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Neuronale Korrelate kontextabhängiger Furchtkonditionierung und deren Relevanz für experimentell induzierte Intrusionen

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1. Überblick

Kontextinformationen sind wichtig für die Bewertung der Bedrohlichkeit einer Situation und daher auch von zentraler Bedeutung für die kontextabhängige Modulation konditionierter Furcht (Maren, Phan & Liberzon, 2013): Das Auftreten von Furchtreaktionen auf einen konditionierten Reiz (z.B. Schlange) ist in einem bestimmten Kontext (z.B. im Wald) adaptiv, weil es einer Person hilft, sich auf eine mögliche Bedrohung oder aversive Konsequenz (z.B. Biss) vorzubereiten, die auf den konditionierten Reiz folgen könnte. Im Gegensatz dazu sollte es in einem sicheren Kontext (z.B. Zoo) möglich sein, auf einen konditionierten Reiz, auf den keine aversive Konsequenz folgen kann (da sich Schlange hinter einer Glasscheibe befindet), eine konditionierte Furchtreaktion zu hemmen. Schwierigkeiten in der kontextabhängigen Modulation von konditionierten Furchtreaktionen sind für Personen mit Posttraumatischer Belastungsstörung (PTBS) bekannt (Garfinkel et al., 2014; Milad et al., 2009; Rougemont-Bücking et al., 2011) und werden als ätiologisch relevante Störungsmechanismen bei der PTBS diskutiert (Brewin & Holmes, 2003; Ehlers & Clark, 2000; Liberzon & Abelson, 2016). Bisher ist jedoch unklar, ob Schwierigkeiten in der kontextabhängigen Modulation von konditionierter Furcht Risikofaktoren für die Entwicklung von PTBS-Symptomen wie Intrusionen darstellen.

Im Rahmen der Dissertation wurde daher untersucht, ob Schwierigkeiten in kontextabhängigen Furchtkonditionierungsprozessen und in den zugrundeliegenden neuronalen Mechanismen Intrusionen (sogenannte Analogintrusionen) in Reaktion auf ein experimentelles Trauma vorhersagen (Neudert, Schäfer, Zehtner, Fricke, Seinsche, Stark & Hermann, 2023). Um die Furcht in Abhängigkeit des Kontexts zu zeigen oder zu inhibieren, müssen verschiedene Kontexte trotz ähnlicher Merkmale voneinander unterschieden werden. Eine erfolgreiche Unterscheidung ähnlicher Kontexte erfordert Mustertrennung (Kheirbek, Klemenhagen, Sahay & Hen, 2012; Sahay et al., 2011). Mustertrennung ist generell an der Gedächtnisbildung und an Gedächtnisabrufprozessen beteiligt und für die Diskriminierung von ähnlichen Reizen und Ereignissen bzw. Kontexten wichtig (Leal & Yassa, 2018; Yassa & Stark, 2011; Zotow, Bisby & Burgess, 2020). Daher wurde im Rahmen der Dissertation zudem untersucht, ob die Mustertrennungsfähigkeit mit kontextabhängigen Furchtkonditionierungsprozessen zusammenhängt (Neudert, Schäfer, Zehtner, Fricke, Seinsche, Kruse et al., 2023).

Die folgende Einleitung dient als theoretische Herleitung der Fragestellungen, die im nächsten Kapitel näher beschrieben werden. Nach der Darstellung der Fragestellungen wird die Dissertationsstudie kurz hinsichtlich der Methodik vorgestellt. Im Anschluss werden die Ergebnisse in Bezug auf die Fragestellungen berichtet und kritisch diskutiert. Abschließend werden die Besonderheiten und Limitationen der Studie dargestellt und es erfolgt eine Zusammenfassung der wichtigsten Ergebnisse.

2. Einleitung

2.1 Intrusionen in Reaktion auf ein Trauma

Im Laufe des Lebens erlebt ein Großteil der Menschen ein traumatisches Ereignis oder wird Zeuge eines solchen (Kilpatrick et al., 2013). Ein Trauma wird als Ereignis definiert, in Zuge dessen es zu einer tatsächlichen oder potentiellen Todesdrohung, einer ernsthaften körperlichen Schädigung oder sexueller Gewalt kommt (American Psychiatric Association (APA), 2013). Nach traumatisierenden Ereignissen (z.B. Kriegserlebnisse, sexueller Missbrauch) kann es zur Entwicklung von aufdringlichen Erinnerungen, sogenannten Intrusionen, an das Trauma kommen (Ehlers, Hackmann & Michael, 2004). Intrusionen stellen ein Kernsymptom der PTBS dar (APA, 2013). Sie können als unerwünschte und unwillkürliche Erinnerungen und Eindrücke eines traumatischen Ereignisses beschrieben werden, die Gefühle und Reaktionen verursachen, als ob die traumatische Situation erneut im Hier und Jetzt geschieht, obwohl sich eine Person in einem sicheren Kontext befindet (Ehlers et al., 2004; Hackmann, Ehlers, Speckens & Clark, 2004). Auf konzeptueller Ebene können Intrusionen auch als konditionierte Reaktionen auf einen traumatischen Reiz beschrieben werden (Franke et al., 2021). Zudem sind Intrusionen dadurch charakterisiert, dass der Kontextbezug fehlt (Michael, Ehlers, Halligan & Clark, 2005). Dem kognitiven Modell von Ehlers und Clark (2000) folgend könnte die Ursache dafür darin liegen, dass während des traumatischen Ereignisses Kontextinformationen im autobiographischen Gedächtnis schlecht ein- und abgespeichert werden.

2.2 Schwierigkeiten in der kontextabhängigen Furchtmodulation – ein Mechanismus zur Entstehung und Aufrechterhaltung von Intrusionen?

Ätiologische Störungsmodelle der PTBS (Brewin, Dalgleish & Joseph, 1996; Brewin & Holmes, 2003; Ehlers & Clark, 2000; Liberzon & Abelson, 2016) nehmen an, dass die Entstehung und Entwicklung von Intrusionen mit Furchtkonditionierungsprozessen und einer reduzierten Kontextverarbeitung (Schwierigkeiten in der Einspeicherung und im Abruf von Kontextinformationen des Traumas) verbunden sind. Diese beiden Prozesse könnten im Zusammenspiel zu Schwierigkeiten in der kontextuellen Modulation konditionierter Furcht führen und erklären, warum Personen mit PTBS Furchtreaktionen in Form von Intrusionen in Reaktion auf konditionierte Reize in sicheren Kontexten zeigen (Garfinkel et al., 2014; Milad et al., 2009). Kheirbek und Kolleg:innen (2012) schildern am Beispiel eines Soldaten, wie Schwierigkeiten in der kontextabhängigen Furchtmodulation aussehen könnten: Nachdem ein Soldat aus dem Kriegsgebiet zurückgekehrt ist, zeigt dieser eine Furchtreaktion in Reaktion auf ein Lagerfeuer in einem Park (sicherer Kontext). Bei dem Soldaten kam es vermutlich während seines Kriegseinsatzes durch Konditionierungsprozesse zu einer Verknüpfung des Lagerfeuers (ursprünglich neutraler Reiz) mit einer Bedrohungssituation (feindlicher Angriff während Soldaten am Lagerfeuer saßen), die eine Furchtreaktion (Todesangst) auslöste. In der Folge ist der Soldat auch in sicheren Kontexten (Park in seinem Heimatland, in welchem kein Krieg herrscht) sehr ansprechbar für Reize (Feuer bzw. Lagerfeuer), die mit dem traumatischen Ereignis (feindlicher Angriff) verknüpft wurden und Gefahr vorhersagten. Bei Kontakt mit dem konditionierten Reiz (z.B. Feuer) können somit unfreiwillig intrusive Erinnerungen an das Trauma bei dem Soldaten ausgelöst werden, auch wenn er sich in einer sicheren Umgebung befindet. Wie das Beispiel zeigt, können Personen mit PTBS Schwierigkeiten haben, ihre Furchtreaktionen auf konditionierte Reize in sicheren Kontexten zu hemmen, sodass sie Furchtreaktionen in Form von Intrusionen in sicheren Kontexten zeigen.

