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Brain structural connectivity and context-dependent extinction memory

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Abstract

Background: Extinction of conditioned fear represents an important mechanism in the treatment of anxiety disorders. Return of fear after successful extinction or exposure therapy in patients with anxiety disorders might be linked to poor temporal or contextual generalization of extinction due to individual differences in brain structural connectivity. The goal of this magnetic resonance imaging study was therefore to investigate the association of context-dependent extinction recall with brain structural connectivity. **Methods**: Diffusion-tensor imaging was used to determine the fractional anisotropy as a measure of white matter structural integrity of fiber tracts connecting central brain regions of the fear and extinction circuit (uncinate fasciculus, cingulum). Forty-five healthy men participated in a two-day fear conditioning experiment with fear acquisition in context A and extinction learning in context B on the first day. Extinction recall in the extinction context as well as renewal in the acquisition context and a novel context C took place one day later. **Results**: Renewal of conditioned fear (skin conductance responses) in the acquisition context was associated with higher structural integrity of the hippocampal part of the cingulum. **Conclusions**: Enhanced structural integrity of the cingulum might be related to stronger hippocampal modulation of the dorsal anterior cingulate cortex, a region important for modulating conditioned fear output by excitatory projections to the amygdala. This finding underpins the crucial role of individual differences in the structural integrity of relevant fiber tracts for context-dependent extinction recall and return of fear after exposure therapy in anxiety disorders.

KEYWORDS
cingulum, DTI, fear conditioning, hippocampus, uncinate fasciculus

1 | INTRODUCTION

Dysfunctional extinction of conditioned fear reflects a relevant mechanism underlying the development and maintenance of anxiety disorders and the return of fear after successful exposure-based psychotherapy (Mineka & Zinbarg, 2006; Vervliet, Baeyens, van den Bergh, & Hermans, 2013). In laboratory fear conditioning studies, recovery of conditioned fear after extinction learning indicates that extinction does not "erase" conditioned fear but rather initiates new inhibitory learning resulting in two memory traces: the fear and the extinction memory trace (Bouton, 2004; Vervliet et al., 2013). The extent to which these two memory traces are activated relatively to each other during recall is assumed to determine the amount of conditioned fear expression. Among others, conditioned fear reoccurs due to the mere passage of time (spontaneous recovery). Enhanced conditioned fear might also result from a context change (acquisition context or novel context) compared with the context in the extinction phase, the so-called renewal effect (Bouton, 2002). Difficulties in generalizing therapy effects over time or into new contexts might contribute to the return of fear in the clinical field (Boschen, Neumann, & Waters, 2009).

The amygdala is a central brain region for the acquisition and storage of fear and extinction memories (Quirk & Mueller, 2008). During delayed recall, excitatory projections from the dorsal anterior cingulate cortex (dACC; prelimbic cortex in rodents) to the basolateral amygdala are assumed to enhance fear output via the central amygdala. Additionally, inhibitory projections from the ventromedial prefrontal cortex

(vmPFC; infralimbic cortex in rodents) to intercalated cells in the amygdala are supposed to diminish the expression of conditioned fear through the central amygdala. In rodents, contextual modulation of conditioned fear expression is mediated by direct projections from the hippocampus to the basolateral amygdala and indirect projections from the hippocampus to the prelimbic and infralimic cortex (and further on to the amygdala as described above) (Knapska et al., 2012; Maren, Phan, & Liberzon, 2013; Orsini, Kim, Knapska, & Maren, 2011; Orsini & Maren, 2012). Functional neuroimaging studies in humans also indicate an important role of the hippocampus and the vmPFC for (successful) extinction recall (Hermann, Stark, Milad, & Merz, 2016; Kalisch et al., 2006; Milad et al., 2007b; Milad et al., 2009; Phelps, Delgado, Nearing, & LeDoux, 2004), especially in the safe extinction context. Hippocampal together with amygdala activation was furthermore observed during conditioned responding in the acquisition context during delayed recall (Kalisch et al., 2006). In a recent study, we could furthermore show that participants with higher renewal of conditioned skin conductance responses (SCRs) in the acquisition context exhibited stronger activation of amygdala, dACC, hippocampus, and insula (Hermann et al., 2016). Additionally, fear renewal in a novel context resulted in reduced left and enhanced right hippocampal activation. These hippocampal activation foci also showed greater effective connectivity with other structures of the fear and extinction network in individuals with higher fear renewal reflected in SCRs. Altogether, these human neuroimaging studies fit well with the abovementioned model mainly derived from animal findings. A hippocampal–dACC–vmPFC–amygdala network with excitatory and inhibitory interconnections is supposed to modulate the expression of conditioned fear relative to extinction memories. Individual differences in extinction recall and renewal might also be associated with individual differences in the structural connectivity between these regions.

