yeo et al. (2011) as well as to the amygdala and hippocampus. Functional connectivity between all networks was computed for each individual. The resulting functional correlation matrix was used to predict participants' emotional intensity at baseline (day 1). Vis, visual; SomMot, somatomotor; Cont, frontoparietal control; DorsAttn, dorsal attention; SalVenAtt, saliency ventral attention. (*B*) Variable reduction was used to select predictive networks for the emotional intensity of intrusive memories across participants. In a stepwise regression model, two variables were selected as predictive features of intrusions' intensity: the visual network–amygdala connectivity, and the somatomotor–ventral attention connectivity. (*C*) The graph shows the correlation between real intrusions' emotional intensity values and the predicted emotional intensity values based on the two functional connectivity edges in (*B*) ($R^2 = 0.364$, $P = 0.0001$).

X-noiseifier (FIX) (Griffanti et al. 2014), which is a semiautomatic ICA-based method to identify and remove artefactual components from the data.

*Resting-State fMRI Analysis*

To compute functional connectivity at rest, we first parcellated the cortex into 400 regions based on Schaefer and colleagues (Schaefer et al. 2018), where each parcel is assigned to one of seven brain networks. In addition to these seven cortical networks, we considered two subcortical limbic regions—the amygdala and hippocampus—due to their central role in memory and emotion preprocessing. The amygdala and hippocampus were extracted based on the Harvard-Oxford subcortical structural atlas (Frazier et al. 2005). Preprocessed resting-state fMRI time courses were averaged within each of 400 cortical parcels and 4 subcortical regions (right/left amygdala and right/left hippocampus), resulting in a 404 × 240 matrix (regions × measurements) of resting-state time courses for each participant. Pearson correlations between all regions pairs were then calculated, yielding a 404 × 404 Pearson's correlation matrix per participant.

The Pearson's correlation matrix was then averaged within each region (seven cortical + two subcortical), resulting in a functional connectivity matrix of 9*(9 − 1)/2= 36 unique edges. We also calculated within-network connectivity by averaging the pairwise correlations between all nodes within each of the seven cortical networks. Together with the 7 within-network correlations, 43 connections were computed for each participant. The correlation values were normalized using Fisher's z-transformation. These 43 features were then correlated with the intrusions' emotional intensity and frequency, which were measured on day 1 of the study (prior to the rTMS intervention) (Fig. 2A).

To avoid overfitting due to high number of predictors (43) relative to the number of observations ($N = 44$), a stepwise regression was applied with all functional connectivity edges as predictors of intrusions' emotional intensity at baseline (day 1). To ensure the robustness of the features selected by the stepwise regression, we also computed a least absolute shrinkage and selection operator (Lasso) (Tibshirani 1996) as a secondary analysis. Lasso was computed using 10-fold cross-validation, and the mean squared error (MSE) of the model was inspected to determine a regularization parameter ($\lambda$) for which the MSE is the smallest. Corresponding to standard recommendations, the regularization parameter $\lambda$ of the model (controlling the degree of variables shrinkage) was selected to be the largest value of $\lambda$, that is, within one standard error of MSE value (Waldmann et al. 2013).

## Behavioral Analysis

Age, attention paid to the film, postfilm distress, and diary compliance records were compared between groups using independent *t*-tests, while gender was compared using a

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chi-square test. Two-way mixed ANOVA was used to compare mood changes resulting from the trauma film between groups, with time (pre-/postfilm-viewing) as a within-subject factor and group (visual/vertex) as a between-subjects factor. Percent of correct responses in the visual recognition memory test were compared using a two-way mixed-design ANOVA, with time (day 1/day 5) as a within-subject factor and group (visual/vertex) as the between-subjects factor.

