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The memory trace of an intrusive trauma-analog episode

Highlights

- Trauma movies induce higher activity and generalized memory traces in visual areas
- Trauma movies induce lower activity and distinct representations in conceptual areas
- Memory intrusions activate generalized visual representations
- Memory intrusions induce event-specific reactivation in anterior cingulate cortex

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In brief

Kobelt et al. track the formation and reactivation of neural representations during trauma-analog movies and memory intrusions. Trauma movies induce perceptually more generalized and conceptually more distinct representations than neutral movies (as reflected by pattern similarity), which may explain the core features of memory intrusions in PTSD.

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The memory trace of an intrusive trauma-analog episode

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SUMMARY

Intrusive memories are a core symptom of posttraumatic stress disorder. Compared with memories of everyday events, they are characterized by several seemingly contradictory features: intrusive memories contain distinct sensory and emotional details of the traumatic event and can be triggered by various perceptually similar cues, but they are poorly integrated into conceptual memory. Here, we conduct exploratory whole-brain analyses to investigate the neural representations of trauma-analog experiences and how they are reactivated during memory intrusions. We show that trauma-analog movies induce excessive processing and generalized representations in sensory areas but decreased blood-oxygen-level-dependent (BOLD) responses and highly distinct representations in conceptual/semantic areas. Intrusive memories activate generalized representations in sensory areas and reactivate memory traces specific to trauma-analog events in the anterior cingulate cortex. These findings provide the first evidence of how traumatic events could distort memory representations in the human brain, which may form the basis for future confirmatory research on the neural representations of traumatic experiences.

INTRODUCTION

Autobiographical memories define our identity—they allow us to deliberately navigate through our past in order to shape future goals and actions. When we experience overwhelmingly negative events, however, we may get haunted by our past, experiencing intrusions of unwanted memories. Intrusive memories are a core symptom of various psychiatric diseases, most prominently posttraumatic stress disorder (PTSD).[1] PTSD is highly prevalent,[2] but current pharmacological and psychotherapeutic treatments remain ineffective in around half of the patients.[3,4] Understanding how a traumatic experience is represented in the brain and which factors drive its involuntary reactivation may be critical for the development of more tailored and mechanistic treatments.[5] Yet, while animal studies over the last decade have identified the neural activity patterns underlying individual memories in great detail,[6–8] research in humans has only recently developed methods to explore neural representations of specific memory contents.[9–12] As a consequence, no previous study directly investigated the neural representations underlying memory intrusions thus far.

Here, we report results from an exploratory study on the formation and spontaneous re-occurrence of memory intrusions in the human brain via functional magnetic resonance imaging (fMRI). We induced experimental analogs of real-life traumatic events by presenting highly emotional film clips that were embedded in verbal storylines and set to tense background music[13,14] (Figure 1A). This allowed us to track the formation of trauma-analog memory representations and their spontaneous replay during memory intrusions in a subsequent resting-state scan. Representations of individual trauma-analog events (TAEs) were identified using representational similarity analysis (RSA),[15] which quantifies the similarity between voxel activity patterns of specific events. Using RSA, previous studies showed that memory retrieval relies on the reactivation of event-specific representations that were built during encoding.[16–18] Importantly, this reactivation occurs in brain regions that reflect specific memory content, e.g., fear memories particularly reactivated event-specific representations in the fear network including anterior cingulate cortex (ACC) and insula.[19] Previous studies further showed that successful memory retrieval requires a fine balance of neural generalization and distinctiveness between representations of different events[9,11,20]: generalized representations can facilitate memory retrieval of an event by increasing the number of associated memories and cues,[10,21,22] whereas distinct representations are needed to effectively discriminate events from each other in order to avoid false memories[23] or excessive expression of fear.[24]

Processes of memory generalization and distinction in different brain regions may explain three central and seemingly contradictory features of memory intrusions. First, memory intrusions contain highly specific sensory and emotional details

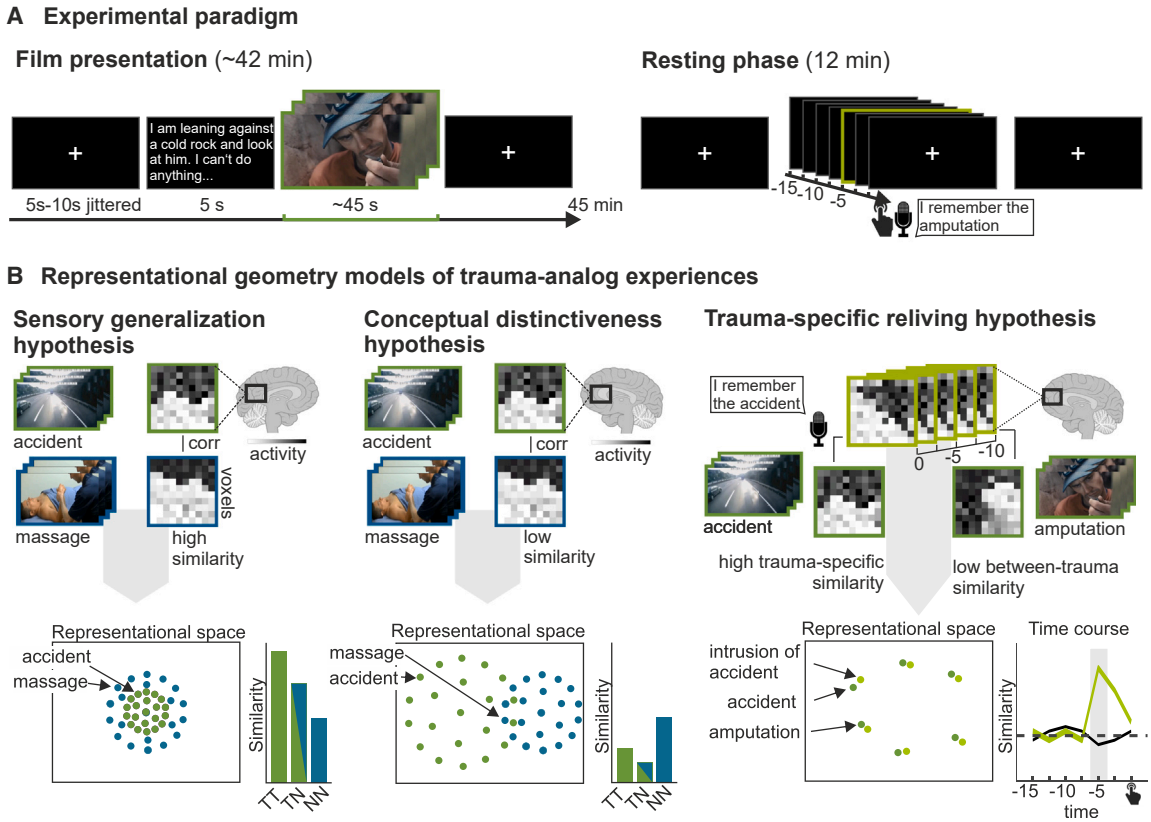

Figure 1. Experimental paradigm and models of neural geometry

(A) Experimental paradigm including film presentation and resting phase.

(B) Representational geometry models of trauma-analog processing. Left: sensory generalization hypothesis. Neural representations of trauma-analog events (TAEs) in sensory areas should be highly similar to neural representations of other events. In representational space, this results in their spatial proximity to representations of other experiences, i.e., neural representations of TAEs should be located in the center of this space. Middle: conceptual distinctiveness hypothesis. In conceptual processing areas, TAEs should be represented by strongly separated neural activity patterns, such that their representations are located in the periphery of representational space. As a consequence, neural representations of TAEs are only poorly related with the conceptual representations of other events, which may impede integration into autobiographical conceptual memory. Right: trauma-specific reliving hypothesis. Memory intrusions of TAEs are supposed to reactivate representations formed during encoding of the corresponding TAE. This effect should occur shortly before intrusion reports via button press (lower right figure).

See also Figures S1 and S2.

about individual traumatic events (memory specificity).[25] Second, these intrusions can be triggered by numerous perceptually similar cues (cue generalization).[26,27] Third, memories of traumatic experiences are typically less coherent and disconnected from memories of other life events.[28,29] Although some models challenge the view that trauma memory narratives are less coherent,[30] PTSD theories propose that memory intrusions derive from excessive data-driven sensory processing and a lack of conceptual and semantic processing during the trauma.[26,31] As a consequence, the traumatic experience may be represented via a distorted neural signature that maintains sensory and emotional details and that is highly distinct from other memories on a conceptual level, but the signature does not adequately discriminate the traumatic event from perceptually similar cues,[31] which generally aligns with other models on fear learning, stress research, and PTSD (for review, see De Quervain et al.,[32] Lissek and Van Meurs,[33] Goodman et al.,[34] and Foa et al.[35]).