Diffusion tensor imaging (DTI) represents a widely used technique in order to determine the structural integrity of white matter fiber tracts connecting different brain regions. It relies on the principle that the diffusion of water molecules is anisotropic (not random) in fibrous tissues as e.g. in the axons in the white matter of the brain. Therefore, higher values of fractional anisotropy (FA) as a measure of local anisotropy characterize a higher structural integrity or neuronal organization of a tract. Relevant fiber tracts for the extinction of conditioned fear include the uncinate fasciculus, connecting the vmPFC to limbic regions as e.g. the amygdala, as well as the cingulum, linking the cingulate gyrus to the hippocampus. Despite the importance of the abovementioned interconnectivity within the fear and extinction network, investigations on the association of extinction indices with brain structural connectivity in humans are rare. In traumatized women without posttraumatic stress disorder (PTSD), cingulum white matter microstructure was associated with attenuated fear potentiated startle responses during extinction learning and reduced PTSD symptoms. Additionally, uncinate fasciculus structural integrity has been related to enhanced fear potentiated startle responses during early extinction learning in recently deployed service members with subthreshold PTSD symptoms (Costanzo et al., 2016).

Despite the high clinical relevance of hippocampal–dACC–vmPFC–amygdala interconnectivity for delayed extinction recall and renewal, studies are lacking that investigate the association of extinction recall and renewal in the acquisition context or in a novel context with white matter structural integrity of relevant fiber tracts. We predicted individual differences in the structural integrity of the uncinate fasciculus and the cingulum to be associated with extinction recall and renewal of conditioned SCRs.

2 | METHODS AND MATERIALS

2.1 | Participants

Forty-eight healthy male students were recruited at the local university and reimbursed with 10 €/h. Owing to sex differences related to fluctuating concentrations of sex hormones over the menstrual cycle and related to the intake of oral contraceptives influencing fear conditioning processes (for a review, see Lebron-Milad and Milad, 2012), we decided to investigate male participants only in this study. Participation was not allowed when at least one of the following conditions was met: magnetic resonance imaging exclusion criteria, chronic or acute illnesses, regular intake of medicine, current medical or psychological treatment, drug use, color blindness, age <18 or >35 years. Only right-handed participants were included as assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971) and all participants had normal or corrected-to-normal vision. According to our previous report on SCR and functional magnetic resonance imaging (fMRI) data of this study (Hermann et al., 2016), two men had to be excluded due to insufficient MRI data quality and one man due to malfunction of the SCR coupler, resulting in a final sample of 45 men (age: $M = 23.7$ years; $SD = 2.8$ years). All procedures were approved by the local ethical review board of the Faculty of Psychology and Sports Science at the Justus Liebig University Giessen and conducted in accordance with the Declaration of Helsinki. Results concerning SCR and fMRI data have been published in a previous report (Hermann et al., 2016).

2.2 | Stimulus material

The procedure and stimuli were adopted from previous studies (Milad et al., 2007b; Milad et al., 2009). Pictures of contexts A and B show an office room and a room with a shelf. Furthermore, we prepared and included context C depicting a conference room (see also Hermann et al., 2016). All three contexts contained a desk lamp indicating the presence and absence of the conditioned stimuli (CS) by turning its lamplight on in one of three different colors (blue, red, and yellow). All pictures were projected via an LCD projector (model EPSON EMP-7250) onto a screen at the end of the scanner. Participants could look at the screen by means of a mirror mounted to the head coil.

The unconditioned stimulus (UCS) consisted of an electrical stimulation (1 ms pulses with 50 Hz for a duration of 500ms; Coulbourn Transcutaneous Aversive Finger Stimulator (E13–22)) via electrodes (surface size: 1 cm^2) attached to the fingertips of the second and third finger of the right hand. We used a gradually increasing rating

procedure to individually set the intensity of the electrical stimulation to be "unpleasant but not painful."

2.3 | Procedure

Before starting the experiment in the MRI scanner, participants provided written informed consent, filled out questionnaires on demographic variables, and were tested for red–green color blindness by use of five Ishihara plates (selected from Ishihara, 1990).

Right before the start of each experimental phase, they were told to carefully look at the stimulus presentation on the screen to observe any regularities between lamplights and electrical stimulation. Participants were informed that in case they discovered such a relationship, it would remain stable over all experimental phases: If a color was safe, it would always be safe; if a color was followed by electrical stimulation, this might or might not occur again. By use of these instructions, learning of contingencies during fear acquisition (a prerequisite for studying extinction memory retrieval) should be facilitated. In addition, it should be avoided that participants would expect a complete reversal of contingencies in the extinction phase (i.e., expecting stimulation to occur after CS−presentations). The actual CS−UCS contingencies were however not communicated to the participants.