To investigate the effect of rTMS on the emotional intensity of intrusive memories, each participant's averaged emotional intensity was computed for the time points pre-rTMS (day 1) and post-rTMS (days 2–5). A two-way mixed-design ANOVA was computed with time (pre-TMS/post-TMS) as a within-subject factor and group (visual/vertex) as the between-subjects factor. To test whether intrusions' emotional intensity values declined gradually over time, we also compared the slope of emotional intensity values throughout study days following the rTMS using growth modeling. Growth modeling enables investigation of longitudinal data by testing individual patterns of change over time and by comparing this change between groups instead of comparing averaged values across time points. The growth modeling portrays a more accurate and complete picture of our data compared with mixed-design ANOVA (see Supplementary Material for results using mixed-design ANOVA): First, it estimates growth parameters on the available data without requiring complete data from all respondents and is thus better suited for this dataset, which contains missing values for individuals not experiencing any intrusions in one or more study days. Second, growth modeling allows the intercept and slope to vary across individuals, thus accounting for interindividual differences in initial emotional intensity values and slope of change across study days. The steps of the growth modeling were applied as shown in Bliese and Ployhart (2002). Briefly, the model contains five steps: Step 1 computes a regression model in which intrusions' intensity are regressed on time. Step 2 accounts for differences in the initial intensity values by allowing the intercepts to randomly vary among respondents. Step 3 adds the random component of time to the model, allowing for the slope of intrusions' intensity change to randomly vary among respondents. Step 4 of the model accounts for autocorrelation resulting from within-person repeated time points to avoid inflated $t$ values. The final fifth step of the model inserts the group variable into the model and tests the time × group interaction effect.

To investigate the effect of rTMS on the frequency of intrusions, the averaged sum of intrusions per day pre-rTMS (day 1) and post-rTMS (days 2–5) was calculated. A two-way mixed-design ANOVA was computed with time (pre-TMS/post-TMS) as a within-subject factor and group (visual/vertex) as the between-subject factor. Two-tailed tests were used for all statistical comparisons.

## Results

### fMRI

In the stepwise regression analysis, two variables were found to have a unique contribution in explaining the variance in the emotional intensity of intrusive memories: "visual network–amygdala" connectivity strength and "somatomotor–ventral attention" connectivity strength. These two features explained a significant portion of the variance in intrusions' intensity ($F(2, 40) = 10.896$, $P = 0.0001$, $R^2 = 0.364$, $R^2_{Adjusted} = 0.331$) (Fig. 2C). Both visual network–amygdala connectivity strength ($\beta = -.892$, $t(38) = -4.582$, $P = 0.00004$) and somatomotor–ventral attention connectivity strength ($\beta = 0.783$, $t(38) = 4.019$, $P = 0.0002$) significantly contributed to the model.

The Lasso model yielded the same two functional connectivity variables as observed in the stepwise regression as well as the functional connectivity strength between the visual–frontoparietal control networks and hippocampus–amygdala connectivity. To ensure the consistency of these results, the Lasso model (using the 10-fold cross-validation) was repeated 1000 times, and the variables selected by each iteration were recorded. Over 1000 iterations, the visual network–amygdala connectivity emerged in 99.7% of the model's iterations, whereas the somatomotor–ventral attention connectivity and visual–frontoparietal control connectivity emerged as additional predictive features in 89% of the model's iterations. Full results of the neural features selected across the 1000 Lasso iterations are shown on the Supplementary Material (Supplementary Table S1). Contrary to the intrusions' emotional intensity, the Lasso model did not yield any predictive features of intrusion frequency.

### Behavior

There were no significant differences between the visual and the vertex groups in age ($t(38) = -0.3878$, $P = 0.700$), attention paid to the film ($t(38) = -0.178$, $P = 0.859$), self-reported postfilm distress ($t(38) = 1.407$, $P = 0.167$), diary compliance ($t(38) = 0.769$, $P = 0.430$), and gender distribution ($\chi^2(1, 40) = 0.123$, $P = 0.726$). Mood deteriorated from pre- to postfilm ($F(1, 38) = 78.688$, $P < 0.001$, $\eta^2_p = 0.674$) and to a similar extent in both groups ($F_{group \times time}(1, 38) = 0.021$, $P = 0.885$).

