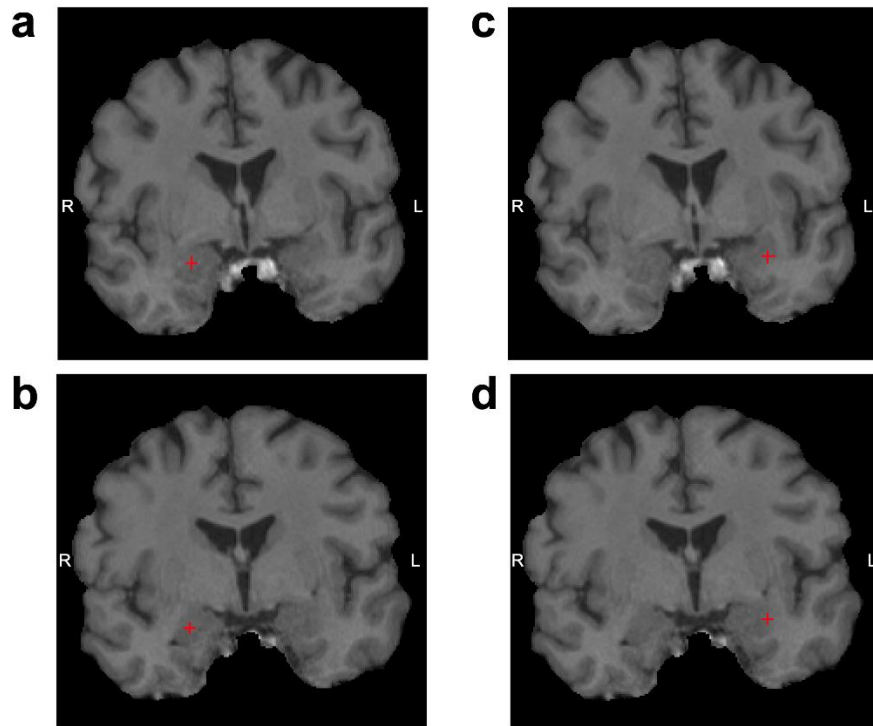
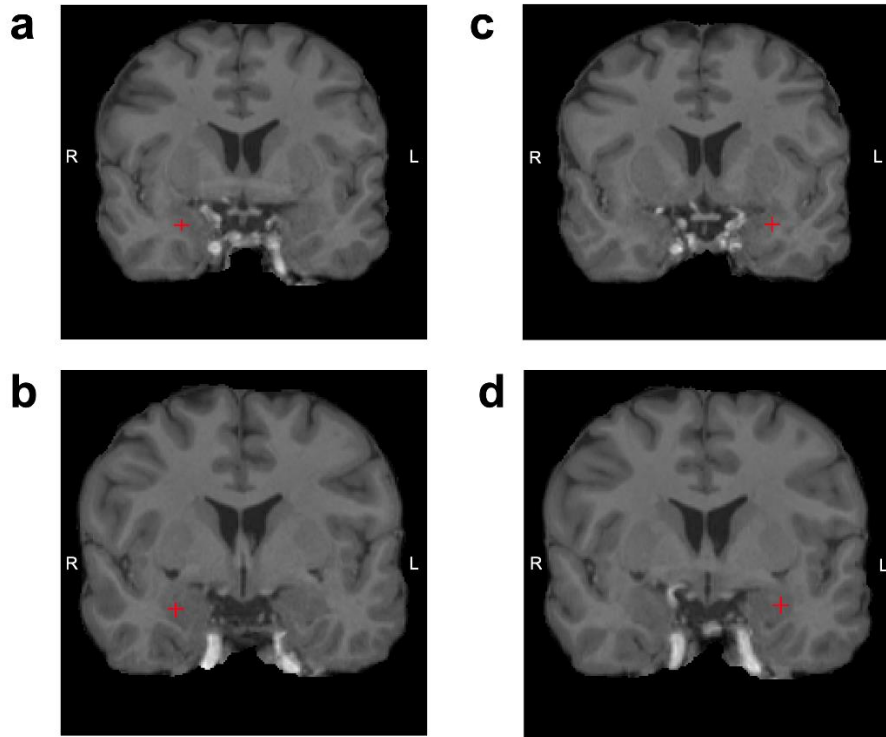