During all experimental phases, the trial structure was identical for all CS types. A black screen with a white fixation cross (jittered duration between 0 and 1.875 s) preceded the presentation of the context without CS (duration: 3 s). After that, the CS was presented for 6 s (lamp within the context picture shining either in red, blue, or yellow representing 3 CS types (see below)). The electrical stimulation was delivered immediately after the offset of the CS during reinforced CS+ trials. The white fixation cross on the black background was shown again from CS offset until the start of the next context presentation for 9.125–11 s (total trial duration: 20 s).

On day 1, fear acquisition took place in context A and extinction learning in context B. On the next day, fear and extinction recall was tested for each participant in the acquisition context A, the extinction context B, and in the new context C. During fear acquisition in context A, two CS+ (CS + E and CS + U (see below); e.g., red and yellow light) were presented eight times each, and both CS+ were coupled with the UCS in five out of eight trials (partial reinforcement rate: 62.5%). The third CS (CS−; e.g. blue light) was never paired with the UCS and shown 16 times. Both CS+ were presented in a blocked fashion: 8 trials of CS + E (or CS + U) intermixed with 8 CS− trials were presented first and 8 trials of CS + U (or CS + E) intermixed with 8 CS− trials were shown afterwards. CS + E and CS + U block presentation was counterbalanced across participants. After a short break (approximately 3 min during measurement of a field-map sequence for functional MRI data processing, participants stayed within the scanner), extinction learning took place in context B. One of the CS+ (CS + E, extinguished) was shown 16 times without UCS administration. The CS + U (CS + U, unextinguished) was not presented during extinction learning. Intermixed with the 16 CS + E trials, 16 CS− trials were shown.

The recall phase on day 2 consisted of the presentation of all 3 CS in contexts A, B and C, respectively, for each participant (within-subjects design). The first and the second half of the recall phase comprised half of the CS trials in each context, respectively. In the first half, a blocked presentation of 4 CS + U (or CS + E) trials intermixed with 4 CS− trials within one context (e.g., in context A) was followed by a blocked presentation of 4 CS + E (or CS + U) trials intermixed with 4 CS− trials within the same context. The same was done for contexts B and C. The order of CS + U and CS + E presentation blocks within the contexts as well as the order of contexts A, B, and C (ABC, ACB, BAC, BCA, CAB, CBA) was counterbalanced across subjects. The second half of the recall phase comprised the same context and CS order as the first half. We used a pseudo-randomized stimulus order for all phases featuring no more than two consecutive presentations of the same CS. During extinction learning and recall, the electrodes for delivery of the electrical stimulation were attached to the fingers but did not provide electrical stimulation.

2.4 | Skin conductance responses and analyses

Sampling of skin conductance responses (SCRs) was realized with an optical fiber SCR coupler built in-house and a sampling rate of 100 Hz. Ag/AgCl electrodes filled with isotonic (0.05 M NaCl) electrolyte medium were attached to the hypothenar of the left hand. Raw SCR data were low-pass filtered afterward with a cutoff frequency of 10 Hz. SCRs toward the CS were defined as maximum amplitudes (using a foot-to-peak analysis) beginning within a window of 1–6.5 s after CS onset. SCRs were range-corrected by dividing the raw data by the largest response to the UCS (acquisition phase) to account for individual variability in electrodermal responding. We had to disregard SCR data of one man due to a malfunction of the SCR coupler (the data of this participant were also excluded from the analyses of DTI data).

Details concerning SCR data analysis of fear acquisition and extinction can be found in our previous report (Hermann et al., 2016). In this report, we tested for individual differences in the amount of conditioned SCRs emerging in contexts A, B, and C during recall on day 2 via analyses of variance (ANOVA) in IBM SPSS Statistics for Windows 22.0. To analyze differences in conditioned responding between contexts the within-subjects factors CS (CS + E, CS + U, CS−) and context (A, B, and C) and the between-subjects factor context order (ABC, ACB, BAC, BCA, CAB, CBA; possible confounding factor) were entered. Greenhouse–Geisser correction was applied if needed and the statistical significance level was set to $p \leq .05$ with additional trends toward significance reported up to $p \leq .10$.

As before (Hermann et al., 2016) means of median splits (based on the difference: CS + E minus CS−; cf. Results section) yielded a high versus a low extinction recall group for context B, a high versus low ABA renewal group for context A (comparing conditioned SCRs from context A minus B), and a high versus low ABC renewal group for context C (comparing conditioned SCRs from context C minus B).