The ANOVA on the emotional intensity of intrusive memories yielded a main effect of time, with a decline in intensity from pre- to post-rTMS ($F_{time}(1, 36) = 53.102$, $P < 0.001$, $\eta^2_p = 0.596$). Critically, and in line with our hypothesis, this main effect was qualified by a group-by-time interaction ($F(1, 36) = 4.314$, $P = 0.045$, $\eta^2_p = 0.107$). Post hoc analysis revealed an ordinal interaction with greater emotional intensity reduction in the visual rTMS group ($t(16) = 5.918$, $P = 0.00002$, $d = 1.435$) relative to the vertex group ($t(20) = 4.119132$, $P = 0.001$, $d = 0.898$) (Fig. 3). The main effect of group was nonsignificant ($F_{group}(1, 36) = 1.475$, $P = 0.232$). Growth modeling showed a gradual decline in emotional intensity throughout study days ($t_{time}(37) = -2.167$, $P = 0.036$), and critically again, this decline was greater in the visual compared with the vertex group ($t_{time \times group}(37) = 2.108$, $P = 0.041$). Time course of intrusions' emotional intensity throughout study days can be found in the Supplementary Material (Supplementary Fig. S1A).

ANOVA on percent of correct responses in the visual recognition memory test about the film revealed a decrease in performance from day 1 to day 5 ($F_{time}(1, 38) = 8.714$, $P = 0.005$, $\eta^2_p = 0.186$) without a difference between groups ($F_{time \times group}(1, 38) = 0.037$, $P = 0.847$). Group main effect was nonsignificant ($F_{group}(1, 38) = 0.147$, $P = 0.702$).

The ANOVA on the averaged sum of intrusions yielded a main effect of time with a decline in the averaged sum of intrusions per day from pre- ($M = 3.875$, $SD = 2.928$) to post-TMS ($M = 1.525$, $SD = 1.513$) ($F_{time}(1, 38) = 34.016$, $P < 0.0001$, $\eta^2_p = 0.472$). However, group main effect ($F_{group}(1, 38) = 0.008$, $P = 0.928$) and the group × time interaction effects ($F_{time \times group}(1, 38) = 0.089$, $P = 0.766$) were nonsignificant. Time course of the sum of

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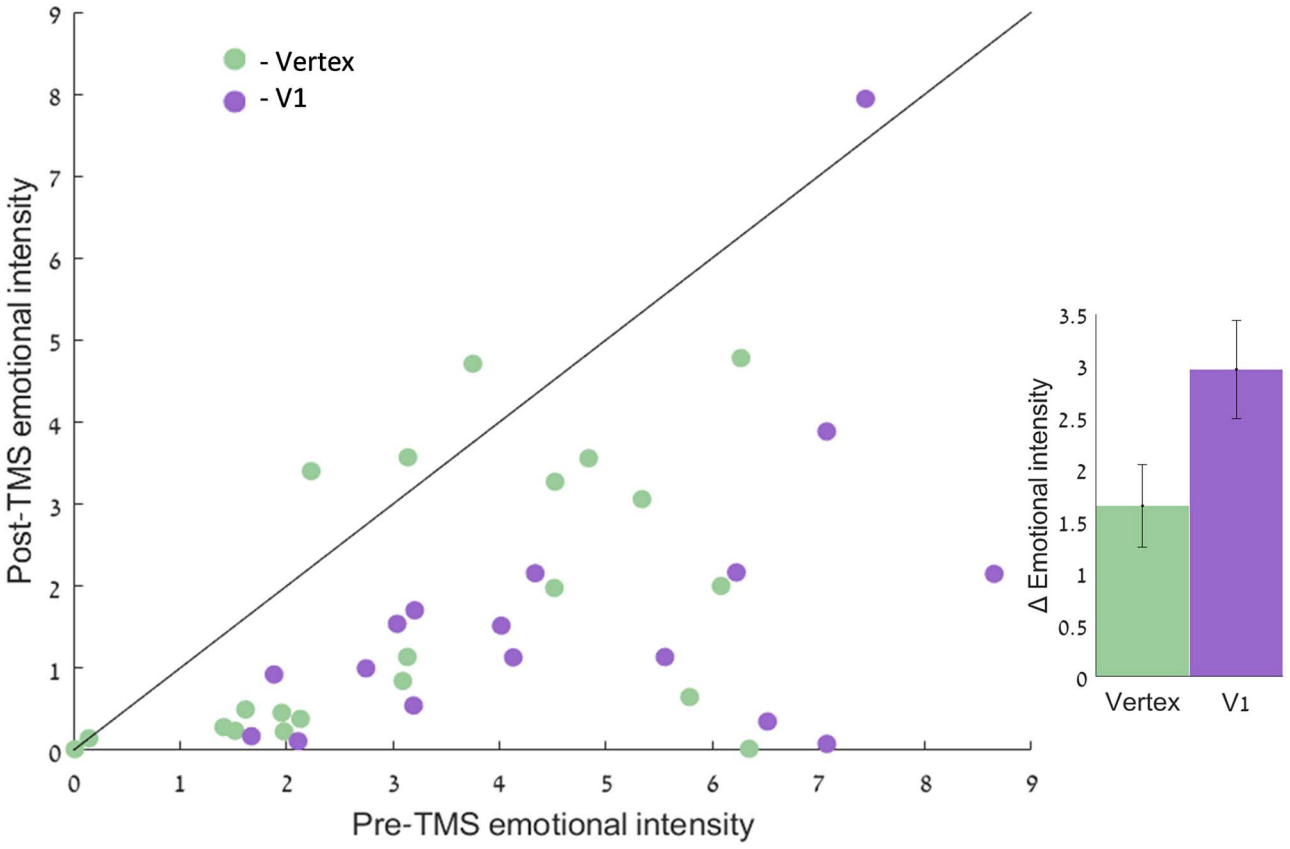