Die kontextuelle Modulation konditionierter Furchtreaktionen (z.B. erfolgreiche Furchtinhibition in sicheren Kontexten) kann mittels eines kontextabhängigen Furchtkonditionierungsparadigmas im Labor untersucht werden (Garfinkel et al., 2014; Maren et al., 2013; Milad, Orr, Pitman & Rauch, 2005; Milad et al., 2008; Milad et al., 2009). Ein kontextabhängiges Furchtkonditionierungsparadigma besteht aus verschiedenen Phasen (Lonsdorf et al., 2017; Milad et al., 2005): Während der Furchtakquisition in Kontext A wird eine Furchtgedächtnisspur erworben. Die Furchtgedächtnisspur besagt, dass in Kontext A auf einen ursprünglich neutralen Reiz (z.B. eine bestimmte Farbe) eine aversive Konsequenz (z.B. elektrische Stimulation) folgt. Anschließend findet das Extinktionstraining in Kontext B statt. Hierbei soll gelernt werden, dass in Kontext B auf den konditionierten Reiz (z.B. auf die Farbe) keine aversive Konsequenz (z.B. keine elektrische Stimulation) folgt. Für Kontext B soll sich eine Extinktionsgedächtnisspur ausbilden, die die Furchtgedächtnisspur hemmt, aber nicht löscht (Bouton, 2004). Nach dem Extinktionslernen kann der Abruf der konkurrierenden Gedächtnisspuren in verschiedenen Kontexten getestet werden. Das Testen des Abrufs im sicheren Kontext B („Extinktionsabruf“) sollte zu einem Abruf der Extinktionsgedächtnisspur führen und eine reduzierte konditionierte Furchtreaktion auslösen (Milad et al., 2005). Wenn konditionierte Reize in einem neuen und potenziell gefährlichen Kontext C präsentiert werden, sollte die die Furchtgedächtnisspur aktiviert werden und eine konditionierte Furchtreaktion auftreten („Furchtrenewal“), die eine Person auf eine mögliche Bedrohung vorbereitet (Hermann, Stark, Milad & Merz, 2016; Milad et al., 2005). Im Rahmen solcher Paradigmen kann untersucht werden, ob Personen entsprechend des Kontexts die Furchtgedächtnis- oder Extinktionsgedächtnisspur erfolgreich abrufen und dementsprechend ihre Furcht auf konditionierte Reize kontextabhängig modulieren können (d.h. eine reduzierte konditionierte Reaktion im sicheren Kontext zeigen, eine verstärkte konditionierte Furchtreaktion in einem (potentiellen) Gefahrenkontext zeigen).

Personen mit PTBS zeigen Schwierigkeiten in der kontextabhängigen Modulation konditionierter Furcht (Garfinkel et al., 2014; Milad et al., 2009): Sie zeigten eine stärkere Wiederkehr konditionierter Furcht in einem sicheren Extinktionskontext (reduzierter Extinktionsabruf), was für einen stärkeren Abruf der Furchtgedächtnisspur anstelle der Extinktionsgedächtnisspur im sicheren Kontext spricht. Gleichzeitig zeigten sie auch eine fehlende Wiederkehr konditionierter Furcht (fehlender Abruf der Furchtgedächtnisspur), wenn ein gefährlicher Kontext präsentiert wurde. Solche Schwierigkeiten in der kontextabhängigen Modulation von Furcht, wie sie bei PTBS-Patient:innen zu sehen sind, deuten auf Probleme bei der Identifizierung des Kontexts als Sicherheits- oder Gefahrensignal hin (Garfinkel et al., 2014; Kheirbek et al., 2012). Auf neuronaler Ebene gilt der Hippocampus als wichtige Region für das Erlernen und den Abruf von Kontextinformationen (Holland & Bouton, 1999). Der Hippocampus moduliert in Abhängigkeit des Kontexts den Ausdruck konditionierter Furcht über die Amygdala (Hermann et al., 2016; Kalisch et al., 2006; Maren et al., 2013). Dies kann einerseits über direkte Verbindungen des Hippocampus zur Amygdala als auch über indirekte Verbindungen über den ventromedialen präfrontalen Kortex (vmPFC) und den dorsalen anterioren cingulären Kortex (dACC) (Maren et al., 2013) geschehen. Der vmPFC projiziert sowohl auf erregende als auch auf hemmende Neuronen der Amygdala und wird daher als furchtmodulierende Region betrachtet (Maren et al., 2013; Motzkin, Philippi, Wolf, Baskaya & Koenigs, 2015). Der dACC gilt als furchtexpressive Region, welche auch auf Neuronen in der Amygdala projiziert, die an der Furchtexpression beteiligt sind (Maren et al., 2013; Milad et al., 2007). Schwierigkeiten in der kontextabhängigen Modulation konditionierter Furcht gingen bei Personen mit PTBS im Vergleich zu Trauma-exponierten Kontrollpersonen mit einer reduzierten Aktivierung von furchtmodulierenden Gehirnregionen wie dem Hippocampus und vmPFC sowie mit einer verstärkten Aktivierung von furchtexpressiven Arealen wie dem dACC und der Amygdala einher (Garfinkel et al., 2014; Milad et al., 2009). Bislang ist unklar, ob Schwierigkeiten in der kontextuellen Modulation von konditionierter Furcht und in den zugrundeliegenden neuronalen Mechanismen Risikofaktoren für die Entwicklung von PTBS-Symptomen wie Intrusionen darstellen.

2.3 Mustertrennung – ein relevanter Prozess für die kontextabhängige Furchtmodulation?

Für eine erfolgreiche kontextabhängige Modulation konditionierter Furcht müssen Kontexte auf (Un-)Ähnlichkeit mit bereits gespeicherten Kontexten überprüft werden, um eine Person auf eine Bedrohung bei Konfrontation mit einem konditionierten Reiz in einem unbekannten und potentiell gefährlichen Kontext (z.B. Schlange im Wald) vorzubereiten oder um sich in einem bekannten sicheren Kontext (z.B. Schlange im Zoo) zu entspannen. Es wird angenommen, dass die Mustertrennungsfähigkeit an der Kontextunterscheidung bzw. generell an der Gedächtnisbildung und an Gedächtnisabrufprozessen beteiligt ist, indem sie die Vielfalt der Erfahrungen und Ereignisse speichert und unterscheidet (Kheirbek et al., 2012; Sahay et al., 2011; Yassa & Stark, 2011; Zotow et al., 2020). Sie extrahiert die Unähnlichkeit eines Reizes bzw. Kontexts (z.B. der heutige Parkplatz in einem Parkhaus) mit einem ähnlichen Reiz bzw. Kontext (z.B. gestriger Parkplatz in demselben Parkhaus) (Leal & Yassa, 2018). Die Mustertrennung kodiert einen Reiz oder ein Ereignis als eine unähnliche, nicht überlappende Gedächtnisrepräsentation trotz seiner Ähnlichkeit mit anderen Reizen oder Ereignissen und ermöglicht dadurch zielgerichtetes Handeln (z.B. jeden Tag den richtigen Parkplatz in demselben Parkhaus zu finden) (Leal & Yassa, 2018). Die (behaviorale) Mustertrennungsfähigkeit kann mit der *Mnemonic Similarity Task* (MST) (Stark, Yassa, Lacy & Stark, 2013; Stark, Kirwan & Stark, 2019) gemessen werden und ist mit der Aktivität in Subregionen des Hippocampus verbunden (Bakker, Kirwan, Miller & Stark, 2008; Leal, Tighe, Jones & Yassa, 2014; Liu, Gould, Coulson, Ward & Howard, 2016).

Wenn zum Beispiel ein neuer Kontext (z.B. Kontext B oder C) Merkmale mit einem gefährlichen Kontext (z.B. Kontext A) aufweist, sollte die Mustertrennung im Hippocampus dazu führen, dass eine Furchtreaktion durch die Aktivierung des dACC, der Insula und der Amygdala ausgelöst wird (Lissek et al., 2014; Webler et al., 2021). Diese Gehirnregionen sind an der Furchterregung und -verarbeitung beteiligt: Die Amygdala wird als Schaltzentrale betrachtet, die Informationen über emotionale Reize erkennt und an verschiedene Verarbeitungskanäle weiterleitet (Sehlmeyer et al., 2009). Die Insula liefert Informationen darüber, wie sich Reize auf den Körperzustand auswirken und ist wichtig für interozeptive Prozesse (Craig, 2002; Paulus & Stein, 2006). Der dACC wird als eine Schlüsselregion für den Ausdruck von konditionierter Furcht betrachtet (Milad et al., 2007) und ist auch an der Verarbeitung von Kontexterinnerungen beteiligt (Rajasethupathy et al., 2015). Die Mustertrennung sollte darüber hinaus den vmPFC, eine Region, die für die Furchtinhibition und –modulierung bekannt ist (Fullana et al., 2018; Motzkin et al., 2015), aktivieren, wenn konditionierte Sicherheitssignale vorhanden sind (Lissek et al., 2014; Webler et al., 2021).

3. Fragestellungen und Hypothesen

In der vorliegenden Dissertation wurden die folgenden Hauptfragestellungen bearbeitet. Die zugrundliegende Studie zur Beantwortung dieser Fragestellungen wird im nächsten Kapitel genauer dargestellt.

<u>Fragestellung 1:</u> Sagen Schwierigkeiten in der kontextabhängigen Modulation konditionierter Furcht Intrusionen in Reaktion auf ein experimentelles Trauma vorher?