2.5 | Diffusion tensor imaging and analysis

A single shot, pulsed gradient EPI protocol was used to acquire diffusion-weighted images (Siemens Symphony with Quantum

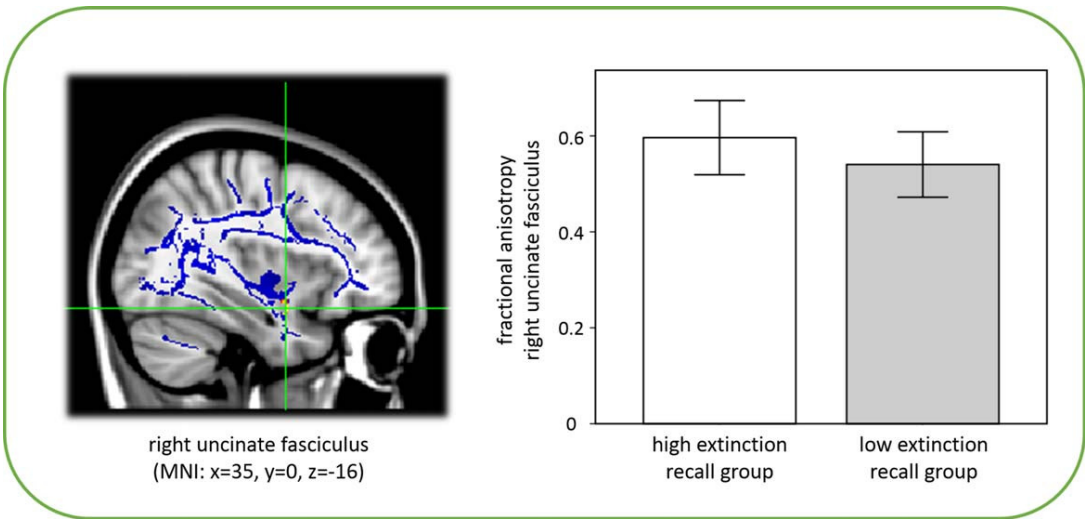

FIGURE 1 (**a**) Enhanced fractional anisotropy (FA) in the right uncinate fasciculus in the high extinction recall group compared with the low extinction recall group (trend); the green crosshair is centered on the peak voxel (MNI coordinates: $x = 35$, $y = 0$, $z = -16$). (**b**) Bar chart of the mean FA values (error bars = standard deviations) for the high and low extinction recall group [Color figure can be viewed at wileyonlinelibrary.com]

gradients, slice thickness = 3mm; interleaved slice procedure; TR = 9.8 s; TE = 111 ms; field of view 192 × 192 mm; matrix size = 128 × 128, 12 directions, *b*-values = 0 and 1000 s/mm^2; 3 averages). The FMRIB software library (FSL) was used for preprocessing of the data including eddy current and head motion correction, brain masking for the DTI data and tensor calculation. Anisotropy was expressed as fractional anisotropy (FA). The Tract-Based Spatial Statistics (TBSS) module implemented in FSL was used to carry out skeletonization. The masks for the fiber tracts of interest (uncinate fasciculus, cingulum (hippocampal part), cingulum (cingulate gyrus part)) were taken from the John Hopkins University (JHU) ICBM-DTI-81 White-Matter Label atlas provided by FSL. FA values were computed for each participant during first-level analysis. Differences between groups based on differential conditioned SCRs (high versus low extinction recall group (ABB), high versus low ABA-renewal group, and high versus low ABC-renewal group) were calculated using the permutation program "randomize" (FSL). A threshold of $p_{corr} < .05$ (threshold free cluster enhancement, TFCE) was used; trendwise results up to $p_{corr} < .10$ are additionally reported.

3 | RESULTS

3.1 | Skin conductance responses

As shown in our previous report comprising fMRI and SCR results of this study (Hermann et al., 2016), differential conditioned SCRs (CS+ vs CS−) occurred during fear acquisition and declined from early to late extinction learning (CS + E vs CS−). ANOVA including data of the recall phase on the next day revealed the context order to interact with context (context × context order: $F_{(8.7,67.7)} = 2.81$; $p = .008$) and with CS and context (CS × context × context order: $F_{(11.7,91.1)} = 1.72$; $p = .076$). These interactions with context order occurred only when comparing CS + U and CS−. Thus, further SCR and DTI analyses were restricted to the comparison between CS + E and CS− that were not confounded by context order.