While the neural representations of traumatic experiences are only poorly understood thus far, previous fMRI studies applied univariate analyses to test mean activity changes during encoding and intrusions of trauma-analog film footage. In line with assumed excessive sensory processing during traumatic experiences, these studies consistently reported increased activity in visual processing areas, the amygdala, and the salience network including insula and left inferior frontal gyrus during encoding of intrusive TAEs.[36–38] Consistently, memory intrusions were associated with increased activity in visual processing areas and the salience network in both healthy participants exposed to trauma films and PTSD patients undergoing symptom provocation.[37,39,40] In addition, symptom provocation tasks in PTSD patients showed first evidence of reduced activity in conceptual processing areas such as the superior temporal cortex,[41,42] an effect that has so far not been observed in healthy participants undergoing the trauma film paradigm. On the basis of these findings and psychopathological models, we aimed to

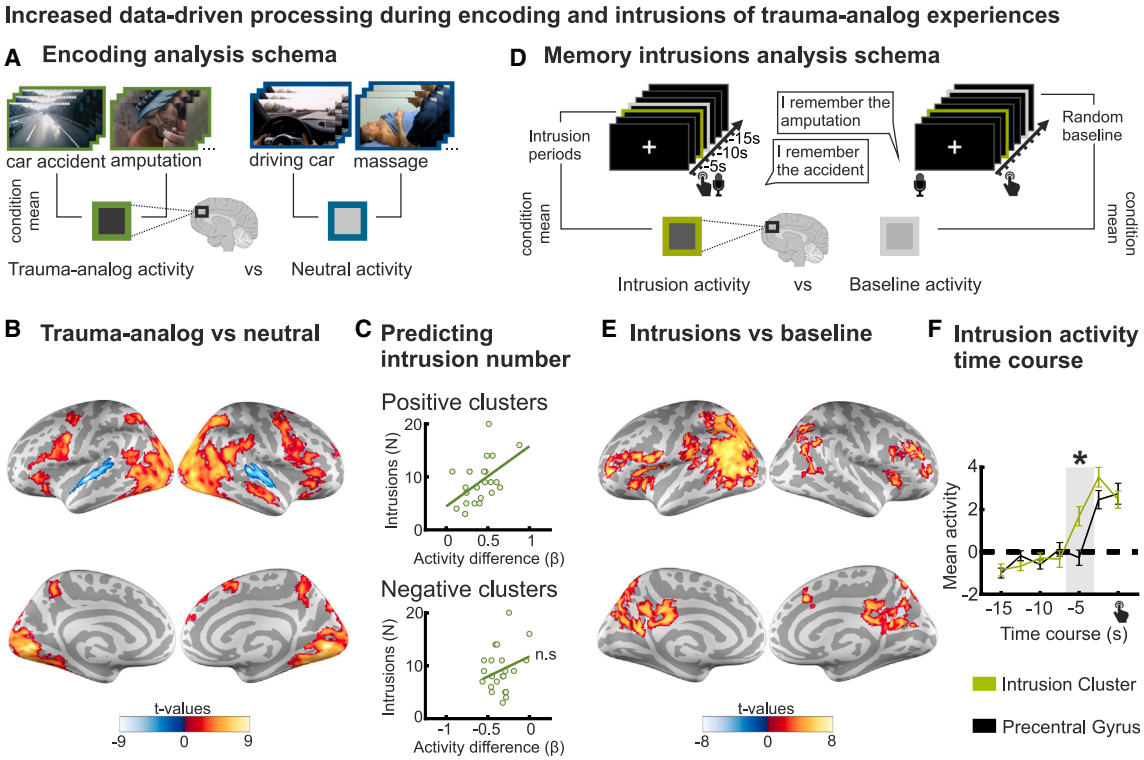

Figure 2. Enhanced sensory and reduced semantic processing during traumatic experiences

(A) Encoding analysis schema: BOLD signal is modeled across all magnetic resonance (MR) volumes of each film clip and then compared between conditions.

(B) Encoding of trauma-analog vs. neutral film clips showing t values of significant clusters.

(C) Correlation of neural activity difference in all positive clusters (top) and negative clusters (bottom) to the number of memory intrusions of TAEs during resting period.

(D) Intrusion analysis schema: memory intrusions are modeled as BOLD signals 5 s before intrusion response. Baseline activity is modeled using a random preceding volume.

(E) Clusters showing differences between memory intrusions and baseline.

(F) Time course of neural activity in the identified intrusion cluster and in the left precentral gyrus for each MR volume. Error bars indicate standard errors of the mean. The gray box highlights the MR volume of interest. n.s, nonsignificant result; *$p < 0.05$.

See also Figures S2–S4 and Tables S1 and S4.

study the brain activity patterns and representational signatures of TAEs during their formation and spontaneous re-occurrence. In an exploratory study, we investigated whether memory intrusions manifest in an imbalance of representational generalization and distinctiveness of their individual memory traces (Figure 1B).

In line with previous studies,[36–38] we expected TAEs to elicit high amounts of activity in visual areas and decreased activity in conceptual processing areas. Moving beyond prior research, we attempted to translate clinical models into hypotheses on neural generalization and distinctiveness of trauma-analog representations. However, we acknowledge that these clinical models provide directional guidance rather than precise predictions about specific brain areas and thus applied exploratory whole-brain analyses. We explored whether TAEs were encoded in more generalized sensory representations, which may be easily triggered as they overlap with seemingly unrelated neutral events (sensory generalization) and, at the same time, show more distinct neural representations in conceptual processing areas (conceptual distinctiveness). Accordingly, memory intrusions may be associated with more generalized sensory representations but distinct conceptual representations. Finally, we conducted exploratory analyses to investigate stimulus-specific reactivation of individual TAEs during memory intrusions (trauma-specific reliving). In the following sections, we show first evidence that memory intrusions may rely on all of these features: sensory generalization, distinct representations in conceptual brain areas, and trauma-specific reactivation in the ACC.

RESULTS

Excessive data-driven and impaired conceptual processing of TAEs and memory intrusions

We analyzed the neural signature of memory intrusions in healthy participants (n = 22) who watched 21 trauma-analog and 21 content-matched neutral film clips and subsequently reported their spontaneous memory intrusions in an MRI scanner (Figure 1A; see Figure S2 for behavioral data). Using an exploratory whole-brain approach, we first contrasted blood-oxygen-level-dependent (BOLD) responses during TAEs to neutral events (Figure 2A). TAEs elicited higher activity in sensory areas including early visual cortex, middle temporal gyrus, and precuneus (Figure 2B; Table S1). In addition, we observed increased BOLD responses

in regions of the salience network including inferior frontal gyrus and insula.[37,43] Neural activity increases in all positive clusters during TAEs correlated with the number of subsequent memory intrusions of a given participant during the resting period (r = 0.51, p = 0.015; Figure 2C). This effect remained significant when excluding an outlier in the number of intrusions during the resting phase (r = 0.55, p = 0.010). Reversely, TAEs induced lower activity than neutral events in the bilateral superior temporal cortex, a core area of modality-selective conceptual processing[44,45] and narrative comprehension of naturalistic events.[46–48] This activation decrease was not related to the number of memory intrusions during the resting period (all participants: r = 0.27, p = 0.233; outlier removed: r = 0.22, p = 0.334; Figure 2C). The relationship to memory intrusions in the resting period did not significantly differ between positive and negative clusters, which we compared using bootstrapping procedures (all participants: p = 0.143; one outlier removed: p = 0.080), suggesting that this brain-behavior relationship was not specific to visual processing areas but instead may be a more global effect. Neural activity in both clusters was not robustly related to the number of memory intrusions in the 7-day diary (positive clusters: all participants, r = 0.14, p = 0.546; outlier removed, r = 0.12, p = 0.602; negative clusters: all participants, r = 0.46, p = 0.033; outlier removed, r = 0.23, p = 0.315).

We next analyzed neural responses during spontaneous memory intrusions. Consistent with the results from encoding, analysis of BOLD responses prior to these intrusions revealed increased processing in sensory areas compared with baseline (Figure 2D). Specifically, memory intrusions were associated with higher activity in visual association cortices including the middle occipital gyrus, middle temporal gyrus, precuneus, and angular gyrus (Figure 2E; Table S1). When compared with TAEs, memory intrusions activated these higher-level visual processing areas more strongly (Figure S3A). In addition, we again found increased activity in areas of the salience network (left inferior frontal gyrus and bilateral insula). All of these responses occurred significantly earlier than BOLD responses in left primary motor cortex associated with the button press, which increased only one MR (m volume) (2.5 s) before participants reported an intrusion (t_{21} = 5.71; p_{corr} < 0.001; Figure 2F).

Sensory generalization and conceptual distinctiveness of trauma-analog representations

Next, we investigated the neural representations of individual TAEs. We compared the similarity patterns between different TAEs with the similarity between different neutral events (Figure 3A; for details, see Figure S1). Using an exploratory whole-brain searchlight approach, we identified a cluster of brain regions in which activity patterns were more similar between different TAEs than between different neutral experiences (Figure 3B). This "generalization cluster" comprised not only early and higher-level visual areas and the angular gyrus as we expected but also additional unexpected areas such as the inferior frontal gyrus and middle frontal gyrus, which may suggest that generalization also occurred in the salience network and higher processing areas (Table S2). We used multidimensional scaling (MDS) to illustrate the representational geometry in this cluster (Figure 3C), i.e., the spatial proximity between representations of different TAEs (green circles) was higher than the proximity between representations of neutral events (blue circles). In line with psychopathological models, this result indicates that different TAEs are represented by relatively more similar (i.e., more generalized) patterns than neutral events. Reversely, we found that representations of different TAEs in superior temporal cortices were less similar to each other than different neutral experiences (Figures 3B and 3D), suggesting that conceptual representations of TAEs are more distinct from each other. Pattern similarity differences were not explained by averaged neural activity differences between TAEs and neutral scenes (Table S3) and were robust to the selected stimulus material, as indicated by split-half reliability measures (Figure S5).