**Figure 3.** Scatterplot showing the emotional intensity values of intrusive memories pre and post rTMS for individuals in the visual group (V1) and control (vertex). Within-participant comparisons between pre- and post-TMS intrusions' emotional intensity is presented in a scatterplot along a unity slope line (x = y), where each point reflects one participant. Points "under" the unity slope line reflect reduced emotional intensity following TMS, whereas points "above" the line reflect higher emotional intensity following TMS. Data points on the line reflect no difference in emotional intensity from pre- to post-TMS. Inset: mean reduction in emotional intensity of intrusive memories following TMS. Error bars represent standard errors of the means.

intrusions throughout study days can be found in the Supplementary Material (Supplementary Fig. S1*B*).

Although the results described here are restricted to diary entries where intrusions were reported as mental images, the results pattern remains the same when including all diary entries (both mental images and pure verbal thoughts) (Supplementary Fig. S1). The supplementary material shows the results for intrusions' emotional intensity (Supplementary Fig. S1*C*) and sum of intrusions (Supplementary Fig. S1*D*) for all diary entries.

## Discussion

The findings of the present study implicate involvement of early visual cortex in the emotional intensity of intrusive visual memories. Connectivity between the visual network and the amygdala, measured immediately prior to the experience of viewing an aversive event (film scenes with traumatic content), was found to predict the emotional intensity of intrusive memories that arose from that event. This offers a potential neuromarker of vulnerability to experiencing traumatic memory intrusions as being highly distressing. Importantly, relative to a control stimulation, inhibitory stimulation of early visual cortex (rTMS) following memory reactivation reduced the intrusions' emotional intensity on subsequent days. These findings suggest that interfering with post-reactivation offline visual processing can have long-term effects on the emotional aspects of the reexperiencing of intrusive memories. This type of approach may thus open up a potential target for specialized interventions for patients suffering from distressing and persistent traumatic intrusions.

The relation between early visual and emotion processing brain areas is supported by recent studies showing alteration of neural activity of the early visual cortex in response to stimuli that have been associated with an aversive event (McTeague et al. 2015; Thigpen et al. 2017; Shalev et al. 2018). The amygdala and visual brain areas are anatomically interconnected not only indirectly but also through the direct white matter tracts of the inferior longitudinal fasciculus (Catani 2003). This anatomical pathway has been suggested to mediate the fast transfer of visual signals to emotional processing regions and neuromodulatory back-projections from the amygdala to early visual areas associated with fear recognition (McFadyen et al. 2019). Relatedly, a recent study found that greater functional connectivity between the amygdala and visual brain regions immediately postencoding was related to better subsequent recognition of negatively valenced pictures (Kark and Kensinger 2019). In the present study, greater functional connectivity between the amygdala and the visual network was associated with lower emotional intensity of intrusions, as reflected by the negative sign of the related beta coefficient. The fact that greater visual–amygdala connectivity postencoding is associated with both

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better recognition memory (Kark and Kensinger 2019) and the lower emotion intensity of intrusions following inhibition of early visual areas in the current study are not surprising, given that the voluntary and involuntary aspects of memory have been shown to be dissociable (Lau-Zhu et al. 2019) and may even show inverse relation between them. For example, it is possible that by enhancing voluntary memory recall, involuntary intrusions can be reduced (Krans et al. 2009; Herszage and Censor 2018).