Bisherige prospektive Studien mit analogen Stichproben untersuchten die Relevanz von Furchtkonditionierungsprozessen (Miedl et al., 2020; Rattel et al., 2019), nicht jedoch kontextabhängiger Furchtkonditionierungsprozesse, obwohl eine reduzierte Einspeicherung von Kontextinformation als ätiologischer Faktor für die PTBS angenommen wird (Brewin & Holmes, 2003; Ehlers & Clark, 2000; Liberzon & Abelson, 2016). Querschnittsstudien zeigten bereits Auffälligkeiten in der kontextabhängigen Modulation konditionierter Furcht bei PTBS-Patient:innen (Garfinkel et al., 2014; Milad et al., 2009). Darauf aufbauend wurde im Rahmen dieser Dissertation mit einem prospektiven Studiendesign untersucht, ob Schwierigkeiten in der kontextabhängigen Modulation konditionierter Furcht und den zugrundeliegenden neuronalen Mechanismen einen Risikofaktor für die Entwicklung von experimentell induzierten Intrusionen darstellen.

Um in einer gesunden Stichprobe zu untersuchen, wer vulnerabel für die Entwicklung von Intrusionen ist, wurde in der Dissertationsstudie das sogenannte Trauma-Film-Paradigma (TFP) genutzt. Das TFP, im Rahmen dessen aversive Filmausschnitte mit Trauma-assoziierten Inhalten gezeigt werden, stellt ein prospektives experimentelles Design zur Untersuchung prä-, peri- und post-traumatischer Risikofaktoren für die Entwicklung von Analogintrusionen dar (Holmes & Bourne, 2008; James et al., 2016). Außerdem durchliefen die Studienteilnehmerinnen ein zweitägiges kontextabhängiges Furchtkonditionierungsparadigma während einer funktionellen Magnetresonanztomographie (fMRT)-Messung, um die kontextabhängige Modulation von konditionierter Furcht zu untersuchen. Das Paradigma umfasste die Furchtakquisition in Kontext A und das Extinktionstraining in Kontext B am ersten Tag sowie den Extinktionsabruf im sicheren Kontext B und das Furchtrenewal in einem neuen Kontext C einen Tag später. Die neuronale Aktivität in furcht- und extinktionsassoziierten Arealen sowie die elektrodermale Reaktion (Hautleitfähigkeit) wurden während des Paradigmas gemessen.

Hypothesen:

Neben einer stärkeren konditionierten Furchtreaktion während der Furchtakquisition wurde angenommen, dass Schwierigkeiten in der kontextabhängigen Modulation der konditionierten Furcht die Entwicklung von Analogintrusionen vorhersagen. Schwierigkeiten in der kontextabhängigen Modulation von Furcht sollten sich in einer stärkeren konditionierten Furchtreaktion im sicheren Kontext B während des Extinktionslernens und -abrufs sowie in einer reduzierten konditionierten Furchtreaktion im neuen Kontext C während des Furchtrenewals (fehlende Furchterneuerung) widerspiegeln. Eine stärkere konditionierte Furchtreaktion sollte mit einer stärkeren elektrodermalen Reaktion und einer stärkeren Aktivität in furchtexpressiven Gehirnarealen (Amygdala, dACC, Insula) und einer geringeren Aktivität in furchtmodulierenden und -hemmenden Regionen (vmPFC, Hippocampus) verbunden sein.

<u>Fragestellung 2:</u> Ist eine bessere Mustertrennungsfähigkeit mit einer erfolgreicheren kontextabhängigen Modulation konditionierter Furcht verbunden?

Mustertrennung ist relevant für die Integration und Unterscheidung von alten und neuen Gedächtnisrepräsentationen und -erinnerungen (Kheirbek et al., 2012; Leal & Yassa, 2018; Zotow et al., 2020). Daher könnte die Mustertrennungsfähigkeit auch am kontextabhängigen Erlernen und Abruf von Furcht- und Extinktionsgedächtnisspuren beteiligt sein. Dies erfordert ähnliche Kontexte, da sie dieselben oder ähnliche Elemente (konditionierte Reize) beinhalten, erfolgreich zu unterscheiden. Bislang gibt es jedoch keine Studie, die den Zusammenhang der Mustertrennungsfähigkeit mit dem Erlernen und Abruf von kontextabhängigen Furcht- und Extinktionserinnerungen untersucht. Frühere Studien konzentrierten sich auf die Untersuchung des Zusammenhangs zwischen Mustertrennungsfähigkeit und Furchtkonditionierungs- bzw. Furchtgeneralisierungsprozessen (Bernstein, van der Does, Orr & McNally, 2021; Lange et al., 2017). In Erweiterung früherer Forschungsarbeiten wurde im Rahmen dieser Dissertationsstudie in einer gesunden weiblichen Stichprobe untersucht, ob ein Zusammenhang zwischen der Mustertrennungsfähigkeit und dem kontextabhängigen Abruf von Furcht- und Extinktionserinnerungen bzw. der kontextabhängigen Modulation konditionierter Furcht besteht. Zur Messung der Mustertrennungsfähigkeit wurde der MST (Stark et al., 2013) durchgeführt. Außerdem durchliefen Studienteilnehmerinnen ein zweitägiges kontextabhängiges Furchtkonditionierungsparadigma während einer fMRT-Messung, um den kontextabhängigen Abruf von Furcht- und Extinktionserinnerungen bzw. die kontextabhängige Modulation konditionierter Furcht zu untersuchen. Die neuronale Aktivität in furcht- und extinktionsassoziierten Arealen sowie die elektrodermale Reaktion (Hautleitfähigkeit) dienten als *Outcome*-Variablen.

Hypothesen:

Es wurde angenommen, dass eine bessere Mustertrennungsfähigkeit, die für die Verarbeitung der (Un-)Ähnlichkeit zwischen Kontexten als relevant gilt (Kheirbek et al., 2012; Sahay et al., 2011), zu einer erfolgreicheren kontextuellen Modulation der konditionierten Furcht beiträgt. Während des Extinktionslernens sollte daher eine bessere Mustertrennungsfähigkeit mit einem stärkeren Aktivitätsanstieg im Hippocampus und im vmPFC und mit einer stärkeren Aktivitätsabnahme in furchtverarbeitenden Gehirnstrukturen (Amygdala, Insula, dACC) sowie einer stärkeren Verringerung der konditionierten elektrodermalen Reaktion verbunden sein. Im Hinblick auf die Abruftests wurde erwartet, dass eine bessere Mustertrennungsfähigkeit mit einer stärkeren Aktivität des Hippocampus und einer geringeren Ausprägung der konditionierten Furcht während des Extinktionsabrufs (Kontext B) sowie einer stärkeren konditionierten Furchtreaktion während des Furchtrenewals (Kontext C) verbunden ist. Eine stärkere konditionierte Furchtreaktion sollte sich in einer verstärkten elektrodermalen Reaktion und in einer verstärkten Aktivität von furchtexpressiven Regionen (Amygdala, Insula, dACC) sowie in einer geringeren Aktivität des vmPFC widerspiegeln.

4. Beschreibung der Studie

Die Studie untersuchte die neuronalen Korrelate kontextabhängiger Furchtkonditionierungsprozesse und deren Relevanz für die Entwicklung von kurz- und langfristigen Analogintrusionen in Reaktion auf ein experimentelles Trauma (Fragestellung 1) (Neudert, Schäfer, Zehtner, Fricke, Seinsche, Stark & Hermann, 2023). Zudem wurde in der Studie der Zusammenhang zwischen Mustertrennungsfähigkeit und kontextabhängigen Furchtkonditionierungsprozessen überprüft (Fragestellung 2) (Neudert, Schäfer, Zehtner, Fricke, Seinsche, Kruse et al., 2023).

4.1 Methodik

Stichprobe. Die Stichprobe bestand aus 94 gesunden weiblichen Studentinnen, die über die Mailingliste der Universität Gießen rekrutiert wurden. Am ersten Untersuchungstag erfolgte die Überprüfung der Ein- und Ausschlusskriterien mittels Interview und Fragebogen. Die Studienteilnehmerinnen sollten zwischen 18 und 35 Jahre alt sein, Rechtshändigkeit aufweisen und Deutsch auf muttersprachlichem Niveau sprechen. Ausschlusskriterien für die Studie waren neben MRT-Kontraindikationen die Einnahme psychoaktiver oder anderer potenziell beeinträchtigender Substanzen (aktueller und/oder regelmäßiger Drogenkonsum in der Vergangenheit), Farbenblindheit, eine aktuelle oder frühere psychotherapeutische/psychiatrische Behandlung oder eine medizinische Behandlung aufgrund einer akuten oder schweren chronischen körperlichen Erkrankung. Zur Beurteilung der psychischen Gesundheit wurde ein strukturiertes klinisches Interview für psychische Störungen (DIPS; Margraf, Cwik, Suppiger & Schneider, 2017; Margraf, Cwik, Pflug & Schneider, 2017) und die *Life-Event*-Checklist in Kombination mit der *Clinician-Administered PTSD Scale* für DSM-5 (Cwik & Woud, 2015) durchgeführt. Teilnehmerinnen wurden von der weiteren Studienteilnahme ausgeschlossen, wenn sie aktuell oder in der Vergangenheit die Kriterien für die Diagnose einer psychischen Störung erfüllten. Weitere Studienausschlusskriterien stellten das Erleben eines traumatischen Ereignisses innerhalb der letzten vier Wochen oder persönliche Erfahrungen mit körperlicher oder sexueller Gewalt dar. Die Teilnehmerinnen wurden vorab informiert, dass sie die Studie jederzeit ohne negative Konsequenzen abbrechen könnten und dass sie im Rahmen der Studie einen Film mit Szenen körperlicher und sexueller Gewalt sehen würden.