A successful recall of the extinction memory was observed in context B, in which conditioned SCRs (CS + E vs CS−) did not increase from late extinction learning to early extinction recall ($F_{(1,39)} = 0.21$; $p = .65$). But SCRs were still higher for the CS + E compared to the CS− during early recall ($T_{(44)} = 2.86$; $p = .007$). In particular, median split analyses showed that the low extinction recall group exerted significantly higher conditioned SCRs compared to the high extinction recall group during early recall ($T_{(34.3)} = 5.10$; $p < .001$).

During early recall in context A, conditioned SCRs toward the CS + E compared to the CS− were higher in comparison to context B ($F_{(1,39)} = 5.93$; $p = .020$) and to late extinction learning ($F_{(1,39)} = 7.85$; $p = .008$), demonstrating fear renewal in context A. Furthermore, median split analyses revealed that the high ABA renewal group exhibited higher differential SCRs relative to the low ABA renewal group ($T_{(27.5)} = 5.26$; $p < .001$).

During early recall in context C, conditioned SCRs (CS + E minus CS−) tended to be higher compared to B ($F_{(1,39)} = 3.23$; $p = .080$) and were significantly higher in comparison to late extinction learning in context B ($F_{(1,39)} = 4.16$; $p = .048$), demonstrating fear renewal in the novel context C. Additionally, median split analyses found the high ABC renewal group to exert significantly higher conditioned SCRs compared to the low ABC renewal group during early recall ($T_{(23.3)} = 4.73$, $p < .001$).

3.2 | Diffusion tensor imaging

The low extinction recall group *(higher SCRs toward CS + E minus CS− in context B on day 2)* compared with the high extinction recall group showed tendentially lower FA values for the right uncinate fasciculus (peak voxel: MNI $x = 35$, $y = 0$, $z = -16$, $p_{corr} = .051$) (Figure 1), while

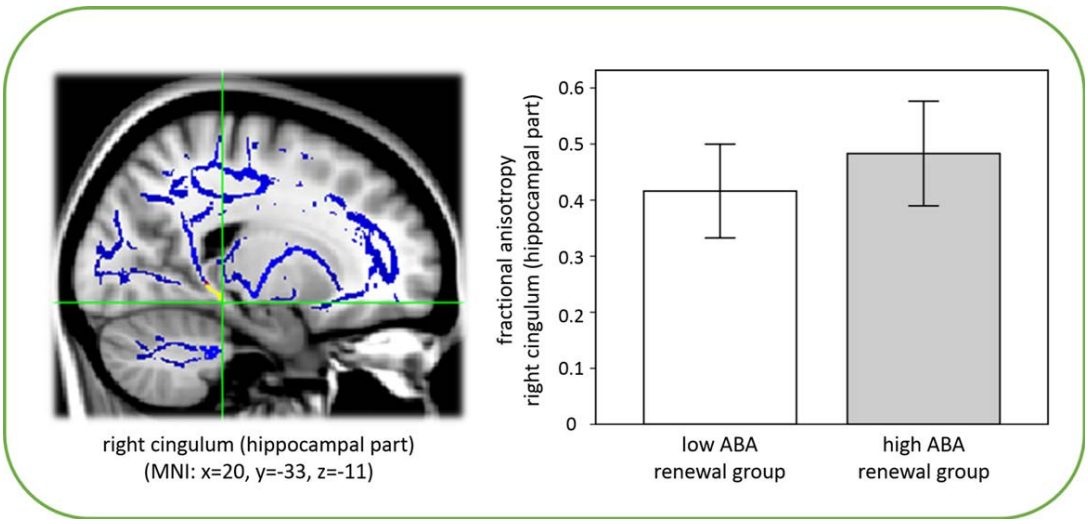

FIGURE 2 (**a**) Enhanced fractional anisotropy (FA) in the right cingulum (hippocampal part) in the high ABA renewal group compared with the low ABA renewal group; the green crosshair is centered on the peak voxel (MNI coordinates: $x = 20$, $y = -33$, $z = -11$). (**b**) Bar chart of the mean FA values (error bars = standard deviations) for the low and high ABA renewal groups [Color figure can be viewed at wileyonlinelibrary.com]

there were no differences in the cingulum between these groups (all $p_{corr} > .18$). Post-hoc correlational analysis furthermore demonstrated that the degree of extinction recall in conditioned SCRs in the whole sample significantly correlated with extracted FA values from the peak voxel in the right uncinate fasciculus ($r = .387$, $p = .009$).