Online Materials

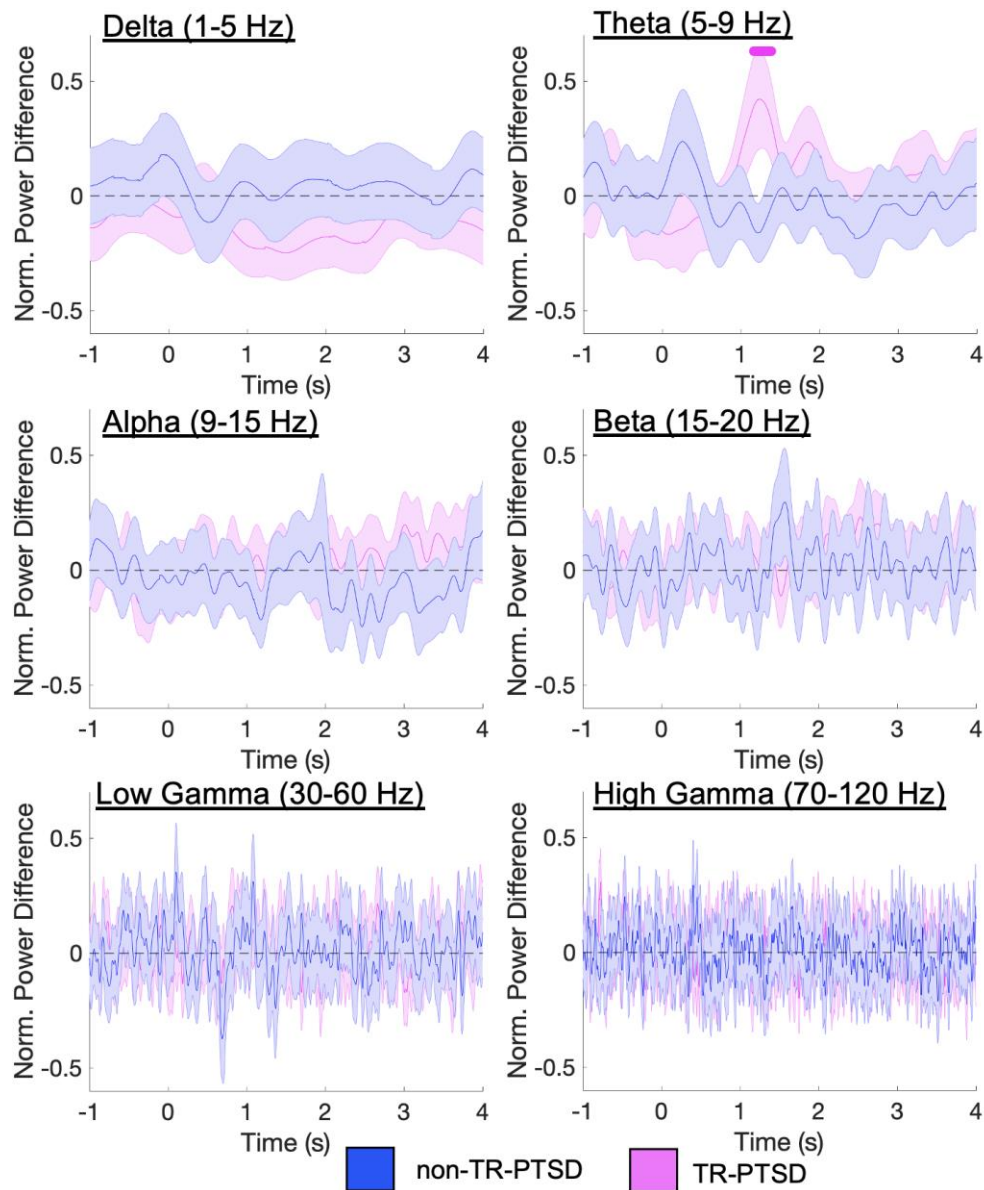
Supplementary Tables and Figures



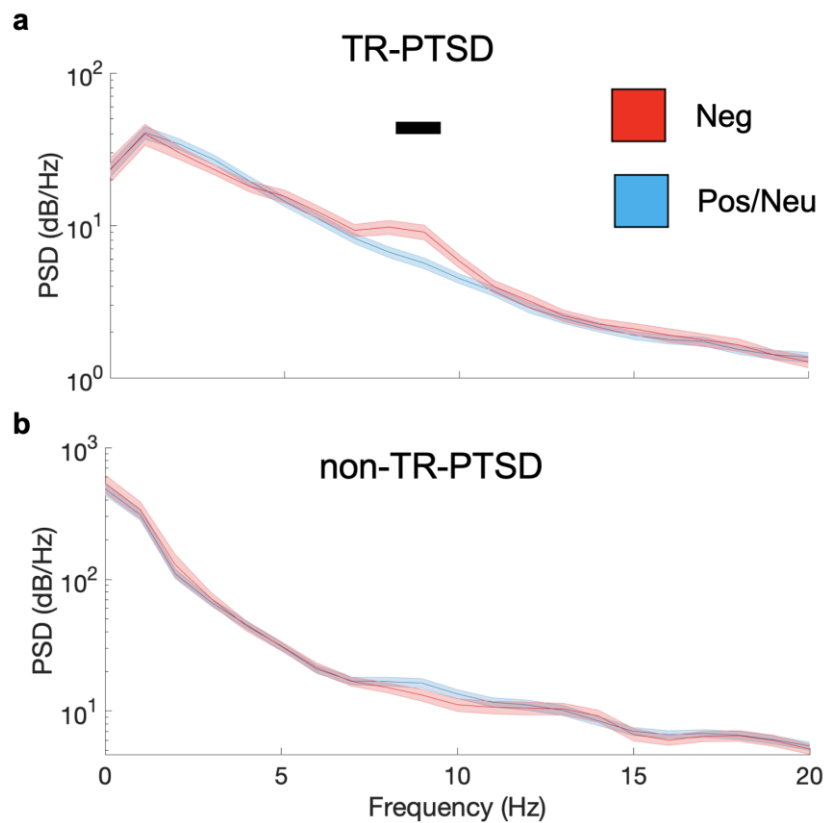
Supplementary Figure 1. TR-PTSD 1 electrode contact localizations. RNS contacts localized in the amygdala that comprise right (a-b) and left (c-d) recording channels in TR-PTSD 1 visualized in participant's anatomical MRI space. a and c = anterior contacts; b and d = posterior contacts, R = right, L = left.



Supplementary Figure 2. TR-PTSD 2 electrode contact localizations. RNS contacts localized in the amygdala that comprise right (**a-b**) and left (**c-d**) recording channels in TR-PTSD 2 visualized in participant's anatomical MRI space. **a** and **c** = anterior contacts; **b** and **d** = posterior contacts, R = right, L = left.