Studienablauf. Das gesamte Projekt umfasste sechs Studientage innerhalb von vier Wochen sowie eine Online-Umfrage 3 Monate nach dem letzten Studientermin. Am ersten Studientag wurde ein Interview durchgeführt, um die psychische und physische Gesundheit festzustellen sowie weitere Ein- und Ausschlusskriterien für die Studie abzuklären (siehe Abschnitt Stichprobe). Am zweiten Studientag (1-3 Tage später) führten die Teilnehmerinnen den MST für Objekte und anschließend den MST für Szenen (Stark et al., 2013; Stark & Stark, 2017; Stark et al., 2019) zur Messung der Mustertrennungsfähigkeit sowie eine neuropsychologische Testbatterie zur Messung exekutiver Funktionen durch. An Studientag 3 (7-10 Tage nach Studientag 1) absolvierten die Teilnehmerinnen den ersten Teil eines Emotionsregulationsparadigmas, während der zweite Teil des Emotionsregulationsparadigmas zu Beginn von Studientag 4 (6-8 Tage nach Tag 3) stattfand. An Studientag 4, nach Abschluss des Emotionsregulationsparadigmas, erfolgte der erste Teil des kontextabhängigen Furchtkonditionierungsparadigmas. Studienteilnehmerinnen absolvierten die Phase der Furchtakquisition in Kontext A und die Phase des Extinktionstrainings in Kontext B. Etwa 24 Stunden später (an Studientag 5) führen die Teilnehmerinnen den zweiten Teil des Furchtkonditionierungsparadigmas durch (Phasen: Extinktionsabruf in Kontext B, Furchtrenewal in Kontext C). Anschließend wurde das TFP als letztes Untersuchungsparadigma an Studientag 5 durchgeführt. Nach einer Woche, an Studientag 6, wurde die Entwicklung von (kurzfristigen) Analogintrusionen sowie das explizite Filmgedächtnis mittels Fragebogen und verschiedener Aufgaben erfasst. Drei Monate nach Studientag 6 wurden die Teilnehmerinnen per Mail erneut kontaktiert, um an einer Online-Umfrage teilzunehmen, um u.a. langfristige Analogintrusionen sowie explizite Gedächtnisinhalte in Bezug auf den Traumfilm zu messen.

Beschreibung der Untersuchungsparadigmen

Mnemonic Similarity Task (MST). Zur Messung der behavioralen Mustertrennungsfähigkeit führten alle Teilnehmerinnen den MST für Objekte und anschließend den MST für Szenen durch. Jeder MST (Stark et al., 2013; Stark & Stark, 2017) bestand aus zwei Phasen, der Enkodierung und der anschließenden Testphase (siehe Abb. 1): In der Enkodierungsphase betrachteten die Teilnehmerinnen 128 Bilder von Objekten nacheinander auf weißem Hintergrund, die auf dem Monitor eines Laptops (15,6 Zoll) jeweils für 2 (Objekte) bzw. 3 Sekunden (Szenen) präsentiert wurden. Die Teilnehmerinnen sollten per Tastendruck auf der Tastatur jede(s) Objekt/Szene nach bestimmten Kategorien klassifizieren (Objekte: Verwendung innerhalb oder außerhalb eines Hauses; Szenen: Zeigt die Szene etwas Natürliches oder etwas vom Menschen Gemachtes). Unmittelbar nach der Enkodierungsphase erfolgte die Testphase, bei der es sich um einen Gedächtnistest für die zuvor gesehenen Bilder handelte. Während der Testphase wurden 64 Bilder von Objekten/Szenen, die während der Enkodierungsphase präsentiert wurden (Bedingung: „alt“), 64 Bilder von neuen Objekten/Szenen (Bedingung: „neu“) und 64 Bilder, die ähnliche, aber nicht identische Objekte/Szenen der Enkodierungsphase zeigten (Bedingung: „ähnlich“), in einer randomisierten Reihenfolge präsentiert. Für jedes Bild sollten die Teilnehmerinnen entscheiden, ob es sich bei dem präsentierten Bild um ein altes, ein neues oder ein ähnliches Bild handelt (*forced choice*, keine Zeitbegrenzung). Die Mustertrennungsfähigkeit wurde mittels des *„Lure Discrimination Index (LDI)“* ermittelt. Ein höherer Index spricht für eine bessere Identifizierung ähnlicher Objekte/Szenen (= bessere Mustertrennungsfähigkeit).

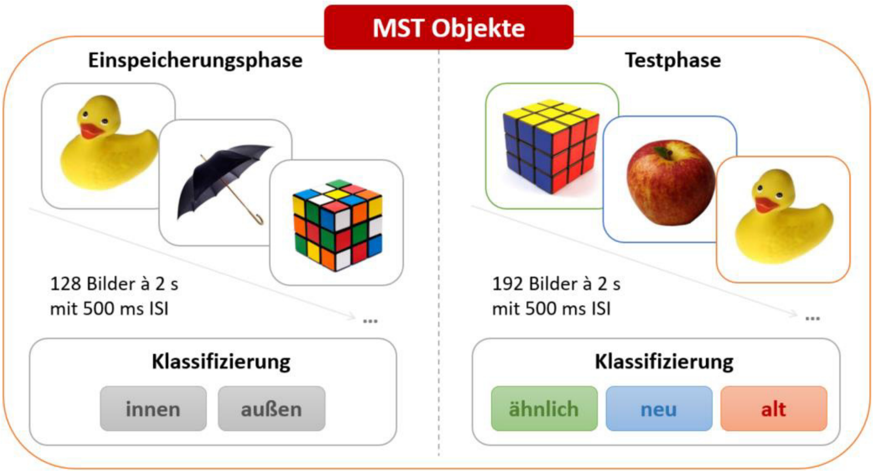

Abb. 1: Design der Mnemonic Similarity Task (MST) für Objekte

Emotionsregulationsparadigma (fMRT). Das Paradigma bestand aus einer aktiven Regulationsphase, die an Studientag 3 durchgeführt wurde, und einer Re-Expositionsphase 6-8 Tage später (Studientag 4) (Hermann et al., 2021). Das Emotionsregulationsparadigma wird an dieser Stelle nicht weiter beschrieben, da die Dissertation nicht auf diesen Daten basiert.

Kontextabhängiges Furchtkonditionierungsparadigma (fMRT). Das zweitägige differentielle Furchtkonditionierungsparadigma zur Untersuchung der kontextuellen Modulation konditionierter Furcht bestand aus vier experimentellen Phasen (siehe Abb. 2): Furchtakquisition in Kontext A, Extinktionstraining in Kontext B (Studientag 4), Extinktionsabruf im sicheren Kontext B und Furchtrenewal in einem unbekannten Kontext C nach ca. 24 Stunden (Studientag 5). Während der Furchtakquisition wurde zunächst eine ausgeschaltete Schreibtischlampe in Kontext A (z.B. Büroraum) für 3 Sekunden präsentiert, die anschließend für 6 Sekunden blau oder gelb aufleuchtete. In 62,5 Prozent der Fälle folgte auf eine der beiden Lichtfarben (CS+:

konditionierter Reiz) eine elektrische Stimulation für 500ms (UCS: unkonditionierter Stimulus) über Elektroden, die an Zeige- und Mittelfinger angebracht waren. Auf die andere Lichtfarbe der Lampe (CS-: Sicherheitsreiz) folgte nie eine elektrische Stimulation (kein UCS). Während der Furchtakquisitionsphase gab es jeweils 8 CS+ sowie 8 CS- Durchgänge, die in pseudorandomisierter Reihenfolge präsentiert wurden. Zwischen den Durchgängen erschien für mehrere Sekunden ein weißes Fixationskreuz auf schwarzem Hintergrund. Die Furchtkonditionierung galt als erfolgreich, wenn Personen eine stärkere Furchtreaktion (elektrodermale Aktivität als Maß für Erregung und neuronale Aktivität in furchtverarbeitenden Gehirnregionen) auf den CS+ im Vergleich zum CS- zeigten. Das Extinktionstraining folgte unmittelbar auf die Furchtakquisition. Während des Extinktionstrainings wurde die Lampe in einem Kontext B für 3 Sekunden gezeigt, die anschließend wieder für 6 Sekunden blau oder gelb aufleuchtete. Der CS+ und CS- wurden jeweils 16x ohne elektrische Stimulation in pseudorandomisierter Reihenfolge dargeboten. Im Rahmen des Extinktionstrainings sollte die konditionierte Reaktion abnehmen und sich eine Extinktionsgedächtnisspur ausbilden, die in Konkurrenz zur Furchtgedächtnispur stand, welche während der Furchtakquisition in Kontext A erworben wurde. Einen Tag später sollte der Abruf der Gedächtnisspuren in dem sicheren Kontext B (Extinktionsabruf) und in einem neuen Kontext C (Furchtrenewal) getestet werden. Beim Extinktionsabruf als auch beim Furchtrenewal wurden der CS+ und CS- jeweils 8x ohne elektrische Stimulation (UCS) dargeboten. Die konditionierte Reaktion (CS+ minus CS-) auf neuronaler und elektrodermaler Ebene wurde während jeder Phase gemessen.