Comparing the high with the low ABA renewal group *(higher vs lower SCRs toward CS + E minus CS− in context A minus B on day 2)*, higher FA values were observed for the right cingulum (hippocampal part) (peak voxel: MNI $x = 20$, $y = -33$, $z = -11$, $p_{corr} = .006$; see Figure 2). There were no further differences between the ABA renewal groups (all $p_{corr} > .10$). Furthermore, the degree of ABA renewal in conditioned SCRs in the whole sample was significantly associated with extracted FA values (peak voxel) in the right cingulum (hippocampal part, $r = .325$, $p = .029$) as revealed by post-hoc correlational analysis.

The high versus low ABC renewal group *(higher vs lower SCRs towards CS + E minus CS− in context C minus B on day 2)* showed (at a trend level) reduced FA in the left uncinate fasciculus (peak voxel: MNI $x = -34$, $y = 0$, $z = -14$, $p_{corr} = .087$; see Figure 3). There were no further group differences concerning the right uncinate fasciculus or the cingulum (all $p_{corr} > .31$). An additional post-hoc correlational analysis

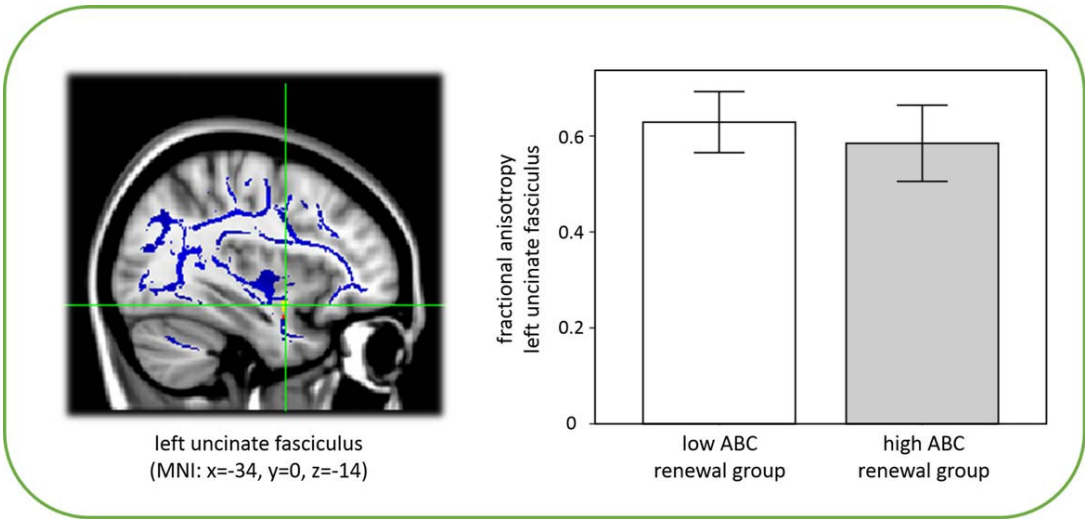

FIGURE 3 (**a**) Reduced fractional anisotropy (FA) in the left uncinate fasciculus in the high ABC renewal group compared with the low ABC renewal group; the green crosshair is centered on the peak voxel (MNI-coordinates: $x = -34$, $y = 0$, $z = -14$). (**b**) Bar chart of the mean FA values (error bars = standard deviations) for the low and high ABC renewal group [Color figure can be viewed at wileyonlinelibrary.com]

showed that the degree of ABC renewal in electrodermal responses in the whole sample was not significantly associated with extracted FA values (peak voxel) in the left uncinate fasciculus ($r = -.117$, $p = .445$).

4 | DISCUSSION

The current findings indicate that the structural integrity of white matter fiber tracts connecting relevant structures of the fear and extinction circuit is related to extinction recall and conditioned fear renewal. Higher renewal of conditioned SCRs in the acquisition context was associated with higher structural integrity of the hippocampal part of the cingulum, a fiber tract connecting the cingulate cortex and the hippocampus among others. The right uncinate fasciculus, a fiber tract linking prefrontal (e.g., vmPFC) to temporal regions (e.g., amygdala), displays a lower structural integrity (trend) in participants with poor compared with those with better extinction recall in conditioned SCRs. Reduced left uncinate fasciculus microstructure was furthermore related to higher conditioned fear renewal in the novel context (trend).

Altogether, these findings are in line with the abovementioned model mainly derived from animal findings indicating that excitatory projections from the dACC and inhibitory projections from the vmPFC to different subnuclei of the amygdala modulate the amount of conditioned fear expression (Maren et al., 2013). The contextual modulation of conditioned fear expression is furthermore assumed to be associated with hippocampal influences on dACC, vmPFC and amygdala (Maren et al., 2013). The higher structural integrity of the cingulum in individuals with stronger conditioned fear renewal (SCRs) in the acquisition context is probably related to a stronger hippocampal modulation of dACC activation resulting in higher fear renewal. Enhanced activation of amygdala, dACC, hippocampus and insula was also found during fear renewal in the acquisition context in the fMRI study of this sample (Hermann et al., 2016) and corresponds with the present findings. Enhanced structural integrity of the uncinate fasciculus in individuals with better extinction recall and with reduced ABC renewal in the current study might most likely reflect an inhibitory influence of the vmPFC on conditioned fear output via the amygdala. Accordingly, functional imaging results from this sample demonstrate enhanced vmPFC activation in individuals with better extinction recall (Hermann et al., 2016).