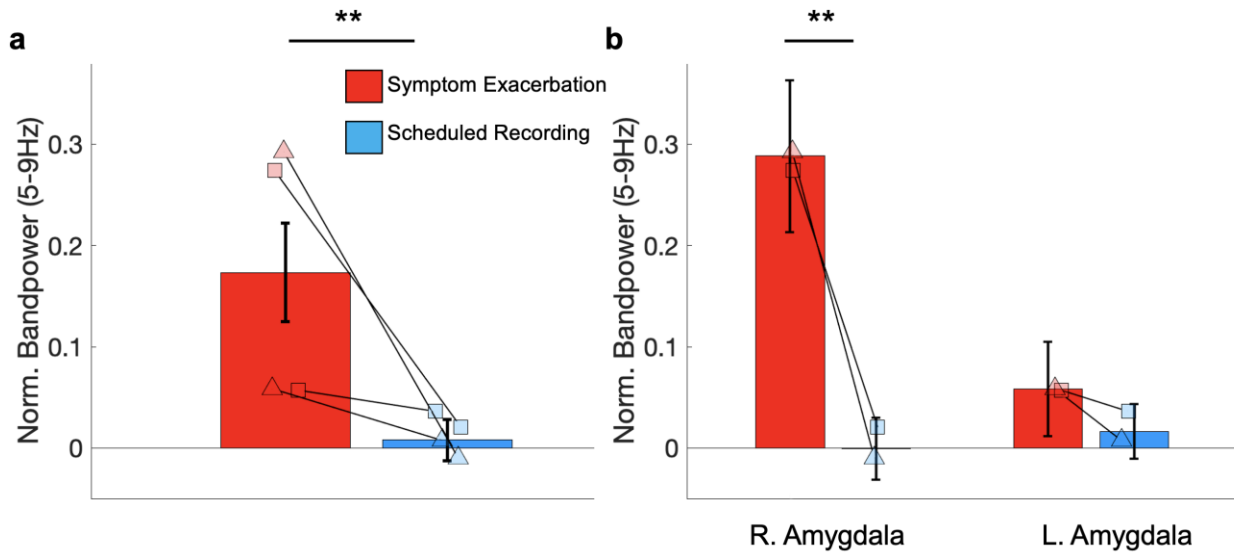


Supplementary Figure 3. Amygdala valence-related oscillatory changes in TR-PTSD are specific to the theta band. Normalized (Norm.) difference in frequency bandpower (delta, theta, alpha, beta, low and high gamma) between negative and positive/neutral conditions (negative – positive/neutral) during the Emotional Image Task (related to Fig. 2a) over time separately for TR-PTSD (magenta) and non-TR-PTSD (blue) participants relative to image onset (time 0). Positive norm. power difference = negative > positive/neutral; negative norm. power difference = positive/neutral > negative. For each frequency band, the mean \pm 2 s.e.m. (standard error of the mean) across channels is shown for TR-PTSD ($N_{\text{participants}} = 2$, $N_{\text{channels}} = 4$) and non-TR-PTSD ($N_{\text{participants}} = 6$, $N_{\text{channels}} = 9$) participants. Horizontal bars indicate time points where there were significant differences, which occurred only in theta bandpower (5-9 Hz) between negative and positive trials in TR-PTSD (magenta) but not non-TR-PTSD (blue) participants ($p < 0.05$, Bonferroni corrected) using linear mixed effects models (Methods).

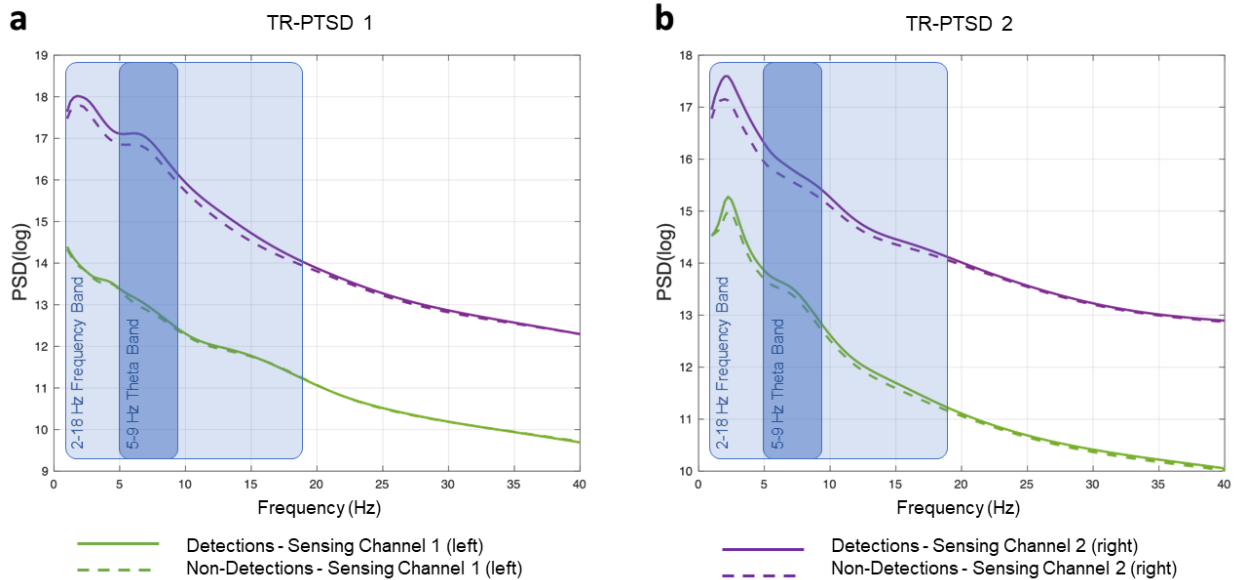


Supplementary Figure 4. Negative-valence-related amygdala changes only in TR-PTSD participants. **a**, Mean \pm s.e.m. power spectral density (PSD, dB/Hz) during negative (red) and positive/neutral images (blue) at specified frequency steps (1–20 Hz) for TR-PTSD participants ($N_{\text{participants}} = 2$, $N_{\text{channels}} = 4$) during the pre-stimulation period. Black bar = $p < 0.05$, linear mixed model, Bonferroni corrected. **b**, Mean \pm s.e.m. PSD in non-TR-PTSD participants ($N_{\text{participants}} = 6$, $N_{\text{channels}} = 9$) during negative (red) and positive/neutral images (blue) at specified frequency steps (1–20 Hz). Significance ($p < 0.05$, linear mixed model, Bonferroni corrected) not found.