We were interested in how the most distressing moments of a trauma ("hotspots") relate to neural generalization. We therefore analyzed the time course of pattern similarity between TAEs in the generalization cluster (Figure S4) and linked them to a hotspot rating of an independent group of raters (n = 7). Interestingly, time periods of TAEs that were more often rated as hotspots showed more pronounced generalization (linear mixed model: $F_{1,7486}$ = 486.14; p < 0.001; Figure 3E), emphasizing that this effect increases during the most distressing moments of TAEs.

Critically, the concept of cue generalization would predict that sensory representations of TAEs are not only more similar to each other than neutral events but also resemble sensory representations of neutral events, which may thus act as trigger cues. Indeed, we found that representations of TAEs were more similar to representations of neutral events than different neutral experiences were to each other in early visual areas (including bilateral lingual gyrus and cuneus) and in right angular gyrus (Figures 3F–3H; Table S2). By contrast, representations were more distinct between TAEs and neutral experiences in conceptual/semantic areas in superior temporal cortex as we expected. We additionally found more distinct representations in the salience network (including bilateral dorsal ACC, left inferior frontal gyrus, and left insula). In contrast to the previous analysis, we did not find pattern similarity differences in higher processing areas such as medial frontal gyrus, highlighting that generalization most prominently occurred in sensory processing areas.

We next investigated whether not only TAEs but also memory intrusions rely on generalized sensory representations and/or distinct conceptual representations. Using a time-resolved RSA approach (Figure 4A; Figure S1), we found increased representational similarity between different memory intrusions in early visual areas (including bilateral lingual gyrus and cuneus) and in the precuneus. These effects emerged prior to intrusion responses (Figures 4A and 4B) and remained elevated for several seconds (Figure 4C). We did not find any areas showing decreased pattern similarity. This result underlines that not only traumatic experiences but also ensuing memory intrusions were related to more generalized sensory representations.

Content-specific reactivation of trauma representations

While the results so far may explain why ubiquitous sensory cues can trigger traumatic memory intrusions, they cannot explain why these experiences are nevertheless clearly distinguishable and distinctly related to individual traumatic contents. We thus conducted a complementary exploratory analysis and correlated the representation of a specific memory intrusion to

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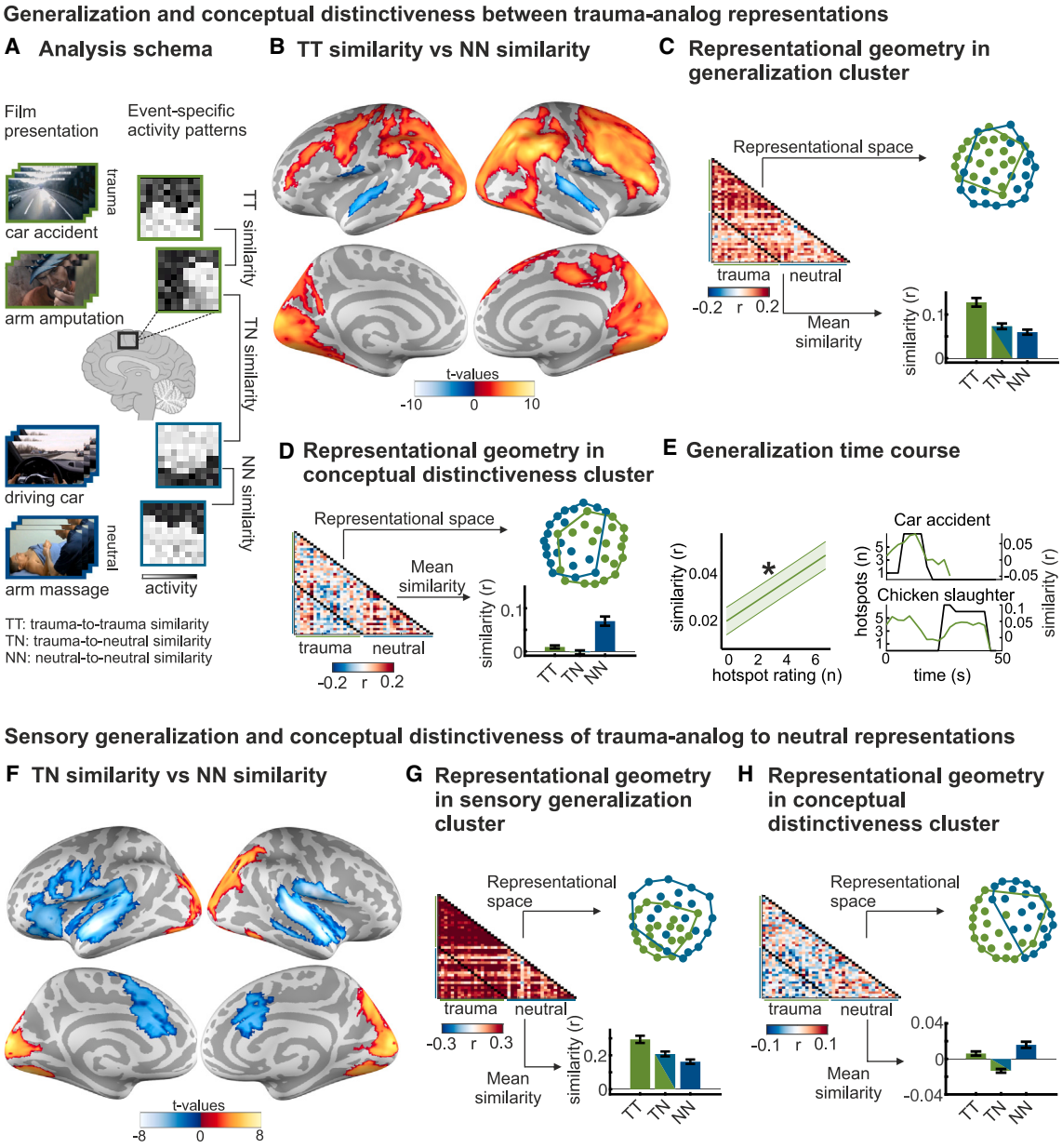


Figure 3. Representational geometries of TAEs

(A) Analysis schema to compare trauma-trauma (TT) similarity to neutral-neutral (NN) similarity and trauma-neutral (TN) similarity to neutral-neutral (NN) similarity.

(B) Clusters showing significant differences between TT and NN similarity.

(C) Similarity between representations of all film clips within the cluster showing significant generalization of TAEs (i.e., TT > NN). Left, representational similarity (half-) matrix averaged across participants. Top, multidimensional scaling (MDS) plot illustrating distances between neural representations in representational space. Each dot represents one film clip. Higher proximities refer to higher similarities between representations. Bottom, mean similarity values for each condition.

(D) Similarity between representations of all film clips within the cluster showing higher distinctiveness of TAEs vs. neutral experiences (NN > TT).

(E) Relationship between hotspot ratings and neural generalization across time. Left, fixed factor regression coefficient from a linear mixed model predicting neural generalization (on the x axis), with hotspot ratings as fixed factor (y axis). Right, two exemplary film clips illustrating how hotspots (black line) and neural generalization (green line) are temporally associated.

(F) Clusters showing significant differences between TN and NN similarity.

(G) Similarity between representations of all film clips within the cluster showing significant generalization of TAEs to neutral experiences (i.e., TN > NN).

(H) Similarity between representations of all film clips within the cluster showing reduced similarity of TAEs to neutral experiences (i.e., NN > TN). Error bars indicate standard errors of the means. *p < 0.05.

See also Figures S4 and S5 and Tables S2–S4.