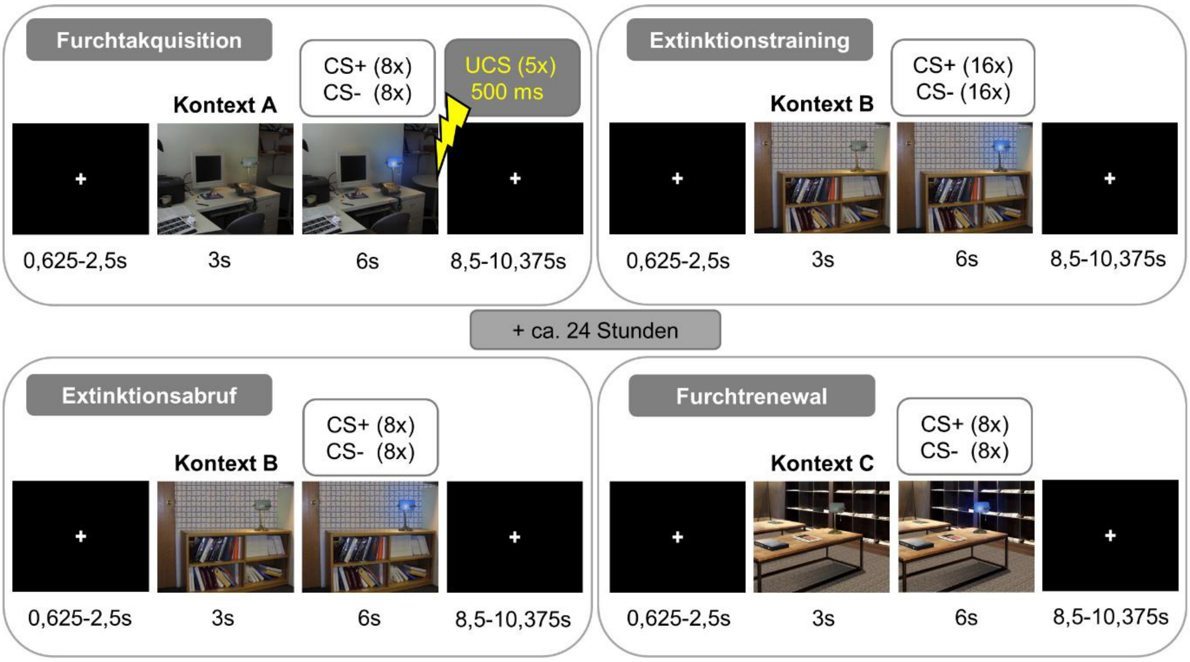

Abb. 2. Design des kontextabhängigen Furchtkonditionierungsparadigmas

Trauma-Film-Paradigma (TFP). Während des Paradigmas sahen die Studienteilnehmerinnen aversive Filmszenen aus dem Film „Irreversible“ von Gaspar Noé (2002) mit der expliziten Darstellung von körperlicher und sexueller Gewalt (Dauer: 11 Minuten). Atmung, Herzfrequenz und elektrodermale Reaktionen wurden während des Films und während einer Ruhephase vor der Filmvorführung aufgezeichnet. Sowohl Filmintrusionen (Analogintrusionen) als auch das explizite Filmgedächtnis wurden an Studientag 6 und 3 Monate später im Rahmen einer Online-Umfrage erfasst. Die Intrusions-Skala der *Impact of Event-Scale Revised* (IES-R; Maercker & Schützwohl, 1998) wurde als Haupt-*Outcome*-Variable für die Entwicklung von Analogintrusionen genutzt.

4.2 Ergebnisse zu Fragestellung 1

Analysen in den a-priori definierten „*Regions of Interest*“ und explorative Ganzkopfanalysen sowie die Analyse der elektrodermalen Daten zeigten, dass die konditionierte Reaktion während der einzelnen experimentellen Phasen zwar nicht die Entwicklung von kurzfristigen Analogintrusionen (alle Analysen: p>.05), jedoch von langfristigen Analogintrusionen (nach 3 Monaten) vorhersagte.

Langfristige Analogintrusionen in Reaktion auf ein experimentelles Trauma wurden durch eine stärkere konditionierte Reaktion im Gefahrenkontext (Kontext A) während der Furchtakquisition, aber auch durch eine stärkere konditionierte Reaktion im Sicherheitskontext (Kontext B) während des Extinktionstrainings und des frühen Extinktionsabrufs vorhergesagt: So wiesen Personen mit langfristigen Analogintrusionen eine stärkere Aktivität des dACCs (F=21.11, $p_{fwecorr}$=.024, MNI: x=14, y=12, z=34) und eine stärkere elektrodermale Reaktion auf den CS+ im Vergleich zum CS- (z=2.277, p=.023) während der Furchtakquisitionsphase in Kontext A auf als Personen ohne langfristige Analogintrusionen. Während der frühen Extinktionstrainingsphase in Kontext B zeigten Personen mit langfristigen Analogintrusionen eine stärkere Aktivität der rechten Amygdala (F=46.55, $p_{fwecorr}$<.001, MNI: x=20, y=-4, z=-12) und des linken vmPFC (F=26.38, $p_{fwecorr}$=.012, MNI: x=-6, y=44, z=-6) auf den CS+ im Vergleich zu CS-, aber keine signifikant stärkere konditionierte Reaktion auf elektrodermaler Ebene (z=1.495, p=.135) als Personen ohne langfristige Analogintrusionen. Während des frühen Extinktionsabrufs in Kontext B, wenn Kontext B als Sicherheitsreiz genutzt werden sollte, wiesen Personen mit langfristigen Analogintrusionen im Vergleich zu Personen ohne langfristige Analogintrusionen eine stärkere konditionierte Reaktion auf elektrodermaler Ebene (z=2.616, p=.009) auf, was für eine stärkere Furchtreaktion spricht. Auf neuronaler Ebene zeigten Personen mit langfristigen Analogintrusionen eine stärkere Aktivität des dACCs auf den CS+ im Vergleich zum CS- als Personen ohne langfristige Analogintrusionen, allerdings war dieser Gruppenunterschied statistisch nicht signifikant (F=17.46, p_{fwecorr}=.073, MNI: x=0, y=26, z=24). Personen mit und ohne langfristige Analogintrusionen unterschieden sich weder auf neuronaler noch auf elektrodermaler Ebene signifikant in der Wiederkehr der konditionierten Reaktion während des Furchtrenewals in Kontext C (alle Analysen: p>.05).

4.3 Diskussion zu Fragestellung 1

Die Ergebnisse der Studie zeigten, dass eine stärkere konditionierte Reaktion auf neuronaler oder elektrodermaler Ebene im Gefahrenkontext während der Furchtakquisition, aber auch im sicheren Kontext während des Extinktionstrainings und des Extinktionsabrufs einen Risikofaktor für die Entwicklung langfristiger Analogintrusionen darstellte. Kurzfristige Intrusionen hingegen wurden nicht durch kontextabhängige Furchtkonditionierungsprozesse vorhergesagt. Im Gegensatz zu langfristigen Intrusionen treten kurzfristige (Analog)-Intrusionen häufig nach einem (experimentellen) Trauma auf und sind nicht per se pathologisch (Carper et al., 2015; Ehlers & Steil, 1995). Dies könnte erklären, warum in der vorliegenden Studie keine signifikanten Assoziationen zwischen kurzfristigen Analogintrusionen und elektrodermalen und neuronalen Indikatoren für kontextabhängige Furchtkonditionierungsprozesse gefunden wurden.

Personen, die langfristige Analogintrusionen entwickelten, wiesen Schwierigkeiten auf, ihre Furcht in Abhängigkeit des Kontexts zu modulieren und zeigten daher auch im sicheren Kontext eine stärkere Furchtreaktion auf konditionierte Reize als Personen ohne langfristige Analogintrusionen. Eine stärkere konditionierte Reaktion in gefährlichen und in sicheren Kontexten deutet auf Schwierigkeiten in der kontextabhängigen Modulation konditionierter Furcht hin. Furchtreaktionen im sicheren Kontext sprechen zudem für ein dekontextualisiertes Furchtgedächtnis, was ätiologische Annahmen zur PTBS bestätigt (Ehlers & Clark, 2000; Liberzon & Abelson, 2016). Ein dekontextualisiertes Furchtgedächtnis könnte dazu führen, dass eine konditionierte Reaktion auf konditionierte Reize immer auftritt, unabhängig davon, in welchem Kontext sich eine Person befindet. Eine stärkere konditionierte Furchtreaktion in einem sicheren Kontext während des Extinktionslernens und -abrufs, wie sie durch elektrodermale oder neuronale Indikatoren angezeigt wurde, könnten auf Schwierigkeiten bei der Nutzung des Kontexts als Sicherheitssignal hindeuten (Jovanovic, Kazama, Bachevalier & Davis, 2012; Rougemont-Bücking et al., 2011; Sangha, Diehl, Bergstrom & Drew, 2020). Defizite bei der Nutzung von Kontextinformationen zur Furchtmodulation gelten als ätiologisch relevante Risikofaktoren für PTBS (Brewin & Holmes, 2003; Ehlers & Clark, 2000; Liberzon & Abelson, 2016) und könnten erklären, warum Personen mit PTBS konditionierte Furchtreaktionen in Form von Intrusionen in sicheren Kontexten zeigen.