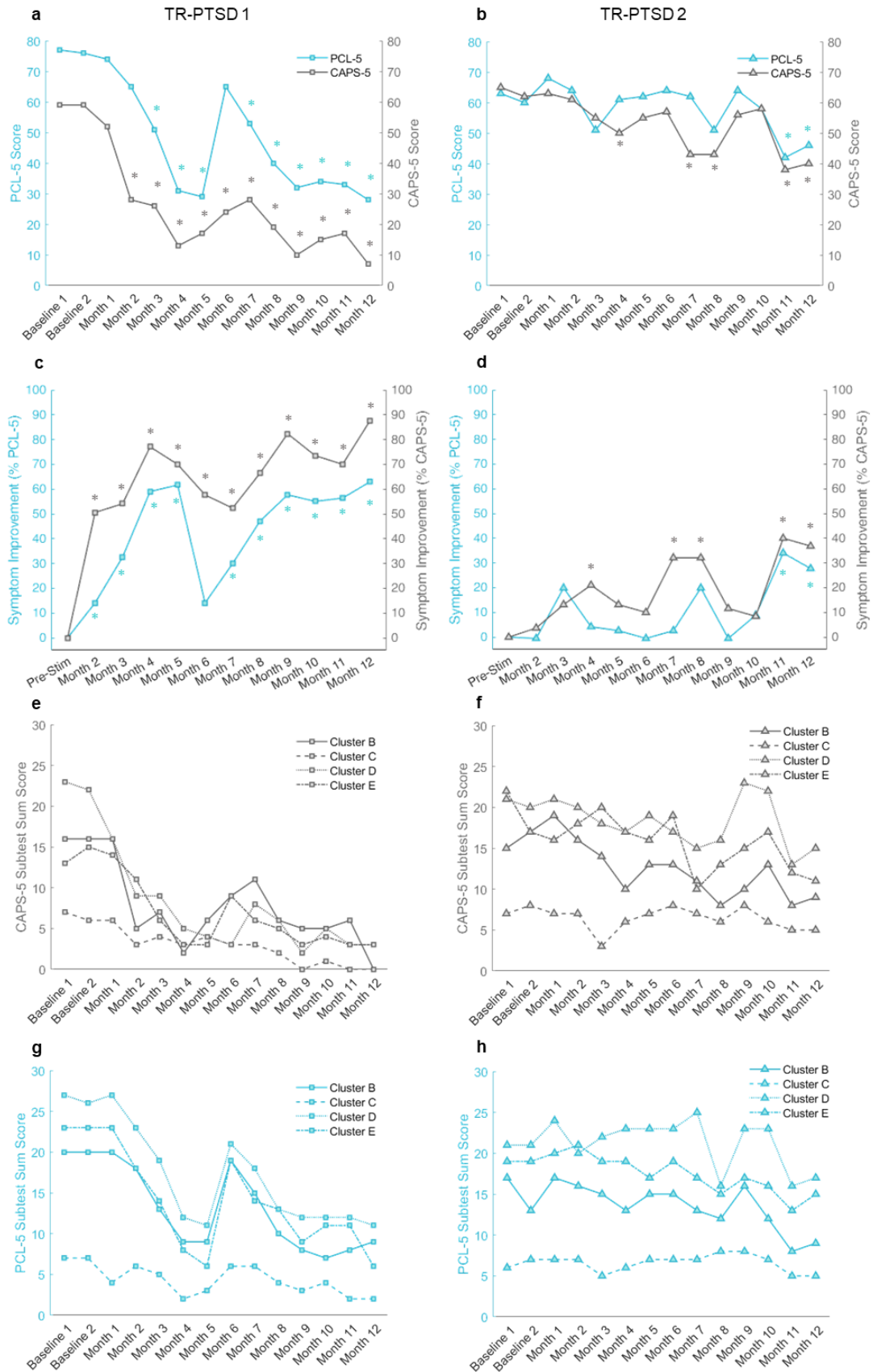
At-Home Recordings



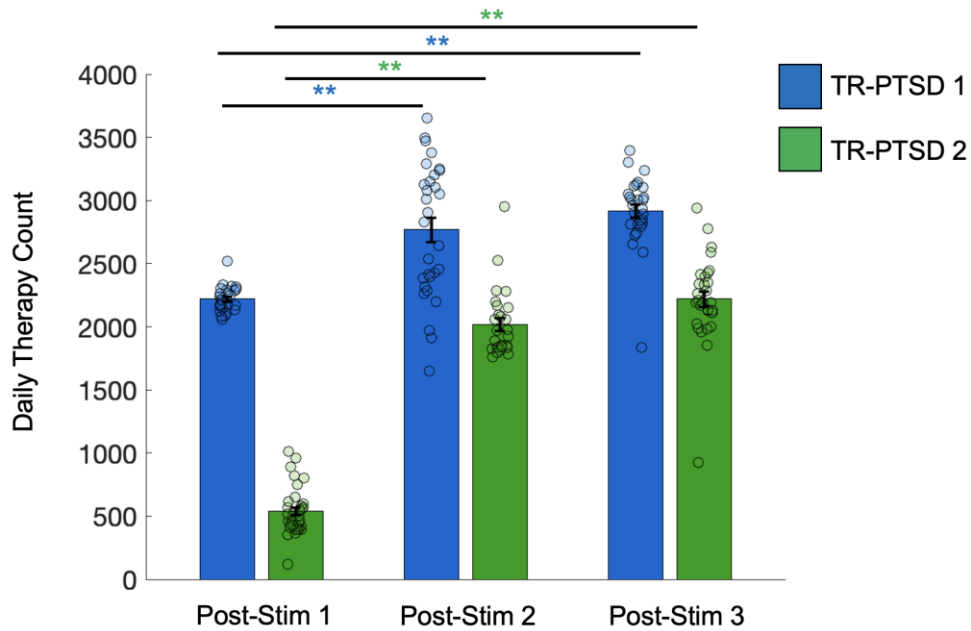
Supplementary Figure 5. Increased amygdala theta activity during PTSD-related symptomatic episodes. **a.** Normalized (Norm.) mean \pm s.e.m. theta (5-9 Hz) bandpower within the amygdala of TR-PTSD participants during symptomatic (red) and asymptomatic (blue) periods (For each bar $N_{\text{participants}} = 2$, $N_{\text{channels}} = 4$ (left and right amygdala), squares = TR-PTSD 1, triangles = TR-PTSD 2). ** = unadjusted $p = 0.007$ using linear mixed model (Methods). **b.** Same as **a**, but separated by hemisphere (R = Right, L = Left; For each bar $N_{\text{participants}} = 2$, $N_{\text{channels}} = 2$, squares = TR-PTSD 1, triangles = TR-PTSD 2). ** = unadjusted $p = 0.002$ using linear mixed model (Methods).