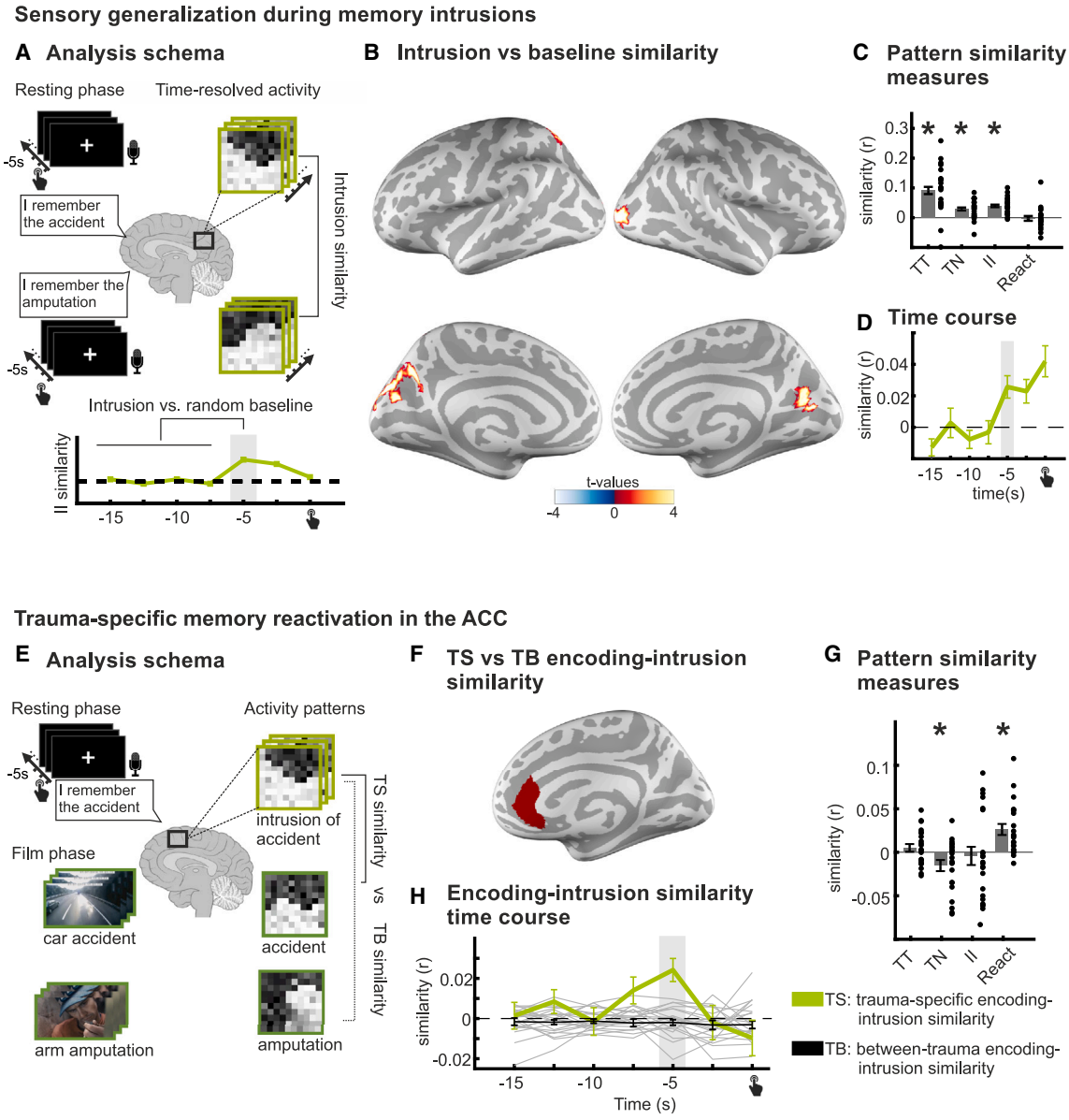


Figure 4. Representational formats and geometries of memory intrusions

(A) Analysis schema to calculate intrusion-intrusion similarity and to compare intrusion-intrusion similarity across time.

(B) Intrusion-intrusion similarity in significant cluster increases 5 s prior to intrusion response.

(C) Overview of pattern similarity scores in neural generalization cluster during memory intrusions.

(D) Time course of intrusion-intrusion similarity in the significant cluster.

(E) Analysis schema to assess encoding-intrusion similarity for all pairs and to measure trauma-specific reactivation.

(F) Brain parcel showing significantly higher trauma-specific reactivation.

(G) All pattern similarity measures in the rostral ACC.

(H) Time course of trauma-specific and between-trauma encoding-intrusion similarity in the rostral anterior cingulate cortex (ACC). TT, trauma-trauma similarity; NN, neutral-neutral similarity; TN, trauma-neutral similarity; II, intrusion-intrusion similarity 5 s prior to response vs. baseline; react, trauma-specific encoding-retrieval similarity vs. trauma encoding-retrieval similarity; TS, trauma-specific encoding-intrusion similarity; TB, between-trauma encoding-intrusion similarity; Error bars indicate the standard error of the mean *p < 0.05.

representations of either the same or of different TAEs during encoding (similar to the measures of encoding-retrieval similarity in episodic memory paradigms; Figure 1C).[49] Notably, we did not analyze memory intrusions of neutral events because of their low number. Using a whole-brain parcellation approach (Figure 4E),[36,50] we observed reactivation of trauma-specific representations shortly before intrusion responses (5s before response) in several areas of the right medial prefrontal cortex including rostral ACC (t_{21} = 4.11, p < 0.001), caudal ACC (t_{21} = 2.38, p = 0.027), medial orbitofrontal cortex (t_{21} = 2.27,

p = 0.034), and lateral orbitofrontal cortex (t_{21} = 2.57, p = 0.018). We also found evidence for trauma-specific reactivation in the right parahippocampal gyrus (t_{21} = 2.95, p = 0.008), right lateral occipital cortex (t_{21} = 2.57, p = 0.025), and a reversed effect in the left inferior parietal gyrus (t_{21} = −2.40, p = 0.026). Yet, out of all brain parcels, only trauma-specific reactivations in the right rostral ACC survived Benjamini-Hochberg false discovery rate (FDR)-correction for 72 parcels (p_{corr} = 0.036; Figures 4F and 4G).

This episode-specific reactivation occurred at the same time as sensory generalization, suggesting simultaneous involvement of multiple representational formats with different geometries (i.e., characteristics of specificity and generalization) during memory intrusions. Indeed, the representational geometry in rostral ACC differed strikingly from the geometry in sensory areas: the rostral ACC did not show any differences in representational similarity between TAEs and neutral experiences during encoding (t_{21} = 1.10, p = 0.283), and representations of TAEs were more distinct from neutral experiences than different neutral experiences were from one another (t_{21} = −2.40, p = 0.026). This region also did not exhibit similarity increases during memory intrusions (t_{21} = −0.41, p = 0.685), underlining that it reactivates trauma-specific representations during intrusions rather than generalized representations (Figure 4H). Reversely, the visual areas that showed generalized representations during memory intrusions additionally showed higher similarity between TAEs than between neutral experiences (t_{21} = 5.33, p < 0.001) and higher similarity between TAEs and neutral experiences than between different neutral experiences (t_{21} = 4.23, p < 0.001), but no trauma-specific reactivation (t_{21} = −0.31, p = 0.762; Figure 4D). Thus, memory intrusions may rely on memory traces with different representational geometries in visual areas and in the rostral ACC.

Excessive amygdala activity during TAEs correlates with sensory generalization and predicts the number of intrusions

Excessive sensory and impaired conceptual processing during traumatic experiences has been hypothesized to rely on amygdala overactivity and reduced hippocampal recruitment,[31] but neuroimaging evidence for this hypothesis remains scarce. We therefore investigated neural activity in these areas using anatomically defined ROIs. Compared with neutral events, TAEs induced higher activity in the amygdala (t_{21} = 3.13, p = 0.005) but not in the hippocampus (t_{21} = 1.44, p = 0.165; Figure 5A), and effects differed significantly between these regions (t_{21} = 3.14, p = 0.005). The increases in amygdala activation during TAEs were related to TAE hotspots (Table S4). These results support the idea that the formation of traumatic memories relies on excessive amygdala activation, but we did not find evidence for reduced hippocampal recruitment (see Figure S3B for activation differences during memory intrusions).

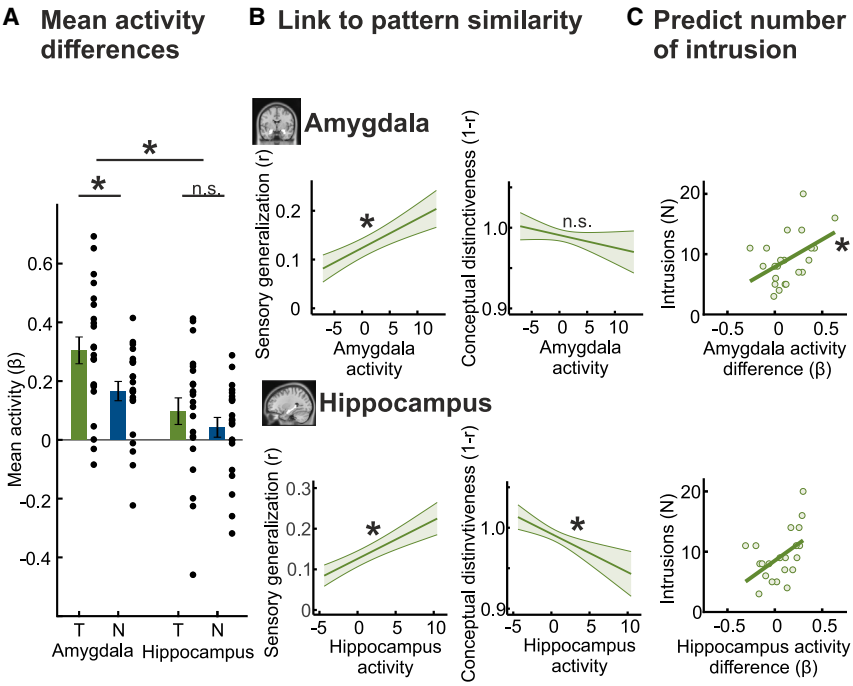
Does increased amygdala activation relate to sensory generalization and/or to conceptual distinctiveness? To address this question, we calculated neural generalization scores for each TAE, computing the similarity of its representation to the representations of all other TAEs in the generalization cluster. Conceptual distinctiveness was calculated as the representational dissimilarity to other TAEs (1 − correlation) in the conceptual distinctiveness cluster. We then applied linear mixed models with generalization scores of each TAE as criterion, activity in amygdala or hippocampus as predictors, and subject as random factor. Generalization during TAEs was related to activity in both amygdala ($F_{1,443.4}$ = 21.91; p < 0.001) and hippocampus ($F_{1,443.75}$ = 29.20; p < 0.001; Figure 5B). Conceptual distinctiveness of TAEs was not predicted by amygdala activity ($F_{1,455.17}$ = 2.49; p = 0.115) but was negatively related to hippocampus activity ($F_{1,455.91}$ = 12.27; p < 0.001). Moreover, amygdala activity was related to hippocampus activity ($F_{1,458.49}$ = 268.12; p < 0.001), and generalization in sensory and salience processing areas was negatively linked to conceptual distinctiveness ($F_{1,447.69}$ = 95.86; p < 0.001; see Table S5 for the relationship of insula and inferior frontal gyrus activity to neural generalization). Notably, this negative relationship between generalization and conceptual distinctiveness was calculated within the trauma-analog condition and does not allow any inferences on differences to neutral events. Our findings suggest that amygdala activity relates to excessive generalization in sensory and salience processing areas, while hippocampus activity relates positively to generalization in sensory and salience processing areas and negatively to conceptual distinctiveness.