Taken together, our results fit well with findings showing lower cingulum microstructure in patients with PTSD (Fani et al., 2012, 2016, but see Costanzo et al., 2016 in subclinical PTSD), and lower uncinate fasciculus microstructure in subclinical PTSD (Costanzo et al., 2016). Considering the current results, reduced uncinate fasciculus and cingulum microstructure in PTSD might point to decreased extinction recall as well as diminished renewal of conditioned fear. Accordingly, PTSD patients exhibit impaired extinction recall in the safe and attenuated renewal in the acquisition context as measured by conditioned SCRs (Garfinkel et al., 2014; Milad et al., 2009). Additionally, cingulum white matter microstructure was also related to reduced fear potentiated startle during extinction learning and reduced PTSD symptoms in a previous study in traumatized women (Fani et al., 2015). Similarly, uncinate fasciculus structural integrity has been associated with enhanced fear potentiated startle responses during early extinction learning in subthreshold PTSD (Costanzo et al., 2016). These results support the view of a dysfunctional regulation of conditioned fear responses due to alterations in brain structural connectivity between dACC, vmPFC, amygdala, and hippocampus in PTSD. Beyond this, studies investigating altered white matter microstructure in patients with anxiety disorders also found (but are not limited to) reduced integrity of the white matter in the uncinate fasciculus and cingulum (Ayling, Aghajani, Fouche, & van der Wee, 2012).

Our current findings also complement previous studies relating higher grey matter volume of the vmPFC (Hartley, Fischl, & Phelps, 2011; Milad et al., 2005) and medial orbitofrontal cortex (Rauch et al., 2005) to enhanced extinction recall in humans. Furthermore, dACC thickness (Milad et al., 2007a) was associated with stronger conditioned fear expression during fear acquisition.

Limitations of this study encompass the transferability of findings to women, especially regarding the impact of sex hormones on (context-dependent) learning processes (Lebron-Milad & Milad, 2012; Merz & Wolf, 2017). Additionally, due to the restricted age range of the participants in this study (18–35 years), it is unclear if the current findings can be generalized to children and adolescents as well as elderly people, for example, due to developmental differences in fear learning and extinction (Shechner, Hong, Britton, Pine, & Fox, 2014).

5 | CONCLUSIONS

In conclusion, this study supports the relevance of a hippocampal–dACC–vmPFC–amygdala network with excitatory and inhibitory interconnections for modulating the expression of conditioned fear relative to extinction memories. Improved knowledge about individual differences in brain structural connectivity might shed light onto the crucial question which individuals are more prone to develop an anxiety disorder or PTSD.

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FINANCIAL DISCLOSURES

All authors report no biomedical financial interests or potential conflicts of interest.

REFERENCES

Ayling, E., Aghajani, M., Fouche, J.-P., & van der Wee, N. (2012). Diffusion tensor imaging in anxiety disorders. *Current Psychiatry Reports*, *14*(3), 197–202.

Boschen, M. J., Neumann, D. L., & Waters, A. M. (2009). Relapse of successfully treated anxiety and fear: Theoretical issues and recommendations for clinical practice. *Australian & New Zealand Journal of Psychiatry*, *43*(2), 89–100.

Bouton, M. E. (2002). Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biological Psychiatry*, *52*(10), 976–986.

Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learning and Memory*, *11*(5), 485–494.

Costanzo, M. E., Jovanovic, T., Pham, D., Leaman, S., Highland, K. B., Norrholm, S. D., & Roy, M. J. (2016). White matter microstructure of the uncinate fasciculus is associated with subthreshold posttraumatic stress disorder symptoms and fear potentiated startle during early extinction in recently deployed Service Members. *Neuroscience Letters*, *618*, 66–71.

Fani, N., King, T. Z., Brewster, R., Srivastava, A., Stevens, J. S., Glover, E. M., … Jovanovic, T. (2015). Fear-potentiated startle during extinction is associated with white matter microstructure and functional connectivity. *Cortex*, *64*, 249–259.