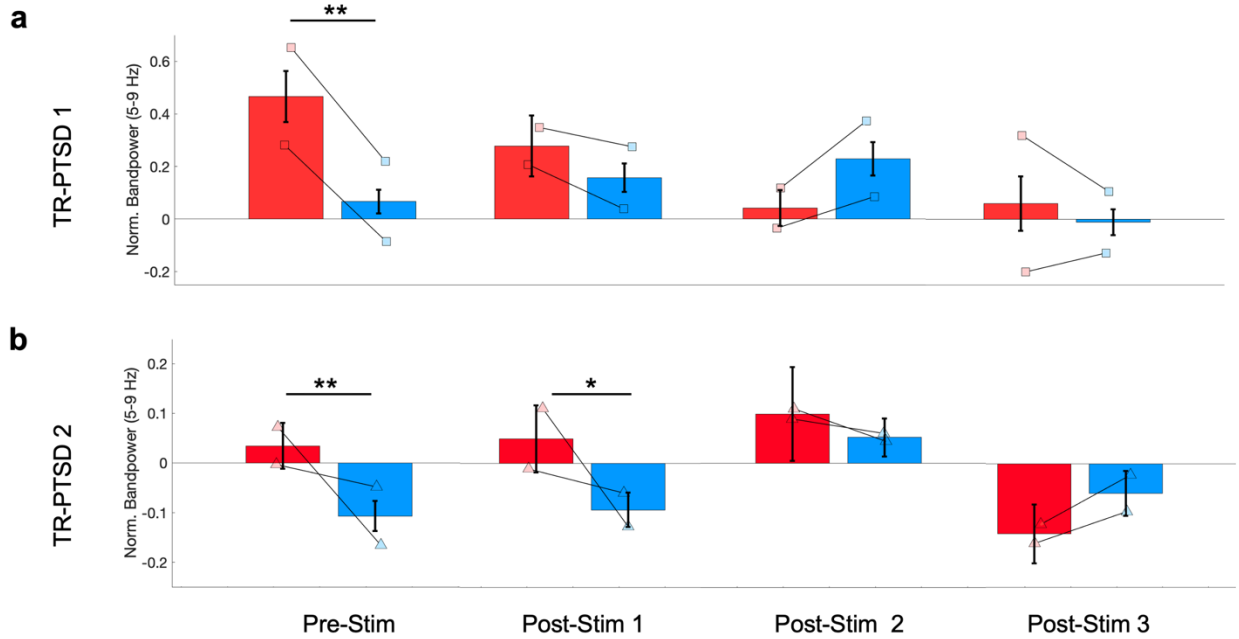
Supplementary Figure 6. Increased low frequency activity during stimulation-triggering detections. Power spectral density (PSD) for TR-PTSD 1 (**a**) and TR-PTSD 2 (**b**) during Trigger 1 (Suppl. Table 5) demonstrating elevations in 2-18 Hz bandpower (light blue shaded areas) and 5-9 Hz theta power (dark blue shaded areas) in left (green) and right (purple) sensing channels during detection (solid curve) periods compared to non-detection (dashed curve) periods.



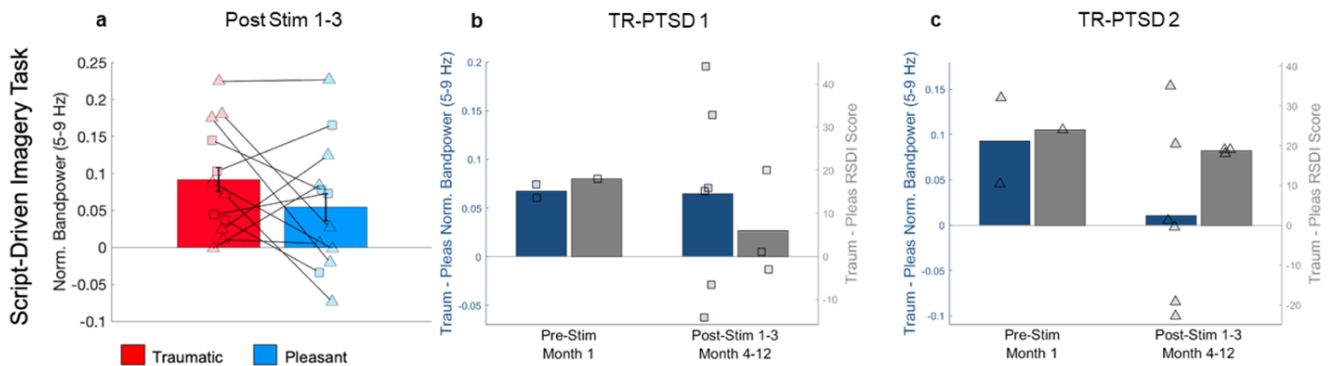
Supplementary Figure 7. CAPS-5 and PCL-5 subtest scores over time. Changes in CAPS-5 scores (gray) and PCL-5 scores (cyan) for TR-PTSD 1 (a) and TR-PTSD 2 (b) during Pre-Stim periods (baseline 1, 2, and month 1) and Post-Stim periods (months 2-12). Gray/cyan * = reliable change in CAPS-5 or PCL-5 scores, respectively, according to threshold for sample 1 reported in Marx et al.¹ relative to pre-stimulation baseline assessments (mean of baseline 1, 2, and month 1). **c-d:** % Symptom improvement on CAPS-5 (gray) and PCL-5 (cyan) during Pre-Stim periods (baseline 1, 2, and month1) and Post-Stim periods (months 2-12). Gray/cyan * = reliable change in CAPS-5 or PCL-5 scores, respectively, according to threshold for sample 1 reported in Marx et al.¹⁰ relative to pre-stimulation baseline assessments (mean of baseline 1, 2, and month 1). **e-h:** CAPS-5 (gray) and PCL-5 (cyan) subtests including Cluster B (intrusive symptoms), Cluster C (avoidance), Cluster D (negative alterations to mood and cognition), and Cluster E (alterations in arousal and reactivity) over the Pre-Stim and Post-Stim periods for TR-PTSD 1 and TR-PTSD 2.



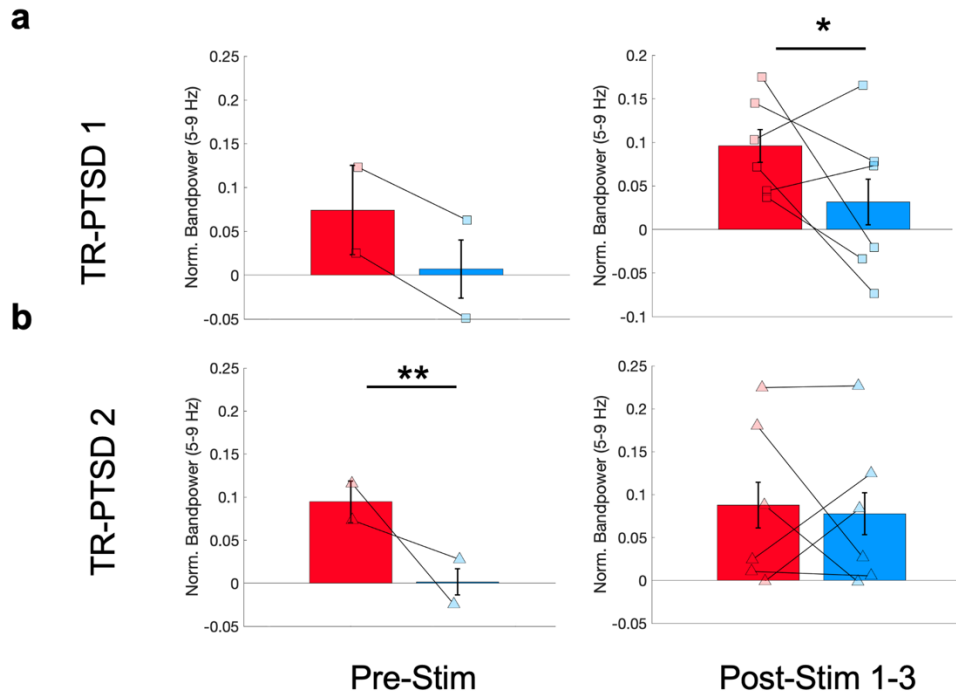
Supplementary Figure 8. Daily stimulation (therapy) counts in TR-PTSD. Mean (\pm s.e.m.) number of daily stimulation therapies delivered prior to Post-Stim 1 (months 2-3), Post-Stim 2 (months 5-6), and Post-Stim 3 (months 10-11) of closed-loop neuromodulation in TR-PTSD 1 (blue) and TR-PTSD 2 (green). TR-PTSD 1: Post-Stim 1 $N_{\text{therapy counts}} = 26$, Post-Stim 2 $N_{\text{therapy counts}} = 30$, Post-Stim 3 $N_{\text{therapy counts}} = 28$; TR-PTSD 2: Post-Stim 1 $N_{\text{therapy counts}} = 35$, Post-Stim 2 $N_{\text{therapy counts}} = 27$, Post-Stim 3 $N_{\text{therapy counts}} = 30$. ** = $p < 0.001$, Wilcoxon rank sum test, Bonferroni corrected.