Finally, we tested whether excessive amygdala activation predicts the number of memory intrusions of a given participant (across subjects). Indeed, participants showing higher activation of amygdala during TAEs vs. neutral events reported more memory intrusions during the resting period (all participants: r = 0.46, p = 0.035; controlled for outlier: r = 0.44, p = 0.047; Figure 5C). Similar effects were observed in the hippocampus (r = 0.49, p = 0.023). However, this relationship was only a trend when controlling for the outlier (r = 0.40, p = 0.075). Neural activity in these areas did not predict memory intrusions of neutral events during the resting period (all p > 0.183) and did not predict the number of memory intrusions in the 7-day diary (amygdala: r = 0.12, p = 0.607; hippocampus: r = 0.21, p = 0.344).

DISCUSSION

A novel, strongly immersive trauma film paradigm allowed us to measure the formation of memory traces for TAEs and their reoccurrence as memory intrusions. Using exploratory whole-brain analyses, our results provide first insights into the distorted signatures of memories for traumatic events: they exhibited more generalized sensory representations and distinct conceptual representations, which may account for core characteristics of memory intrusions.

Analyses of representational geometries during encoding and memory intrusions of TAEs revealed highly generalized representations in sensory areas, which may explain why ubiquitous neutral trigger cues can elicit traumatic memory intrusions, as long as they share sensory features with the initial traumatic event. Previous fear conditioning studies showed that generalized representations in the amygdala and salience network predict fear expression and impair the ability to discriminate perceptually similar cues from threat cues.[51–53] Our results extend these findings to sensory processing areas, possibly reflecting the rich naturalistic sensory input with which participants were confronted in our study and the highly perceptual nature of memory intrusions. These results are also in line with the concept of perceptual priming, which refers to the



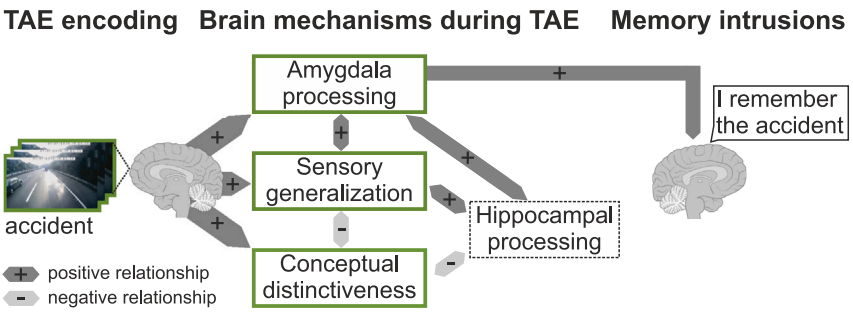


Figure 5. Amygdala and hippocampus activity changes accompany representational changes

(A) Mean activity during encoding of TAEs and neutral clips. Bar plots depict mean, standard error, and individual data points.

(B) Relationship between trial-level activity and pattern similarity.

(C) Relationship between activity differences in amygdala and hippocampus to memory intrusions of TAEs during the resting period across participants.

(D) Schematic overview of all neural measures during encoding, their relationships on trial-level, and how they predict the number of intrusions across subjects. T, TAEs; N, neutral events; error bars indicate the standard error of the mean. N.s., nonsignificant result; *$p < 0.05$.

See also Figure S3 and Tables S4 and S5.

formation of strong and easily accessible implicit memories after trauma exposure that facilitate perceptual processing but reduce discriminability from perceptually similar memory cues.[26,54] As a result, even remotely similar memory cues may exceed perceptual thresholds to trigger involuntary memory intrusions. Indeed, behavioral studies suggest better perceptual identification of trauma-related than non-trauma-related items in healthy participants, they show that PTSD patients exhibit heightened perceptual priming compared with healthy participants, and report that perceptual priming predicts the number of memory intrusions in both groups.[55,56] These results also align with excessive visual processing during encoding and memory intrusions of TAEs observed in our study and previous research comparing intrusive and non-intrusive film footage.[37,38] Our results further suggest that sensory generalization relates to increased amygdala activity. This may reflect interactions between fear-related processing and sensory generalization, as proposed by psychopathological theories of PTSD.[31] As a consequence of these interactions, the discrimination of perceptually similar cues from the traumatic experience may be disrupted, resulting in a plethora of possible triggers for memory intrusions.

Sensory generalization, however, cannot explain the highly detailed reliving of particular traumatic experiences during memory intrusions. We therefore conducted exploratory encoding-retrieval similarity analyses. We argue that reactivation of the neural representation of specific traumatic experiences in the ACC may account for this event-specific reliving. This reactivation may reflect the specificity of emotional memories, consistent with previous findings on the involvement of the ACC in the acquisition and retrieval of fear memories.[19,24] Recurring trauma-specific representations may also be related to reports in PTSD patients of structural[57,58] and functional alterations in the ACC.[59–61]

In addition to sensory generalization, we found that representations of TAEs in conceptual/semantic areas were more distinct from each other. Psychopathological models suggest that traumatic memories are not sufficiently well integrated into autobiographical memory.[26,31] This may reduce their accessibility via voluntary recall. In addition, this may explain why traumatic memories are often described as fragmented and less coherent than normal episodic memories[28,29] (but see Engelhard et al.[62]). One may speculate that this could explain our findings of reduced similarity among TAEs in superior temporal cortex, in particular as this area is relevant for narrative comprehension[47,48] and memory.[46] In addition, this would explain why we found neural activity decreases in the superior temporal cortex during TAEs compared with neutral experiences, which was not reported by previous studies comparing intrusive vs. non-intrusive trauma film footage.[36–38] Potentially, these divergent findings may suggest that reduced conceptual processing results from differences in the intrinsic properties of TAEs and may be more related to narrative coherence rather than their intrusiveness. It also fits to our observation that conceptual distinctiveness was related to lower amounts of hippocampal activation during TAEs because psychopathological models proposed a role of deficient hippocampal processing during

trauma exposure[29,63] and previous studies linked hippocampal processing to memory coherence.[64] Notably, however, we did not observe conceptual distinctiveness during memory intrusions, and we did not directly measure the coherence of traumatic memories. Thus, whether our finding of higher conceptual distinctiveness indeed reflects reduced conceptual integration of TAEs remains unclear and should be addressed by future studies. These insights may be especially valuable as PTSD-specific psychotherapies, such as the narrative exposure therapy, aim at integrating the trauma narrative into autobiographical memory,[65] possibly counteracting these impaired semantic representations.

We furthermore found that encoding and intrusions of TAEs modulated activity within the salience network including the insula and inferior frontal gyrus,[37,38,66] which is assumed to detect and integrate internal emotional states and sensory input during threatening events.[67] Specifically, the insula has been implicated in fear generalization, as its activity increases with the similarity of a stimulus to a conditioned fear stimulus.[68] Moreover, during encoding of trauma-analog movies, the insula was identified as part of a network including higher visual processing areas such as the inferior temporal cortex,[69] underlining its involvement in valence processing and potential modulation of sensory representations. However, our results do not show a clear link between insula activity during TAEs and neural generalization across widespread visual processing areas. This may suggest that insula activity is only related to trauma-analog processing in specific higher-level visual brain regions or that it modulates sensory memory formation in ways other than by increasing sensory generalization.