Betrachtet man die neuronalen Befunde, so spiegelte sich eine stärkere konditionierte Furchtreaktion im sicheren Kontext bei Personen mit im Vergleich zu Personen ohne langfristige Analogintrusionen in einer erhöhten Aktivität der Amygdala und des vmPFCs während des Extinktionslernens wider. Die Amygdala ist eine Hirnregion, die für den Ausdruck von Furcht relevant ist (Cheng, Knight, Smith & Helmstetter, 2006), während der vmPFC einen moderierenden Einfluss auf die Amygdala hat (Andrewes & Jenkins, 2019; Maren et al., 2013; Motzkin et al., 2015). Eine Hyperaktivität in furchtverarbeitenden und furchtexpressiven Gehirnregionen wie der Amygdala könnte zu einem verstärkten Furchterwerb (verstärkte Konditionierbarkeit) und zu einem Abruf der Furchtgedächtnisspur auch in sicheren Kontexten führen. Zudem gelten eine Hyperaktivität der Amygdala, aber auch des dACCs, als prädisponierende Risikofaktoren für die Entwicklung einer PTBS (Admon, Milad & Hendler, 2013).

Die neuronalen Befunde zum Extinktionslernen und Abruf stimmen im Wesentlichen mit den Ergebnissen früherer Studien zur kontextabhängigen Furchtkonditionierung bei PTBS-Patient:innen überein, die eine stärkere Aktivität der Amygdala während der frühen Extinktion im Kontext B und eine erhöhte Aktivität des dACCs, aber auch eine Hypoaktivität des vmPFC und des Hippocampus während des Extinktionsabrufs im Kontext B zeigten (Garfinkel et al., 2014; Milad et al., 2009). Darüber hinaus spricht eine stärkere konditionierte Furchtreaktion in sicheren Kontexten für Extinktionsschwierigkeiten, die als Risikofaktor für Analogintrusionen betrachtet werden (Miedl et al., 2020). Die Ergebnisse der Studie stehen zudem in Einklang mit einer Meta-Analyse, die bei PTBS-Patient:innen ebenfalls auf Extinktionsdefizite während des Extinktionslernens und des Extinktionsabrufs hindeutet (Suarez-Jimenez et al., 2019).

In Bezug auf das Furchtrenewal in Kontext C zeigten die Ergebnisse, dass es keinen signifikanten Gruppenunterschied in der Rückkehr der Furcht gab, wenn ein neuer, potenziell gefährlicher Kontext präsentiert wurde. Allerdings zeigte sich in weiterführenden *within-group*-Analysen nur bei Personen ohne, nicht aber bei Personen mit langfristigen Analogintrusionen ein signifikanter Anstieg der konditionierten Furcht auf der elektrodermalen Ebene vom späten Extinktionsabruf in Kontext B zur frühen Furchtrenewalphase in Kontext C. Dieses Ergebnis weist auf eine reduzierte oder fehlende Furchtrückkehr bei Personen mit langfristigen Analogintrusionen hin, wenn ein neuer potentiell bedrohlicher Kontext präsentiert wurde. Ein reduziertes Furchtrenewal ist auch für PTBS-Patient:innen bekannt (Garfinkel et al., 2014). Es ist möglich, dass Personen mit langfristigen Analogintrusionen keine erfolgreiche Rückkehr der Furcht zeigten, da sie nicht bemerkten oder nicht darauf reagierten, dass sich der Kontext während des Experiments veränderte.

Zusammenfassend sprechen die neuronalen und elektrodermalen Ergebnisse dafür, dass Schwierigkeiten in der kontextuellen Modulation von konditionierter Furcht langfristige

Analogintrusionen vorhersagten und daher als Risikofaktoren für die Entwicklung von PTBS-Symptomen betrachtet werden können.

4.4 Ergebnisse zu Fragestellung 2

Alle Korrelationsanalysen wurden für die visuell-räumliche Merkfähigkeit kontrolliert. Eine bessere Mustertrennungsfähigkeit war mit einer geringeren Aktivität des dACCs (T_{max}=3.99, p_{fwe}=.046, MNI: x=−2; y=32; z=30) und der Insula (Trend: T_{max}=3.73, p_{fwe}=.089, MNI: x=36; y=−12; z=10) während des Furchterwerbs in Kontext A korreliert. In Bezug auf die Hypothesen konnte gezeigt werden, dass eine bessere Mustertrennungsfähigkeit mit einer stärkeren Abnahme der konditionierten Reaktion auf elektrodermaler Ebene vom frühen zum späten Extinktionstraining im Kontext B verbunden war (r_s=.299, p=.025), wenn die Extinktionsgedächtnisspur erlernt werden sollte. Auf neuronaler Ebene zeigte sich kein derartiger Zusammenhang (alle Analysen: p>.10). Entgegen der Hypothese fanden wir ebenfalls keinen Zusammenhang zwischen der Mustertrennungsfähigkeit und dem frühen Extinktionsabruf weder auf neuronaler noch auf elektrodermaler Ebene (alle Analysen: p>.10). Analysen zeigten jedoch, dass eine bessere Mustertrennungsfähigkeit mit einer stärkeren konditionierten elektrodermalen Reaktion (Trend: r_s=.259, p=.054) und einer stärkeren Aktivität des dACCs (T_{max}=4.03, p_{fwe}=.014, MNI: x=0; y=32; z=30) während des Furchtrenewals verbunden war.

4.5 Diskussion zu Fragestellung 2

Die Mustertrennungsfähigkeit korrelierte mit Indikatoren von kontextabhängigen Furchtkonditionierungsprozessen: Die Ergebnisse der elektrodermalen Daten deuten darauf hin, dass Personen mit einer besseren Mustertrennungsfähigkeit erfolgreicher im Extinktionslernen sind. Diese Interpretation ist jedoch begrenzt, da die neuronalen Indikatoren des Extinktionslernens keinen signifikanten Zusammenhang mit der Mustertrennungsfähigkeit aufwiesen. Extinktionslernen wird als ein Hauptmechanismus für die Furchtreduktion während der Expositionstherapie angesehen (Hamm, Wendt & Volkmann, 2017; Kindt, 2014). Die Mustertrennung könnte während des Extinktionslernens im Kontext B erforderlich sein, um Unterschiede zwischen Kontext A und Kontext B trotz identischer Merkmale (konditionierte Reiz: Lampe) herauszuarbeiten und damit das kontextabhängige Extinktionslernen zu erleichtern. Im Gegensatz zur Hypothese korrelierte die Mustertrennung nicht mit elektrodermalen oder neuronalen Indikatoren eines besseren Extinktionsabrufes in Kontext B. Kontext B stellte einen bekannten Kontext während des Extinktionsabrufs dar. Kontext B sollte daher als sicherer Kontext wiedererkannt werden. Dies könnte jedoch eher Mustererkennung, d. h. die Fähigkeit, sich an bekannte Reize zu erinnern, als Mustertrennung erfordern, die sich auf die Unähnlichkeit von Reizen konzentriert (Colgin, Moser & Moser, 2008; Stark et al., 2013).