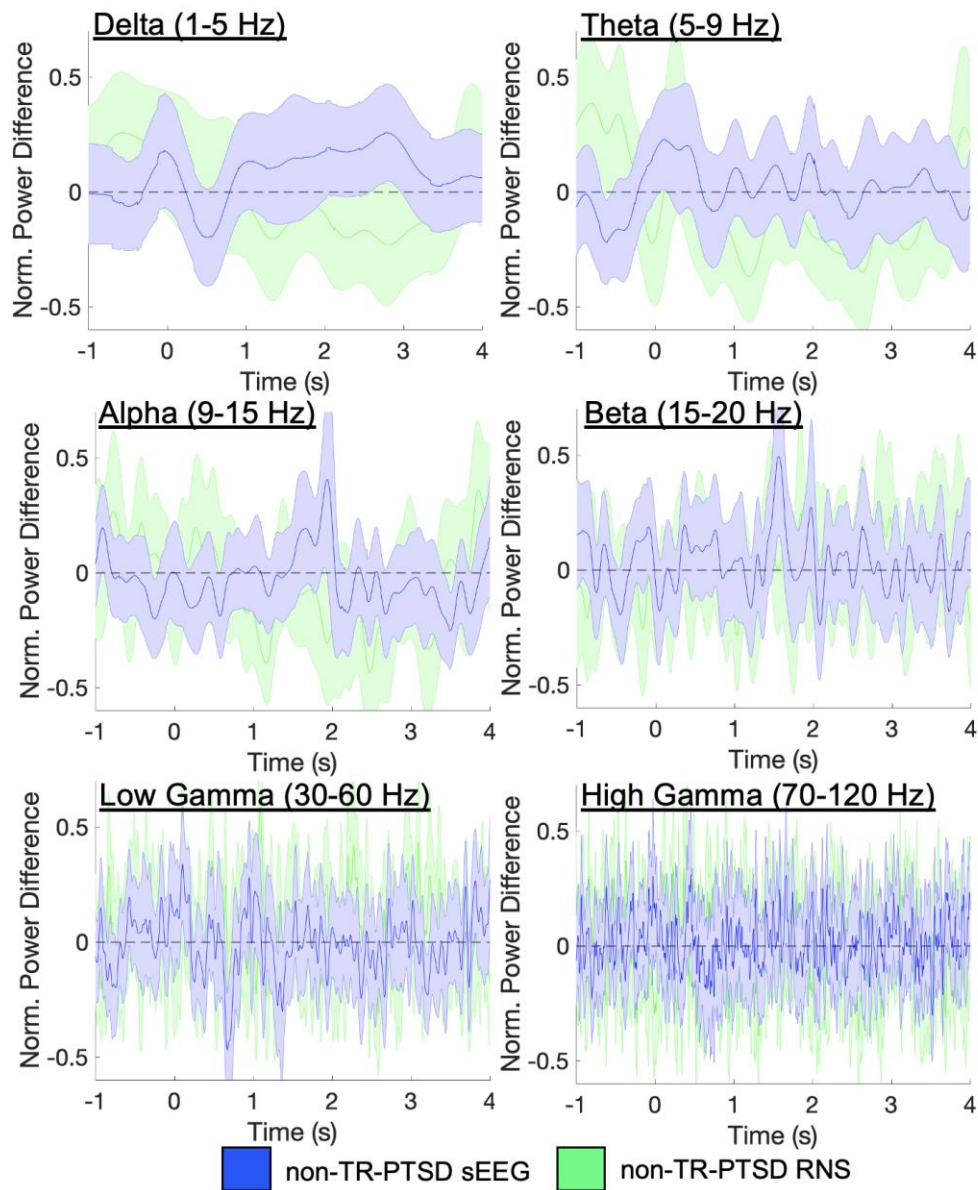
Supplementary Figure 9. Reduction in negative-image-related amygdala theta following stimulation. **a**, Normalized (Norm.) mean \pm s.e.m. amygdala theta bandpower during negative (red) and positive/neutral (blue) images in TR-PTSD 1 (squares) and TR-PTSD 2 (triangles) during Pre-Stim and Post-Stim 1-3 (Fig. 1a) of the Emotional Image Task. For each bar $N_{\text{participants}} = 1$, $N_{\text{channels}} = 2$ (left and right amygdala). ** = unadjusted $p < 0.001$ using linear mixed model (Methods). **b**, Same as **a**, but for TR-PTSD 2. For each bar $N_{\text{participants}} = 1$, $N_{\text{channels}} = 2$ (left and right amygdala). Pre-Stim * = unadjusted $p = 0.008$, Post-Stim 1 * = unadjusted $p = 0.04$, using linear mixed model (Methods).