Fani, N., King, T. Z., Jovanovic, T., Glover, E. M., Bradley, B., Choi, K., … Ressler, K. J. (2012). White matter integrity in highly traumatized adults with and without post-traumatic stress disorder. *Neuropsychopharmacology*, *37*(12), 2740–2746.

Fani, N., King, T. Z., Shin, J., Srivastava, A., Brewster, R. C., Jovanovic, T., … Ressler, K. J. (2016). Structural and functional connectivity in Posttraumatic Stress Disorder: Associations with FKBP5. *Depression and Anxiety*, *33*(4), 300–307.

Garfinkel, S. N., Abelson, J. L., King, A. P., Sripada, R. K., Wang, X., Gaines, L. M., & Liberzon, I. (2014). Impaired contextual modulation of memories in PTSD: An fMRI and psychophysiological study of extinction retention and fear renewal. *Journal of Neuroscience*, *34*(40), 13435–13443.

Hartley, C. A., Fischl, B., & Phelps, E. A. (2011). Brain structure correlates of individual differences in the acquisition and inhibition of conditioned fear. *Cerebral Cortex*, *21*(9), 1954–1962.

Hermann, A., Stark, R., Milad, M. R., & Merz, C. J. (2016). Renewal of conditioned fear in a novel context is associated with hippocampal activation and connectivity. *Social Cognitive and Affective Neuroscience*, *11*(9), 1411–1421.

Ishihara, S. (1990). *Ishihara's tests for color blindness* (38 plate ed.). Tokyo/Kyoto: Kanehara.

Kalisch, R., Korenfeld, E., Stephan, K. E., Weiskopf, N., Seymour, B., & Dolan, R. J. (2006). Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. *Journal of Neuroscience*, *26*(37), 9503–9511.

Knapska, E., Macias, M., Mikosz, M., Nowak, A., Owczarek, D., Wawrzyniak, M., … Sheng, M. (2012). Functional anatomy of neural circuits regulating fear and extinction. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(42), 17093–17098.

Lebron-Milad, K., & Milad, M. R. (2012). Sex differences, gonadal hormones and the fear extinction network: Implications for anxiety disorders. *Biology of Mood & Anxiety Disorders*, *2*, 3.

Maren, S., Phan, K. L., & Liberzon, I. (2013). The contextual brain: Implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience*, *14*(6), 417–428.

Merz, C. J., & Wolf, O. T. (2017). Sex differences in stress effects on emotional learning. *Journal of Neuroscience Research*, *95*(1–2), 93–105.

Milad, Quinn, B. T., Pitman, R. K., Orr, S. P., Fischl, B., & Rauch, S. L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(30), 10706–10711.

Milad, M. R., Pitman, R. K., Ellis, C. B., Gold, A. L., Shin, L. M., Lasko, N. B., … Rauch, S. L. (2009). Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biological Psychiatry*, *66*(12), 1075–1082.

Milad, M. R., Quirk, G. J., Pitman, R. K., Orr, S. P., Fischl, B., & Rauch, S. L. (2007a). A role for the human dorsal anterior cingulate cortex in fear expression. *Biological Psychiatry*, *62*(10), 1191–1194.

Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., & Rauch, S. L. (2007b). Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biological Psychiatry*, *62*(5), 446–454.

Mineka, S., & Zinbarg, R. (2006). A contemporary learning theory perspective on the etiology of anxiety disorders: It's not what you thought it was. *American Psychologist*, *61*(1), 10–26.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113.

Orsini, C. A., Kim, J. H., Knapska, E., & Maren, S. (2011). Hippocampal and prefrontal projections to the basal amygdala mediate contextual regulation of fear after extinction. *Journal of Neuroscience*, *31*(47), 17269–17277.

Orsini, C. A., & Maren, S. (2012). Neural and cellular mechanisms of fear and extinction memory formation. *Neuroscience and Biobehavioural Reviews*, *36*(7), 1773–1802.

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans. *Neuron*, *43*(6), 897–905.

Quirk, G. J., & Mueller, D. (2008). Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology*, *33*(1), 56–72.

Rauch, S. L., Milad, M. R., Orr, S. P., Quinn, B. T., Fischl, B., & Pitman, R. K. (2005). Orbitofrontal thickness, retention of fear extinction, and extraversion. *NeuroReport*, *16*(17), 1909–1912.

Shechner, T., Hong, M., Britton, J. C., Pine, D. S., & Fox, N. A. (2014). Fear conditioning and extinction across development: Evidence from human studies and animal models. *Biological Psychology*, *100*, 1–12.

Vervliet, B., Baeyens, F., van den Bergh, O., & Hermans, D. (2013). Extinction, generalization, and return of fear: A critical review of renewal research in humans. *Biological Psychology*, *92*(1), 51–58.

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