Wie erwartet, war eine bessere Mustertrennungsfähigkeit mit einer stärkeren konditionierten elektrodermalen Reaktion und einer stärkeren Aktivität im dACC auf den CS+ im Vergleich zum CS- während des Furchtrenewals assoziiert. Der dACC gilt als Struktur, die für den Ausdruck von erlernter Furcht relevant ist (Milad et al., 2007). Diese Ergebnisse könnten daher auf einen stärkeren Abruf der Furchtgedächtnisspur in einem neuen unbekannten und potentiell bedrohlichen Kontext bei Personen mit einer besseren Mustertrennungsfähigkeit hinweisen. Der Abruf des Furchtgedächtnisses in einem neuen, potenziell gefährlichen Kontext ist adaptiv, indem eine Person auf eine potenzielle Bedrohung vorbereitet wird. Beeinträchtigte Mustertrennungsprozesse könnten daher zu Schwierigkeiten in der Rückkehr der Furcht in einem bedrohlichen Kontext beitragen, die beispielsweise für Patient:innen mit PTBS bekannt sind (Garfinkel et al., 2014). Kontext C stellte während des Furchtrenewals einen neuen Kontext dar. Neue Kontexte müssen auf Un(ähnlichkeit) zu früheren Kontexten überprüft werden. Neuronalen Modellen zufolge (Lissek et al., 2014; Webler et al., 2021) sollte die Mustertrennung im Falle einer Ähnlichkeit zwischen einem neuen Reiz bzw. einer neuen Situation und bereits gespeicherten Gefahrenreizen/Situationen Strukturen des Furchtnetzwerks aktivieren. Kontext C wies Merkmale zu einem gefährlichen Kontext (Kontext A) auf. Daher sollte während des Furchtrenewals in Kontext C auch eine Furchtreaktion ausgelöst werden, was Personen mit einer besseren Mustertrennungsfähigkeit auf neuronaler und elektrodermaler Ebene auch zeigten. Interessanterweise gab es auf neuronaler Ebene keinen Zusammenhang der Mustertrennung mit der Aktivität im Hippocampus während des Furchtrenewals. Jedoch zeigte auch eine andere Studie keinen Zusammenhang zwischen der Mustertrennungsfähigkeit und der Aktivierung des Hippocampus während der Furchtgeneralisierung (Lange et al., 2017), obwohl neuronalen Modellen zufolge die Unterscheidung von Stimuli, die dem konditionierten Reiz ähneln, Mustertrennung im Hippocampus erfordern sollte (Lissek et al., 2014; Webler et al., 2021). Die fehlende Hippocampus-Aktivierung könnte mit methodischen Problemen zusammenhängen, wie z.B. der begrenzten Auflösung der Bildgebungsdaten, die die Untersuchung von Unterregionen des Hippocampus (z.B. Gyrus dentatus) verhindert, die speziell für die Mustertrennung sowie für die Enkodierung und den Abruf von Erinnerungen besonders wichtig sind (Bakker et al., 2008; Bernier et al., 2017).

Die Ergebnisse dieser Studie zeigten auch, dass die Mustertrennung mit neuronalen Korrelaten (dACC, Insula (Trend)) des Furchterwerbs in Kontext A korrelierte. Während der Phase des Furchterwerbs ist die Mustertrennung möglicherweise weniger erforderlich, da Kontext A mit keinem anderen Studien-Kontext verglichen werden konnte. Dies könnte die verringerte Aktivierung in furchtverarbeitenden Strukturen während der Furchtakquisition bei Personen mit einer besseren Mustertrennungsfähigkeit erklären. Die Ergebnisse sind jedoch nicht eindeutig interpretierbar, da es keinen Zusammenhang zwischen der Mustertrennungsfähigkeit und der elektrodermalen Reaktion gab.

5. Zusammenfassende Diskussion und Ausblick

Diese Dissertationsstudie untersuchte, inwiefern kontextabhängige Furchtkonditionierungsprozesse experimentell induzierte Intrusionen vorhersagten. Eine Besonderheit der Studie lag darin, dass nicht nur, wie üblich in Studien, die das TFP nutzen, kurzfristige Analogintrusionen, sondern auch langfristige Analogintrusionen sowie explizite Gedächtnisinhalte in Bezug auf den Traumafilm (siehe auch: Neudert, Schäfer, Zehtner, Fricke, Seinsche, Stark & Hermann, 2023) 3 Monate nach dem experimentellen Trauma erhoben wurden. Es ist bekannt, dass die Häufigkeit von Intrusionen innerhalb der ersten Wochen nach dem traumatischen Ereignis abnimmt; wenn diese jedoch länger anhalten, können sie ein Hinweis für eine PTBS darstellen (Carper et al., 2015; Ehlers & Steil, 1995). Nach den DSM-5-Kriterien müssen Symptome wie Intrusionen mindestens 1 Monat bestehen, damit die Diagnose einer PTBS erfüllt ist (APA, 2013). Langfristige Analogintrusionen entsprechen aus diesen Gründen stärker den pathologischen Intrusionen der PTBS und waren daher in dieser Studie von besonderem Interesse. Im Vergleich zu früheren Furchtkonditionierungsstudien mit analogen Stichproben, die die Vorhersage von intrusiven Symptomen untersuchten (Miedl et al., 2020; Rattel et al., 2019), war eine weitere Besonderheit der Studie, dass ein kontextabhängiges Furchtkonditionierungsparadigma genutzt wurde. Dies ermöglichte nicht nur Furchtkonditionierungsprozesse, sondern auch speziell die kontextuelle Modulation konditionierter Furcht für die Entwicklung von Intrusionen zu betrachten. Die Untersuchung der kontextuellen Modulation konditionierter Furcht entspricht stärker ätiologischen Modellen der PTBS (Ehlers & Clark, 2000; Liberzon & Abelson, 2016), die ein Zusammenspiel von Furchtkonditionierungsprozessen und Schwierigkeiten in der Verarbeitung von Kontextinformationen bei der Entwicklung der PTBS annehmen.

Die Ergebnisse der Dissertation zeigten, dass Schwierigkeiten in der kontextuellen Modulation konditionierter Furcht, welche sich in einer stärkeren konditionierten Furchtreaktion im Gefahrenkontext und im sicheren Kontext auf elektrodermaler und/oder neuronaler Ebene zeigten, langfristige (jedoch nicht kurzfristige) Analogintrusionen vorhersagten. Querschnittsstudien mit PTBS-Patient:innen demonstrierten in Übereinstimmung mit den Ergebnissen dieser Studie (Garfinkel et al., 2014; Milad et al., 2009), dass die Nutzung von Kontextinformationen zur kontextuellen Modulation konditionierter Furcht bei Personen mit PTBS eingeschränkt scheint, sodass dekontextualisierte Furchterinnerungen entstehen könnten. Indem die Dissertationsstudie für die Untersuchung dieser Fragestellung ein prospektives Studiendesign wählte, konnte erstmals gezeigt werden, dass Schwierigkeiten in der kontextuellen Modulation konditionierter Furcht bereits einen Risikofaktor für die Entstehung von PTBS-Symptomen darstellen und nicht erst infolge der Störung oder des Traumas bzw. des traumatischen Stresses entstehen. Zudem validieren die Ergebnisse neuere Behandlungsansätze zur PTBS, die den Aspekt der Kontextualisierung zur Behandlung von dekontextualisierten Furchterinnerungen in Bezug auf das Trauma fokussieren (Al Abed et al., 2020; Desmedt, 2021).

Weiterhin konnte die Studie erstmals zeigen, dass eine bessere Mustertrennungsfähigkeit mit elektrodermalen Indikatoren für ein besseres Extinktionslernen in Kontext B sowie mit elektrodermalen (Trend) und neuronalen Indikatoren für ein stärkeres Furchtrenewal in Kontext C verbunden war. Die Ergebnisse deuten darauf hin, dass eine bessere Mustertrennungsfähigkeit sich positiv auf die kontextuelle Modulation konditionierter Furcht auswirken und somit z.B. auch kontextabhängige Extinktionsprozesse verbessern könnte, was von klinischer Bedeutsamkeit ist. Es könnte daher zur Optimierung der Behandlung von PTBS-Patient:innen sinnvoll sein, ein Training der Mustertrennungsfähigkeit in die Therapie zu integrieren. Neuere Psychotherapiemodelle (z.B. „*The Integrated Neuropsychological Therapy*" (Salzano, Zappullo, Baiano & Conson, 2023)) sprechen sich auch für die Integration von Trainings neuropsychologischer Funktionen in die kognitive Verhaltenstherapie aus.

Neben den Besonderheiten weist die Dissertationsstudie auch Limitationen auf. Die Studienergebnisse sind in ihrer Übertragbarkeit limitiert, da die Stichprobe nur weibliche Personen mit einem hohen Bildungsstand umfasste. Somit können die Ergebnisse nicht auf andere Geschlechter, andere Bildungsstände oder klinische Populationen übertragen werden. Auch wenn das TFP viele Vorteile zur Untersuchung der Entwicklung von Analogintrusionen bietet (wie z.B. die Standardisierung des experimentellen Traumas) könnte die Übertragbarkeit der Ergebnisse eingeschränkt sein. Das Anschauen eines Films, auch wenn Trauma-spezifische Inhalte (wie z.B. sexuelle Gewalt) präsentiert werden, kann nicht per se (von der Intensität) mit dem (direkten) Erleben eines Traumas gleichgesetzt werden (James et al., 2016). So erfüllt das Anschauen eines Films mit Trauma-typischen Inhalten nicht eindeutig das Kriterium für ein traumatisches Ereignis (James et al., 2016), auch wenn dieses im Zuge des DSM-5 weniger streng als zuvor definiert wurde (APA, 2013). Die Definition eines Traumas wurde im DSM-5 um die indirekte Traumaexposition durch elektronische Medien, Fernsehen und Filme bei wiederholter Betrachtung im Rahmen der beruflichen Tätigkeit (z.B. wiederholte Durchsicht von beschlagnahmten Videomaterial über Kindesmissbrauch durch die Polizei) erweitert (APA, 2013). Daran anknüpfend ist eine weitere Kritik an dem TFP, dass die durch einen Traumafilm hervorgerufenen Reaktionen und Symptome nicht vergleichbar mit „echten" Symptomen nach einem Trauma sein könnten (Holmes & Bourne, 2008; James et al., 2016). Jedoch gibt es gute Evidenz dafür, dass auch Filme mit Trauma-typischen Inhalten intrusive Symptome provozieren können, welche ähnliche Merkmale zu denen nach einem tatsächlichen

Trauma aufweisen (Holmes, Brewin & Hennessy, 2004; Holmes & Bourne, 2008; James et al., 2016; Weidmann, Conradi, Groger, Fehm & Fydrich, 2009).