Supplementary Figure 10. Reduction in trauma-related amygdala theta following stimulation during the Script-Driven Imagery Task over all Post-Stim sessions and in relation to changes in state PTSD symptoms. **a**, Normalized (Norm.) mean \pm s.e.m. amygdala theta bandpower during traumatic (red) and pleasant (blue) audio scripts in TR-PTSD 1 (squares) and TR-PTSD 2 (triangles) during Post-Stim 1-3 (Fig. 1a) combined due to limited trials obtained within each session (4 trials per condition). Each bar contains 12 data points ($N_{\text{participants}} = 2$, $N_{\text{channels}} = 2$ (left and right amygdala), $N_{\text{sessions}} = 3$). **b**, Difference in normalized (Norm.) amygdala theta (5-9 Hz) bandpower between traumatic (Traum) and pleasant (Pleas) audio scripts from the Emotional Image Task (navy) and RSDI scores (gray) for TR-PTSD 1 (squares) during Pre-Stim and Post-Stim 1-3. **c**, Same as **b** but for TR-PTSD 2 (triangles).



Supplementary Figure 11. Changes in trauma-related amygdala theta following stimulation. **a**, Normalized (Norm.) mean \pm s.e.m. amygdala theta bandpower during traumatic (red) and pleasant (blue) audio scripts in TR-PTSD 1 (squares) during Pre-Stim and Post-Stim sessions 1-3 (Fig. 1a) combined due to limited trials obtained within each session (4 trials per condition). Pre-Stim (Left) $N_{\text{participants}} = 1$, $N_{\text{channels}} = 2$, $N_{\text{sessions}} = 1$. Post-Stim 1-3 (Right) $N_{\text{participants}} = 1$, $N_{\text{channels}} = 2$, $N_{\text{sessions}} = 3$. * = unadjusted $p = 0.04$, using linear mixed model (Methods). **b**, Same as **a** but in TR-PTSD 2. Pre-Stim (Left) $N_{\text{participants}} = 1$, $N_{\text{channels}} = 2$, $N_{\text{sessions}} = 1$. Post-Stim 1-3 (Right) $N_{\text{participants}} = 1$, $N_{\text{channels}} = 2$, $N_{\text{sessions}} = 3$. ** = unadjusted $p = 0.0057$, using linear mixed model (Methods).



Supplementary Figure 12. Lack of amygdala valence-related changes in sEEG and RNS non-TR-PTSD participants.

Normalized (Norm.) difference in frequency bandpower (delta, theta, alpha, beta, low and high gamma) between negative and positive/neutral conditions (negative – positive/neutral) during the Emotional Image Task (related to Fig. 2a) over time separately for sEEG (blue) and RNS (green) non-TR-PTSD participants relative to image onset (time 0). Positive norm. power difference = negative > positive/neutral; negative norm. power difference = positive/neutral > negative. For each frequency band, the mean ± 2 s.e.m. across channels is shown for non-TR-PTSD sEEG ($N_{\text{participants}} = 3$, $N_{\text{channels}} = 3$) and non-TR-PTSD RNS ($N_{\text{participants}} = 3$, $N_{\text{channels}} = 6$) participants. Significant valence-related changes using linear mixed effects models (see Supplemental Appendix) were not present in non-TR-PTSD, irrespective of recording modality.

Participant	Age (\pm s.e.m)	Gender	Handedness	Implanted System	Clinical Diagnoses that led to Electrode Implantation
TR-PTSD 1 and 2	38 \pm 2	M	Ambidextrous	RNS-320	TR-PTSD
non-TR-PTSD 1	44	M	R	sEEG	Epilepsy
non-TR-PTSD 2	35	M	L	sEEG	Epilepsy
non-TR-PTSD 3	40	M	R	sEEG	Epilepsy
non-TR-PTSD 4	68	M	R	RNS-320	Epilepsy
non-TR-PTSD 5	28	M	R	RNS-320	Epilepsy
non-TR-PTSD 6	36	M	R	RNS-300M	Epilepsy

Supplementary Table 1. Participant demographics, implanted electrode systems, and treatment-resistant clinical diagnoses that led to electrode implantation. (sEEG = stereoelectroencephalography, NeuroPace RNS-320 and RNS-300M Systems). TR-PTSD = treatment-resistant post-traumatic stress disorder.

Participant	Left Amygdala	Right Amygdala
non-TR-PTSD 1	X	X
non-TR-PTSD 2		X
non-TR-PTSD 3		X
non-TR-PTSD 4	X	
non-TR-PTSD 5		X
non-TR-PTSD 6	X	

Supplementary Table 2. Electrode localizations for each epilepsy (non-TR-PTSD) participant showing whether each had a left and/or right amygdala channel that was included in the study.

Participant	Right Amygdala C1 (x,y,z)	Right Amygdala C2 (x,y,z)	Left Amygdala C1 (x,y,z)	Left Amygdala C2 (x,y,z)
TR-PTSD 1	(35,64,26)	(35,61,26)	(60,64,26)	(60,62,28)
TR-PTSD 2	(34,64,27)	(34,62,28)	(59,65,28)	(59,62,29)
non-TR-PTSD 1*	(37,62,25) (32,62,25)	(35,62,25) (30,62,25)	(55,63,25) (59,63,25)	(57,63,25) (62,63,25)
non-TR-PTSD 2	(34,62,27)	(31,62,27)		
non-TR-PTSD 3	(29,62,29)	(29,62,29)		
non-TR-PTSD 4			(56,63,30)	(57,61,30)
non-TR-PTSD 5	(32,65,23)	(32,61,25)		
non-TR-PTSD 6			(58,62,26)	(58,66,24)

Supplementary Table 3. Electrode localizations showing specific MNI coordinates (x,y,z) of both contacts (C1 and 2) of the left and right amygdala bipolar channels in each TR-PTSD participant that were used for iEEG recording and closed-loop stimulation. *Non-TR-PTSD 1 had two bipolar channels located within the amygdala bilaterally. MNI152_T1_2mm was used to register all images.