In the current study, inhibitory stimulation of the early visual area reduced the emotional intensity of intrusions but did not reduce visual recognition of the negative events or intrusion frequency. Specific downregulation of the emotional aspects of involuntary memories while leaving voluntary memory intact is a desirable outcome for therapeutic goals (Brewin et al. 2010; Iyadurai et al. 2019). Moreover, specific reduction of intrusions' emotional intensity, rather than frequency, is in line with some previous studies indicating that the intrusions' emotional intensity show only a moderate association with their frequency and may be more predictive of persistent PTSD symptoms (Steil and Ehlers 2000; Michael et al. 2005).

In addition to the visual network–amygdala connectivity, somatomotor–ventral attention and visual–frontoparietal control connectivities emerged as predictive features of the intrusions' emotional intensity. The ventral attention network was shown to be active upon detection of salient stimuli in the environment and is thought to represent involuntary orienting of attention (Fox et al. 2006). The frontoparietal control network, on the other hand, is linked to executive control processes that represent top-down strategic control (Seeley et al. 2007). The involvement of these networks in the regulation of intrusions' intensity suggests that both involuntary attention allocation as well as effortful cognitive control processes play a role in predicting the emotional intensity provoked by memory intrusions. Indeed, threat-related attention biases are widely identified as a risk factor for anxiety disorders (Bar-Haim et al. 2007) and PTSD (Wald et al. 2013; Naim et al. 2015). Further, attention bias modification treatment was found to reduce PTSD symptoms and to modulate activity in visual processing pathways (Badura-Brack et al. 2018; Lazarov and Bar-Haim 2021).

The current results point to important future research directions. First, the findings open the possibility that connectivity between early visual regions and emotion processing areas may constitute a unique neuroscience-derived target for neuromodulatory interventions for intrusive reexperiencing symptoms. Additional research could further establish the long-term effects of such interventions and the specific neural pathway modulated by them. For example, acquiring resting-state fMRI not only prior to but also postintervention could elucidate whether visual network–amygdala coupling is specifically modulated by inhibitory stimulation over early visual areas. In addition, future studies may enable to test whether other stimulation parameters (e.g., stimulation site, duration, or number of stimulation sessions) could lead to a greater reduction in intrusion intensity. Although, in this study, resting-state fMRI data were used as converging evidence for our a priori site selection, future studies could examine the use of the participant's visual–amygdala functional connectivity map to guide site selection in an individually tailored manner (Fox et al. 2012). Second, as in previous reports (Amar-Halpert et al. 2017; Bang et al. 2018; Shmuel et al. 2021), we applied a visual memory reactivation procedure prior to the rTMS intervention, here, memory reminder cues in the form of static pictures, given the use of trauma film as stimuli. It is conceivable that much stronger effects could be achieved if more potent types of memory reactivation procedures, such as imagery scripts (Rauch et al. 1996), written accounts (Kessler et al. 2018), or brief hotspot procedures (Kanstrup et al. 2021), could be applied—for example, in clinical populations with reexperiencing symptoms. However, future studies are required to examine the boundary conditions for reminder cues and the hypothesized role of memory reactivation in inducing putative reactivation–reconsolidation processes. Finally, our experiment was performed with healthy individuals and film material, and it also requires a test of replication before strong conclusions can be permitted. The act of intrusions reporting may have primed intrusions, thus lowering the ecological validity of our study relative to real-life intrusions where deliberate cues of the memory are usually absent, although similar to clinical work in which patients are asked to keep a diary of their intrusions. Future studies could explore the clinical potential of the rTMS intervention approach for patients suffering from highly distressing intrusions of real-life traumatic events.

## Conclusion

This study reveals a mechanistic role for early visual cortex in the intensity of the affective response (emotional intensity) associated with intrusive trauma memories. Critically, we showed that it is possible to modulate the emotional intensity of intrusive memories of traumatic film material by rTMS following a memory reminder cue. The specific neuromodulation of visual–amygdala connectivity by rTMS and the boundary conditions for reducing intrusions' emotional intensity in clinical populations remain to be investigated.

## Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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## Notes

*Conflict of Interest*: None declared.

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