Psychopathological models suggest that extreme stress and emotional responses during trauma disrupt hippocampal processing, leading to pathological forms of intrusive memories and impairing voluntary recall. However, our results based on trauma-analog film footage do not support this view. Instead, we observed a positive correlation between amygdala and hippocampal activity. Moreover, elevated hippocampal processing during encoding did not predict lower numbers of memory intrusions; if anything, it had the opposite effect. Furthermore, memory intrusions were accompanied by increased hippocampal activity. Certainly, TAEs are incomplete models of trauma exposure and most likely induce lower levels of stress and emotional responses, potentially insufficient to disrupt hippocampal processing. This aligns with animal models showing that extreme stress impairs, while moderate stress enhances hippocampal functioning.[32] Alternatively, hippocampal processing may be selectively disrupted in PTSD patients, consistent with structural and functional alterations in the hippocampus of PTSD patients.[63] Finally, our findings would be consistent with models suggesting that memory intrusions stem from hippocampus-dependent memory processes and thus propose simultaneous activity increases in hippocampus and amygdala during trauma exposure.[30]

Despite several strengths of the trauma film paradigm, it has certain limitations. First, analyses of memory intrusions in trauma-analog paradigms inherently rely on relatively low numbers of events; thus, we optimized our paradigm to induce more memory intrusions than previous studies[32] by using novel trauma film footage, more trauma-analog scenes, and longer resting periods. Second, TAEs are not equivalent to real-life trauma, especially with respect to the distressing impact and subjective significance of the event potentially affecting salience network activation and its interaction with sensory-visual areas. Third, trauma exposure processing and memory intrusions are assumed to substantially differ between healthy participants and PTSD patients, including higher cue generalization and a lack of contextual processing in PTSD patients. In fact, these individual differences likely predict the development of PTSD. However, prospective studies are difficult to conduct, time consuming, and cannot be used to test for neurocognitive mechanisms during trauma exposure, making trauma-analog paradigms invaluable for gaining fundamental neurocognitive insights and developing efficient study designs to test PTSD models.[70]

We assessed whether our findings on sensory generalization and conceptual distinctiveness were confounded by mean activity differences during TAEs. On a conceptual level, excessive sensory processing and generalized sensory representations would be expected to co-occur but to account for different aspects of trauma memory: excessive sensory processing may account for the sensory nature and vividness of memory intrusions, while sensory generalization may explain why perceptually similar cues can easily trigger them. However, one might argue that sensory generalization is a statistical artifact of excessive sensory processing. Specifically, higher mean activity may increase the variance in the spatial activity pattern of a given brain region, which may in turn affect pattern similarity measures. This scenario is unlikely in our study for several reasons. First, one would need to assume opposing effects of mean activity on pattern similarity in different brain areas to explain why, for instance, visual brain areas show higher mean activity and higher trauma-neutral similarity, whereas left inferior frontal gyrus exhibits higher mean activity, but lower trauma-neutral similarity compared with neutral-neutral similarity. Second, additional pattern similarity analyses controlling for activity differences between conditions confirmed sensory generalization and conceptual distinctiveness of TAEs. Third, memory intrusions were accompanied by pattern similarity increases without or very limited co-occurring activity differences in these areas, again suggesting that the two effects can be dissociated. Future studies should tackle the distinct contributions of representational geometry and mean activity to specific behavioral outcomes such as cue generalization or memory fragmentation in order to disentangle their unique roles in trauma-related memory.

Psychotherapeutic treatment for PTSD is fundamentally rooted in psychopathological models of memory intrusions. Therefore, most interventions aim to reduce the aversiveness or amount of memory intrusions via a reduction of the excitability of sensory representations or an increased coherence in the narrative and conceptual representations of traumatic experiences. Specifically, visual imagery interventions aim to disrupt the reconsolidation of sensory-visual representations by playing Tetris after the presentation of a trauma reminder.[71,72] Reversely, sleep interventions aim to facilitate consolidation of conceptual, gist-based representations of the traumatic experience.[73,74] Cognitive behavioral therapy of PTSD aims to target both pathways, as perceptually similar trigger cues are systematically discriminated from trauma memories, and on the other hand,

trauma narratives will be elaborated and updated.[54] Likewise, although less structured, contemporary psychodynamic approaches emphasize the role of symbolization as a fundamental ability to understand and process traumatic experiences, acquired through repeated re-experiencing of memories embedded in the idiosyncratic situation of the treatment and the individual's narrative about themselves.[75,76] Although these interventions are clearly linked to psychopathological models, their precise mechanisms of action remain unclear. Specifically, it is uncertain whether they truly transform memory traces of a trauma, or they primarily change emotional responses or cognitive appraisal, or if all these processes interact with each other. To inform clinical interventions how they transform memory traces of a traumatic experience, future studies may test how playing Tetris alters generalization of sensory-visual representations, how sleep changes conceptual distinctiveness in superior temporal cortex, or how these representations change after psychotherapy. In tandem with clinical research, this would allow us to identify common neural mechanisms of action across interventions to inform clinicians on the selection of appropriate treatment.

In this study, we explored—to our knowledge for the first time—the neural representations of memory intrusions, which is necessarily an exploratory endeavor in need of future replication. This is especially crucial given that results from smaller samples, such as this one, may be less reproducible and prone to overestimation of effect sizes. Additionally, underspecified theoretical (clinical) models and a lack of neuroimaging studies made it very challenging to derive clear a priori hypotheses on the specific visual or conceptual processing areas representing altered neural representations of TAEs. We therefore did not pre-register this study and applied exploratory whole-brain analyses, which are arguably less reproducible compared with approaches that combine exploratory and/or confirmatory samples or use pre-registration. Notably, all our whole-brain analyses revealed large clusters and were highly consistent across the vast majority of participants. In addition, split-half reliability analyses showed that sensory generalization and conceptual distinctiveness were consistently observed in independent stimulus sets. Nonetheless, exploratory studies such as ours need future pre-registered replication studies in larger and independent samples and meta-analyses to assess their replicability and generalizability.

Overall, our findings represent a first step toward a novel translational framework for preclinical research on traumatic memory intrusions since they describe neural markers that may reflect critical features targeted in clinical interventions. They pave the way for future studies examining how sensory generalization, conceptual distinctiveness, and trauma-specific reactivation change for traumatic memory intrusions and may help to test how therapeutic interventions and brain stimulation techniques influence these neural processes. Ultimately, reducing sensory generalization or conceptual distinctiveness or interfering with trauma-specific reactivation might provide new therapeutic targets for PTSD treatment.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.cub.2024.03.005.

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AUTHOR CONTRIBUTIONS

M.K., G.T.W., A.R., H.K., and N.A. developed the conceptualization and methodology of the study. A.R. and G.T.W. collected data. M.K. analyzed data with support of R.H., E.M.B.R., G.T.W., and N.A. Code validation was conducted by E.M.B.R. M.K., G.T.W., H.K., and N.A. wrote the manuscript with support of all authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Scripts	https://osf.io/zyj7e/	DOI: DOI 10.17605/OSF.IO/ZYJ7E
Preprocessed data	https://osf.io/zyj7e/	DOI: DOI 10.17605/OSF.IO/ZYJ7E
Software and algorithms		
Matlab 2022b	https://www.mathworks.com	RRID: SCR_001622
Presentation	https://www.neurobs.com	RRID: SCR_00252
SPM 12	http://www.fil.ion.ucl.ac.uk/spm	RRID: SCR_007037
Fmriprep	https://www.fmriprep.org/en/stable	RRID: SCR_016216
R 3.5.0	http://www.r-project.org	RRID: SCR_001905

RESOURCE AVAILABILITY

Lead contact

Further information and request for resources should be directed to and will be fulfilled by the lead contact, Malte Kobelt (Malte.Kobelt@rub.de).

Materials availability

There are restrictions to the availability of the collected new stimulus set of trauma-analog film clips due to copyright laws. Although the use of the film and soundtrack material for the purpose of scientific research is in accordance with German copyright laws, we are cautious whether the upload of the material to an unrestricted public repository might result in a copyright violation. Furthermore, although none of the material was legally restricted, some of the depicted scenes may be inappropriate for minors and we do not see a possibility, how to restrict access other than via personal contact. We are happy to provide interested researchers with access to the material upon request.

Data and codes availability

Data and code has been deposited on Open Science Framework (https://osf.io/zyj7e/?view_only=2982cd97ed0843f3b2d6f45ce861da77). DOIs are listed in the key resources table. Any additional information required to reanalyze the data reported in this paper is available upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Participants

Twenty-four German native-speaking, right-handed volunteers (24.0 y ± 4.1 y, mean ± standard deviation) were recruited based on the outcome of the clinical screening and completed the whole course of the experiment without technical difficulties. Only women were included in this study. As we were particularly interested in memory intrusions, we analyzed a subset of participants who had at least three distinguishable memory intrusions during the resting period in the MR scanner (n = 23). One additional participant was excluded due to excessive motion. Overall, the final sample included 22 right-handed volunteers (24.5 y ± 3.9 y). Participants gave written informed consent. All procedures were approved by the Ethics committee of the Faculty of Psychology, Ruhr University Bochum, Germany.

METHOD DETAILS

Procedure

The experiment consisted of three sessions conducted on three different days: a screening session, a trauma film MRI session and a behavioral follow-up session. Screening and MRI sessions were no more than six weeks apart. The follow-up session took place exactly seven days after the MRI session.

Screening session

Eligibility of participants was determined through a structured interview consisting of a basic demographic questionnaire, Essener Trauma Inventory (ETI), PTSD Checklist for DSM-5 (PCL-5), Symptom Checklist 90 Standard (SCL-90-S), Beck Depression Inventory II (BDI II), White Bear Suppression Inventory (WBSI), Dissociative Experience Scale (DES II), Modified Tellegen Absorption Scale (MODTAS), Spontaneous use of imagery scale (SUIS), Defense Style Questionnaire (DSQ) and the Saarbrücken Personality Questionnaire (SPF). Furthermore, MRI compatibility was checked using an MRI compatibility checklist.