Participant	Event	Symptom Description	SUDS Score
TR-PTSD 1	1°	“Fireworks around neighborhood. Hypervigilant racy feeling.”	8
TR-PTSD 1	2°	“Saw a very gory scene flash in my mind, weak knees, cold sweat, shaking, vision.”	Not reported
TR-PTSD 2	1°	“Sad, depressed”	5
TR-PTSD 2	2°	“Angry, irritable, somewhat suicidal thoughts”	4-5

Supplementary Table 4. Examples of self-reported descriptions related to self-triggered recordings of symptom exacerbations (magnet swipe recordings) for TR-PTSD 1 and TR-PTSD 2. °These events triggered intrusive recollections of combat trauma. SUDS = Subjective Units of Distress Scale

Participant	Stimulation Logic	Proportion of Detection
TR-PTSD 1 (Month 1-12)	Trigger 1 or Trigger 2 (either hemisphere)	96% (Trigger 1) 4% (Trigger 2)
TR-PTSD 2 (Month 1-2)	Trigger 1 or Trigger 2 (both hemispheres)	51% (Trigger 1) 49% (Trigger 2)
TR-PTSD 2 (Month 3-12)	Trigger 1 or Trigger 2 (either hemisphere)	85% (Trigger 1) 15% (Trigger 2)

Supplementary Table 5. RNS programming logic used in closed-loop stimulation. Trigger 1: Greater than 50% change in area under the curve for low frequencies (2-18 Hz) for longer than 0.26 seconds in either posterior amygdala channel. Trigger 2: Greater than 62.5% change in average line length in either left or right posterior amygdala channel. In all cases, activation of stimulation trigger led to delivery of 100 ms of 1.0-3.0 mA current (charge-balanced biphasic square wave pulses) at 200 Hz with a pulse width of 160 microseconds delivered bilaterally, simultaneously to amygdala contacts (estimated charge density: 1.0 $\mu\text{C}/\text{cm}^2$). Daily therapy limit: 5000 stimulations.

Negative	Valence	Arousal	Dominance
TR-PTSD pre-stim	2.33 (0.08)	5.89 (0.11)	3.62 (0.10)
TR-PTSD post-stim 1	2.43 (0.90)	5.51 (0.18)	3.83 (0.18)
TR-PTSD post-stim 2	2.37 (0.10)	5.56 (0.21)	3.66 (0.15)
TR-PTSD post-stim 3	2.39 (.13)	5.42 (0.26)	3.90 (0.22)
non-TR-PTSD	2.39 (0.13)	5.62 (0.28)	3.86 (0.17)
Positive	Valence	Arousal	Dominance
TR-PTSD pre-stim	7.70 (0.05)	5.47 (0.13)	6.23 (0.07)
TR-PTSD post-stim 1	7.58 (0.09)	5.07 (0.21)	6.18 (0.13)
TR-PTSD post-stim 2	7.56 (0.08)	5.12 (0.25)	6.12 (0.15)
TR-PTSD post-stim 3	7.55 (0.13)	4.97 (0.33)	6.20 (0.19)
non-TR-PTSD	7.73 (0.08)	5.13 (0.21)	6.29 (0.10)
Neutral	Valence	Arousal	Dominance
TR-PTSD pre-stim	4.97 (0.07)	3.48 (0.17)	5.67 (0.09)
TR-PTSD post-stim 1	5.12 (0.14)	3.56 (0.16)	5.80 (0.13)
TR-PTSD post-stim 2	5.11 (0.12)	3.55 (0.20)	5.82 (0.12)
TR-PTSD post-stim 3	5.10 (0.21)	3.70 (0.21)	5.73 (0.23)
non-TR-PTSD	5.79 (0.22)	3.90 (0.25)	5.92 (0.12)

Supplementary Table 6. Mean (s.e.m.) valence, arousal and dominance for IAPS emotional image sets used in the study for treatment-resistant post-traumatic stress disorder (TR-PTSD) and non-TR-PTSD (epilepsy) participants calculated from normalized ratings². For TR-PTSD participants, ratings are separated for pre- (Pre-Stim) and post-stimulation (Post-Stim) sessions 1 and 2.

Negative	Brightness	Contrast	Entropy
TR-PTSD Pre-Stim	106.27 (6.27)	67.39 (2.14)	7.06 (0.18)
TR-PTSD Post-Stim 1	100.57 (7.14)	68.96 (3.00)	7.15 (0.22)
TR-PTSD Post-Stim 2	102.86 (7.92)	65.96 (3.24)	7.09 (0.23)
TR-PTSD Post-Stim 3	99.01 (8.49)	71.61 (3.78)	6.94 (0.25)
non-TR-PTSD	110.98 (8.45)	66.30 (3.65)	7.40 (0.10)
Positive	Brightness	Contrast	Entropy
TR-PTSD Pre-Stim	104.74 (7.22)	70.49 (2.74)	6.97 (0.19)
TR-PTSD Post-Stim 1	122.43 (8.27)	71.45 (3.49)	6.89 (0.22)
TR-PTSD Post-Stim 2	108.74 (7.93)	72.10 (2.68)	7.04 (0.19)
TR-PTSD Post-Stim 3	100.32 (7.03)	70.23 (2.72)	7.09 (0.21)
non-TR-PTSD	100.45 (5.98)	70.36 (2.64)	7.13 (0.17)
Neutral	Brightness	Contrast	Entropy
TR-PTSD Pre-Stim	116.89 (8.88)	64.16 (3.68)	6.95 (0.12)
TR-PTSD Post-Stim 1	108.81 (9.49)	63.14 (3.19)	6.89 (0.22)
TR-PTSD Post-Stim 2	102.8 (9.72)	66.05 (3.59)	7.04 (0.22)
TR-PTSD Post-Stim 3	101.15 (10.89)	60.04 (2.73)	6.69 (0.28)
non-TR-PTSD	95.45 (7.69)	60.65 (4.19)	7.05 (0.26)

Supplementary Table 7. Psychophysical properties of emotional images. Mean (s.e.m.) brightness, contrast and entropy for IAPS emotional image sets used in the study. Parameters calculated using previously described methods³. For TR-PTSD participants, ratings are separated for pre- (Pre-Stim) and post-stimulation (Post-Stim) 1 and 2 sessions.

Supplementary References

1. Marx, B. P. *et al.* Reliable and clinically significant change in the clinician-administered PTSD Scale for DSM-5 and PTSD Checklist for DSM-5 among male veterans. *Psychological Assessment* **34**, 197–203 (2022).
2. Lang, P. J., Bradley, M. M. & Cuthbert, B. N. International affective picture system (IAPS): Instruction manual and affective ratings, Technical Report A-8. *Gainesville: The center for research in psychophysiology, University of Florida* (2008).
3. Marchewka, A., Zurawski, Ł., Jednoróg, K. & Grabowska, A. The Nencki Affective Picture System (NAPS): introduction to a novel, standardized, wide-range, high-quality, realistic picture database. *Behav Res Methods* **46**, 596–610 (2014).