Participants were included if they reported generally low levels of psychopathological symptoms and psychological problems (SCL-90-S, T-score < 60), did not report symptoms of major depression (BDI-II, sum score < 14), never experienced a traumatic event (according to the ETI), and never met diagnostic criteria for PTSD (PCL-5). The remaining questionnaires served to identify possible covariates and predictors of the frequency and neural correlates of memory intrusions (results not reported here).

Trauma film material

For the present study, the frequently used trauma film paradigm was adapted to allow for fMRI analyses by including more different traumatic events, selecting content-matched neutral events and ensuring that all trauma-analog events induced a sufficient number of memory intrusions.

Twenty-one trauma-analog and 21 content-matched neutral movie clips were collected on openly accessible video platforms and from previous trauma film studies. Visual content of neutral movie clips matched the one of the trauma-analog events, showing similar objects from similar perspectives but without any potentially stressful aversive content. Neutral scenes were ensured to be about the same length as the corresponding trauma scenes (Trauma: 38.90 s ± 10.50 s; Neutral: 37.33 s ± 10.09 s; $t_{20} = 1.48$, $p = .153$). Furthermore, if paired scenes differed in color or quality, these aspects were adjusted using video filters. Therefore, only the valence of the scenes differed.

To increase the immersiveness of the scenes, movie clips were dubbed with instrumental background music from different genres, which roughly fitted and enhanced the mood and content of the scene (e.g. Arabic music for a desert scene). The same music genre was used for corresponding control and trauma scenes. The matching was based on the subjective evaluation of three raters.

Furthermore, verbal introductions were written to help the participants to immerse themselves into the situation of the subsequent scene. These introductions consisted of one to two short sentences and briefly pictured the location and situation. Each introduction contained the description of one of three sensory impressions (auditory, tactile or olfactory) to increase the feeling of involvement (e.g., "I feel the sweat dripping from my forehead as I cross the street in the tropical heat.").

Trauma film MRI session

Eligible participants were invited to take part in the trauma film paradigm in the MR scanner. The trauma film MRI session consisted of a film presentation task, a resting period, and a reaction time task which is not part of this study. The experiment was presented on MRI-compatible liquid crystal display (LCD) goggles (VisuaStim Digital, Resonance Technology, Northridge, CA, USA) with a resolution of 800 x 600 pixels using Presentation software (Version 18.0, Neurobehavioral Systems, Berkeley, CA, https://www.neurobs.com/).

In the film presentation task, participants watched 21 traumatic and 21 neutral content-matched film clips, which were preceded by a verbal introduction (presented for 5 seconds). Before participants watched the film clips, a black screen was presented for 2 minutes followed by a countdown from three to one to signal the start of the film clips. The length of the inter-trial interval between film clips was jittered between 10 to 15 seconds. Film clips were presented in pseudorandomized order with not more than two scenes of the same condition (traumatic vs. neutral) presented consecutively.

The subsequent resting phase was designed to track memory intrusions during mind wandering. After watching all film clips, participants were instructed to think about nothing particular while a fixation cross was presented on the screen and to signal each spontaneously occurring intrusive memory by pressing a button using the right index finger. After the button press, they were asked to report the content of the intrusive memory within ten seconds. Their answers were recorded using an MRI-compatible microphone attached to the headphones, which was positioned about 3 cm in front of their lips. After verbally reporting the intrusion, participants were asked to classify the memory intrusion as a picture (using the index finger), as a sound (using the middle finger) or as a thought (using the ring finger). Afterwards they were also asked to rate the valence, arousal and vividness caused by the intrusion on a scale from one (=very negative / very calm / very blurred) to four (=very positive / very agitated / very clear) on a self-assessment manakin presented on the screen.[77] The answers were given using the four fingers of the right hand. After the rating, the resting phase continued with a white fixation cross in the middle of the screen. Overall, the resting phase lasted for twelve minutes.

After participants left the MR scanner, they were instructed to fill out a memory intrusion diary across the next seven days.[13] Analogous to the resting period, they had to briefly describe their memory intrusions, mark which sensory modalities were involved, name the potential trigger, and rate the arousal, valence, and vividness on a scale from one to four.

Behavioral follow-up session

Participants came back to the laboratory 7 days after the trauma film MRI session to hand over the memory intrusion diary. All diary entries were checked by the experimenter and unclear scene identification was clarified in consultation with the participant. Furthermore, participants conducted a recognition task by stopping each scene as soon as they were sure to remember the scene via button press (not reported).

MRI data acquisition and preprocessing

Scanning was performed at the Bergmannsheil hospital in Bochum using a 3 T Philips Achieva scanner (Best, the Netherlands) with a 32-channel headcoil. MRI data acquisition consisted of whole-brain structural images using a T1-weighted sequence at 1mm isotropic resolution (FOV: 240 mm x 240 mm, 220 transversally oriented slices) and T2*-weighted gradient echoplanar images at 2.5mm isotropic resolution (EPI; TR = 2500 ms, TE = 30 ms, FA = 90, FOV = 96 mm x 96 mm, 46 transversal slices) sensitive to blood oxygenation level-dependent (BOLD) contrasts. EPI images were acquired in three separated runs for each task, which comprised 1,018 ± 6 volumes for the film presentation run, 298 ± 7 volumes for the resting phase, and 459 ± 52 volumes for the reaction time task.

MRI data were organized according to "Brain Imaging Data Structure" specifications (BIDS)[78] and preprocessed using the FMRIPrep toolbox (20.1.1).[79] Preprocessing of functional data included slice timing correction and susceptibility distortion correction based on fMRIPrep's fieldmap-less approach. For univariate analyses, EPI images were co-registered to the normalized T1-weighted template in MNI space (ICBM 152 Nonlinear Asymmetrical template version 2009c) and spatially smoothed with a kernel of 5 mm full width at half maximum using SPM12. Multivariate pattern similarity analyses were conducted on functional images co-registered to the native T1-weighted template without spatial smoothing to minimize preprocessing-related alterations in voxel-wise relationships. All analyses were performed on the level of voxels and only rendered on brain surface for visualization using brainSurfer toolbox in Matlab.[80]

QUANTIFICATION AND STATISTICAL ANALYSIS

Univariate MRI analyses

We computed voxelwise first level GLMs including the film presentation and resting-state period using SPM12. BOLD signal changes during film presentation were modelled using separate event-related regressors for the presentation of trauma-analog and neutral movie clips modelled as boxcar functions for each film clip. In line with the pattern similarity analysis, onsets were defined as the first MRI volume corresponding to each film clip. To model neural responses of memory intrusions, we defined event-related regressors starting 5s prior to intrusion responses as 2.5 second boxcar functions which represent the first volume prior to each intrusion response without a potential overlap with the button press. In contrast to typical episodic memory tasks, we defined the time period prior to button press as time of interest, as memory intrusions were indicated by the participants after their occurrence.[37] To contrast memory intrusions to periods of no intrusions, we included random baseline regressors by selecting one random volume before each intrusion response starting between 15 to 7.5 seconds with a duration of 2.5 s. We decided to define random baseline periods to control for autocorrelations and to ensure same duration of memory intrusion and baseline parameters. To control for motion responses due to button presses in the GLM, we included motor response regressors at the time point of each button press modelled as stick functions. All event-related regressors were convolved with a canonical hemodynamic response function (HRF). Furthermore, six nuisance motion regressors were included. In each participant, we contrasted trauma-analog to neutral film presentation and memory intrusions to baseline to estimate neural activity changes during trauma-analog encoding and memory intrusions. Whole-brain analyses of both contrasts across participants were conducted using second level dependent t-tests with a voxel-level threshold of $p < .001$ and cluster-level family-wise error correction (FWE) of $p < .05$. Significant clusters were registered to subject specific T1-weighted space to extract volume-wise time courses of mean activity averaged across voxels (see Figure S4 for a comparison of the time courses of neural correlates). We furthermore extracted volume-wise time courses of mean activity from an anatomically defined mask of the left precentral gyrus using the Desikan Killiany atlas to compare time courses in the memory intrusion cluster and left primary motor cortex.

Whole-brain pattern similarity analyses

Multivariate pattern similarity analyses were based on MRI volume activity.[81,82] We applied motion correction and slow artefact detrending to functional runs by calculating GLMs including the six motion parameters and six nonlinear Fourier models (sines and cosines of up to three cycles per run) as predictors.[15] The resulting residuals of neural activity were thus corrected for motion and detrending artefacts and were used for all further multivariate pattern similarity analyses. Furthermore, to account for the latency in the peak of the hemodynamic response, event onsets were shifted by 5 seconds (2 TRs) resulting in the selection of the third volume after event onset. This approach allowed us to calculate RSA on averaged activity patterns of events comparable to previous studies.[11,81] Moreover, we were able to conduct time-resolved pattern analyses to specifically model the time course of pattern similarity across MRI volumes prior to intrusion responses.

Encoding-encoding pattern similarity

We conducted whole-brain searchlight pattern similarity analysis to compare the neural distinctiveness of trauma-analog and neutral representations (Figure S1B). Film-specific activity was calculated by averaging volume activity corresponding to each film clip. For each voxel in the brain, we calculated z-transformed Pearson correlations between all film clips within a 10 mm-radius sphere centered on that voxel using modified scripts of the Matlab Toolbox for RSA.[83] This resulted in a 5-dimensional brain map for each participant consisting of the representational similarity matrix between all film clips for each voxel. Participants' pattern similarity brain maps were normalized from native T1 space to standard MNI space using SPM12 for second level analyses across participants. Generalization scores were calculated by averaging pairwise pattern similarity between all trauma-analog film clips (trauma-trauma similarity), all neutral film clips (neutral-neutral similarity), and between all trauma and neutral film clips

(trauma-neutral similarity). Pairwise similarity between matched trauma and neutral film clips was excluded to control for high similarity between the film material. To investigate neural generalization and specificity of TAEs, we conducted two complementary contrasts within each participant: We first compared trauma-trauma similarity to neutral-neutral similarity to compare the generalization or distinctiveness of representations of the two types of films. Second, we contrasted trauma-neutral to neutral-neutral similarity to measure the generalization of trauma-analog experiences to neutral events. Both contrasts were tested using whole-brain second level analyses across participants in SPM12 with a voxel-level threshold of $p < .001$ and cluster-level FWE correction at a threshold of $p < .05$. Using this whole-brain searchlight approach, we defined a generalization cluster including all clusters showing higher trauma-trauma than neutral-neutral similarity and a conceptual distinctiveness cluster consisting of all clusters showing lower trauma-trauma than neutral-neutral similarity.

To rule out that higher pattern similarity occurred due to higher mean activity of TAEs compared to neutral scenes, we calculated linear mixed models (LMM) in the generalization cluster and conceptual distinctiveness cluster to test for differences in pattern similarity between TAEs and neutral events controlled for mean activity. The LMM included pattern similarity of each event in the generalization cluster or conceptual distinctiveness cluster as outcome, trial-wise mean activity and film category (trauma/neutral) as fixed factors and subject as random factor. Trial wise pattern similarity was calculated within conditions, i.e. pattern similarity for each TAE was computed as the similarity to all other TAEs, while pattern similarity for each neutral event was calculated as the similarity to all other neutral events. Mean activity for each trial was calculated as averaged activity of corresponding volumes and across all voxels in the respective cluster (generalization or conceptual distinctiveness cluster). Pattern similarity differences between TAEs and neutral events were also significant when controlling for trial-level activity (see Table S4).

We also applied a time-resolved pattern similarity analysis to investigate the temporal relationship of generalization between TAEs with trauma-analog "hotspots" during each film clip. Within the generalization cluster, we correlated activity patterns of all volumes between all TAEs. This resulted in a time-by-time similarity matrix for each TAE pair including all possible time point combinations. For each MR volume during a TAE, we averaged the pattern similarity to all other TAEs across time to compute a time course of pattern similarity to all other TAEs (see Figure S4 for a comparison of the time courses of neural correlates). To link pattern similarity to the hotspot of a TAE, we asked 7 independent raters to mark the most distressing scene of each trauma-analog event and resampled the rating into 2.5 s time bins representing the TR of the fMRI scans. For each time bin, the sum of hotspot ratings was calculated resulting in volume-wise hotspot ratings of each TAE. To investigate how time-resolved pattern similarity changed during the hotspot of a TAE, we computed a LMM with pattern similarity in generalization clusters as outcome measure, hotspot ratings and time as predictor and subject as random factor using the R lmerTest-package (Figure 3E; Table S5).

Intrusion-Intrusion similarity

Memory intrusions unfold over time with remarkable differences in onset and duration across participants, which makes it a challenge to study them in the laboratory.[36] We therefore developed a time-resolved whole-brain pattern similarity analysis as a temporally unbiased approach to track the neural representations underlying memory intrusions (Figure S1C). For each memory intrusion, we defined an intrusion time period including all volumes between 15s prior to memory response until the response, which were shifted by 5s to account for the lag in the hemodynamic response. We first correlated time-corresponding intrusion volumes between all pairs of intrusions by calculating z-transformed Pearson correlations within 10 mm-radius spheres centered around each voxel.[83] Pattern similarity was averaged across pairs to model the mean time course of pattern similarity before the intrusion response for each participant. If a participant reported several memory intrusions of the same TAE, only the first memory intrusion was included in the analysis. The resulting 4-dimensional brain map of time-resolved pattern similarity was transformed from T1-weighted native space to MNI space using SPM12. To detect temporal changes in neural generalization and distinctiveness during memory intrusions, we compared pattern similarity during the memory intrusion period, which was defined as the volume 5s before memory response, to pattern similarity during no intrusion periods. To define temporally unbiased periods of no intrusions, we decided to define a random baseline period for each memory intrusion by selecting one random volume between 7.5s to 15s before intrusion response. The exact same volumes were used as for the univariate baseline. We then correlated the selected random volumes between all intrusion pairs by calculating z-transformed Pearson correlations within 10 mm-radius spheres. The resulting brain map of the random baseline pattern similarity was transformed from T1-weighted space to MNI space using SPM12. Finally, we contrasted pattern similarity between the intrusion and random baseline period using whole-brain second level analyses in SPM12 with a voxel-level threshold of $p < .001$ and cluster-level FWE correction of $p < .05$.

Trauma-specific memory reactivation

To estimate how neural representations that were formed during the initial TAEs are reactivated during memory intrusions, we contrasted the trauma-specific encoding-intrusion similarity to trauma-unspecific encoding-intrusion similarity between non-matching pairs (Figure S1C). We first defined trial wise activity by selecting all corresponding volumes of TAEs and memory intrusion time periods (-15s to 0s before memory response). Next, we calculated pattern similarity between all encoding and intrusion trials of TAEs using time-resolved pattern similarity analysis on the level of cortical parcels in the freesurfer Desikan-Killiany atlas and in the amygdala and hippocampus using automatic subcortical segmentation implemented in freesurfer. In each parcel, we conducted z-transformed Pearson correlations between each volume corresponding to the time period of a memory intrusion and each volume belonging to a TAE. The resulting time-resolved representational similarity matrix reflected pattern similarity values at each encoding and intrusion time point (i.e., volume) for all item combinations. The size of this representational similarity matrix differed between

participants depending on the number of memory intrusions. Pairwise pattern similarity was averaged across encoding time to calculate the mean encoding-intrusion similarity during the memory intrusion time period for each item pair. This enabled us to calculate TAE-specific encoding-intrusion similarity in each participant by averaging across all encoding-intrusion pairs comprising the same TAE (e.g., the similarity between watching the car accident and the memory intrusion of the car accident). In contrast, trauma-unspecific encoding-intrusion similarity was defined as the mean similarity between all encoding-intrusion pairs of different TAEs (e.g., the similarity between watching the limb amputation and the memory intrusion of the car accident). We tested trauma-specific reactivation at each memory intrusion time point by contrasting trauma-specific to trauma-unspecific encoding-intrusion similarity in every brain parcel using dependent t-tests. We controlled for multiple tests across brain parcels using the Benjamini-Hochberg false discovery rate.

Univariate ROI analyses

To investigate changes in neural activity during memory encoding of TAEs in the amygdala and hippocampus, we applied region of interest (ROI) analyses. Anatomical masks of bilateral hippocampus and amygdala were defined using the automated anatomical labelling atlas (AAL2) in SPM12. Within both ROIs, we compared differences in averaged beta-values between TAEs and neutral events using dependent t-tests. We also analyzed whether trauma-analog processing differed between ROIs by contrasting activity differences between TAEs and neutral events in the amygdala to the hippocampus using a dependent t-test.

Brain activity and representational geometry

We next investigated the trial-level relationship between amygdala and hippocampal activation to sensory generalization and conceptual distinctiveness using LMMs. To calculate the mean activity of each TAE, we registered anatomically defined bilateral amygdala and hippocampus masks to subject specific T1-weighted space and identified the corresponding voxels of both masks. Within each mask, neural activity of volumes corresponding to each film clip was averaged across time and voxels resulting in trial wise mean activity values. We then calculated pattern similarity scores for each TAE by averaging pattern similarity to all other TAEs in the generalization cluster and averaging pattern dissimilarity (1-correlation) to all other TAEs in the conceptual distinctiveness cluster. We used the lmerTest-package in R to conduct separated LMMs including hippocampal or amygdala activity as fixed factors and subject as mixed factor to predict sensory generalization and conceptual distinctiveness during memory encoding. P-values were calculated using the type III sum of squares method from the lmerTest-package.

Predicting intrusions with encoding activity

As our findings revealed enhanced neural processing during TAEs, we aimed at investigating whether these changes in neural processing during TAEs predicted the number of memory intrusions. Therefore, we calculated trauma-analog processing within each participant as the activity difference between TAEs to neutral experiences in four different ROIs. Visual processing was calculated in a ROI including all clusters showing significantly higher activity during TAEs than neutral experiences. Semantic processing score was computed in a ROI including all clusters showing significantly lower activity during TAEs than neutral experiences. Furthermore, we calculated neural processing in anatomically defined amygdala and hippocampus. These neural processing scores were correlated to the number of memory intrusions of TAEs and neutral experiences in the resting period and 7-day intrusion diary across participants using Pearson correlation. Participants were defined as outliers if they exceeded interquartile range. Finally, we compared correlation coefficients of memory intrusions to positive and negative neural activity clusters using bootstrapping with 10000 permutations.