In Bezug auf das kontextabhängige Furchtkonditionierungsparadigma zeigten Analysen der Haupteffekte (siehe Supplement: Neudert, Schäfer, Zehtner, Fricke, Seinsche, Stark & Hermann, 2023), dass sich eine Rückkehr der konditionierten Furcht im sicheren Kontext während der Extinktionsabrufphase auf elektrodermaler und neuronaler Ebene in der gesamten Stichprobe zeigte. Die Rückkehr der konditionierten Furcht in einem sicheren Kontext kann ein Ergebnis des unmittelbaren Extinktionstrainings nach der Furchtakquisition sein (Merz, Hamacher-Dang & Wolf, 2016). Die Ergebnisse der Gesamtstichprobe zum Extinktionsabruf erlaubten dennoch die Untersuchung der beiden Dissertationsfragestellungen. So legen die Studienergebnisse zum kontextabhängigen Furchtkonditionierungsparadigma nahe, dass Personen mit langfristigen Analogintrusionen aufgrund der stärkeren konditionierten Reaktionen im Gefahren- sowie im sicheren Kontext Kontextinformationen nicht nutzten, um ihre Furcht in Abhängigkeit des Kontexts zu regulieren. Um die Verarbeitung von Kontextinformationen während kontextabhängiger Furchtkonditionierungsprozesse näher zu untersuchen, könnten andere Maße als die elektrodermale und neuronale Aktivität aufschlussreicher sein. In Erweiterung der Dissertationsstudie könnte es für zukünftige Studien interessant sein auch das Blickverhalten mittels *Eyetracking* während des kontextuellen Furchtkonditionierungsparadigmas aufzuzeichnen. Dies könnte Aufschluss darüber geben, wie sichere und (potentiell) gefährliche Kontexte exploriert werden. Ein geringeres Explorationsverhalten in Bezug auf den Kontext und eine stärkere Fokussierung auf den konditionierten Reiz könnten zur Ausbildung von dekontextualisierten Furchterinnerungen führen.

Im Rahmen der zweiten Fragestellung wurde untersucht, ob die Mustertrennungsfähigkeit, die mittels des MST gemessen wurde (Stark et al., 2013; Stark et al., 2019), mit kontextabhängigen Furchtkonditionierungsprozessen korrelierte. Der MST misst die Mustertrennungsfähigkeit in Bezug auf neutrale Alltagsobjekte (Stark et al., 2013). Für die PTBS-Forschung könnte es jedoch besonders interessant sein, die Mustertrennungsfähigkeit in Bezug auf traumatische bzw. konditionierte Reize zu untersuchen, um deren Relevanz z.B. für Furchtgeneralisierungsprozesse aufzuzeigen, wie in theoretischen Modellen angenommen (Webler et al., 2021). Kritisch könnte daher angemerkt werden, dass die Mustertrennungsfähigkeit nicht in Bezug auf konditionierte oder extingierte Reize gemessen wurde, wie z.B. in neueren Studien, die ein Furchtkonditionierungsparadigma mit einer mnemonischen Diskriminationsaufgabe kombinierten (Laing & Dunsmoor, 2023; Starita, Kroes, Davachi, Phelps & Dunsmoor, 2019). Zudem merken die Entwickler:innen des MSTs an, dass eine Verhaltensaufgabe wie der MST keine Aussage über direkte, sondern nur indirekte Verbindungen zu hippocampalen Mustertrennungsprozessen erlaubt (Stark et al., 2019).

Zusammenfassung

Im Rahmen dieser Dissertation wurden schwerpunktmäßig neuronale Korrelate kontextabhängiger Furchtkonditionierungsprozesse und deren Relevanz für experimentell erzeugte Intrusionen untersucht. Langfristige Analogintrusionen in Reaktion auf ein experimentelles Trauma wurden durch eine stärkere konditionierte Furchtreaktion nicht nur im Gefahrenkontext, sondern auch im sicheren Kontext vorhergesagt. Auf neuronaler Ebene zeigte sich eine stärkere konditionierte Reaktion vorwiegend in einer stärken Aktivierung von Strukturen des Furchtnetzwerks, wie der Amygdala und/oder dem dACC. Eine Hyperaktivität in diesen Arealen könnte zu stärkeren Furchtkonditionierungs- und -abrufprozessen führen und wird generell als neuronaler Marker für die Entwicklung von PTBS betrachtet (Admon et al., 2013). Schwierigkeiten in der kontextuellen Modulation konditionierter Furcht bei Personen mit langfristigen Analogintrusionen könnten auf dekontextualisierte Furchterinnerungen hindeuten. Für die erfolgreiche kontextuelle Modulation konditionierter Furcht könnte die Unterscheidung zwischen aversiven Erinnerungen und neuen Lernerfahrungen in neuen Kontexten wichtig sein, für die die Mustertrennungsfähigkeit von Bedeutung sein könnte (Kheirbek et al., 2012; Leal & Yassa, 2018; Yassa & Stark, 2011; Zotow et al., 2020). Im Rahmen der Dissertationsstudie wurde daher ebenfalls der Zusammenhang der Mustertrennungsfähigkeit mit der kontextuellen Modulation von konditionierter Furcht untersucht. Die Ergebnisse zeigten, dass eine bessere Mustertrennungsfähigkeit mit elektrodermalen Indikatoren für ein erfolgreicheres Extinktionslernen in Kontext B und mit elektrodermalen (Trend) und neuronalen Indikatoren für eine stärkeres Furchtrenewal in Kontext C verbunden war. Kontext B während des Extinktionslernens als auch Kontext C während des Furchtrenewals waren für die Teilnehmerinnen zu diesem Zeitpunkt neue Kontexte, die auf Un(ähnlichkeit) zu früheren Kontexten überprüft werden mussten, was Mustertrennung erfordern sollte (Kheirbek et al., 2012). Zusammenfassend validieren die Studienergebnisse, die zeigen, dass Schwierigkeiten in der kontextabhängigen Modulation Risikofaktoren für die Entwicklung von langfristigen Analogintrusionen darstellen, ätiologische Annahmen zur PTBS. Den Modellen zufolge (Brewin & Holmes, 2003; Ehlers & Clark, 2000; Liberzon & Abelson, 2016) können Intrusionen durch dekontextualisierte Furchterinnerungen entstehen. Die Studienergebnisse geben zudem erste Hinweise darauf, dass eine bessere Mustertrennungsfähigkeit zur Verbesserung der kontextuellen Modulation von konditionierter Furcht beitragen und damit ein schützender Faktor gegen dekontextualisierte Furchterinnerungen darstellen könnte.

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Decontextualized fear memories? Stronger conditioned fear responses during extinction learning and extinction recall in a safe context predict the development of long-term analog intrusions

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Abstract

Background. Difficulties in the context-dependent modulation of conditioned fear are known for posttraumatic stress disorder and may explain the occurrence of intrusive memories in safe contexts. The current study therefore investigated if reduced context-dependent modulation of conditioned fear and its underlying neural circuitry constitute risk factors for the development of analog intrusions in response to an experimental trauma.

Methods. Eighty-five healthy women participated in the trauma film paradigm to investigate the development of analog intrusions as well as explicit memory for an experimental trauma after one week and three months, respectively. Before, participants underwent a context-dependent fear conditioning paradigm during functional magnetic resonance imaging with fear acquisition in context A and extinction training in context B on a first day, as well as extinction recall in context B and fear renewal in a novel context C one day later. Skin conductance responses (SCRs) and blood oxygen level dependent responses were main outcome measures.

Results. In addition to stronger fear acquisition in context A, stronger conditioned fear responses in the safe context B, as indicated by stronger conditioned SCRs or stronger activation of fear expressing regions during extinction learning and recall, predicted the development of long-term analog intrusions.

Conclusions. Stronger fear responses in safe and danger contexts were risk factors for the development of long-term analog intrusions and point to decontextualized fear memories and difficulties in the context-dependent modulation of conditioned fear. Altered fear conditioning processes and reduced storage of contextual information may cause the occurrence of fear independent of context.

Introduction

Intrusions are a core symptom of posttraumatic stress disorder (PTSD) (American Psychiatric Association [APA], 2013). They consist of unwanted and involuntary recollections and impressions of a traumatic event and cause feelings and reactions as if the traumatic situation happens again, although a person is in a safe context (Ehlers, Hackmann, & Michael, 2004; Hackmann, Ehlers, Speckens, & Clark, 2004).

Theoretical models of PTSD (Brewin & Holmes, 2003; Brewin, Gregory, Lipton, & Burgess, 2010; Ehlers & Clark, 2000; Liberzon & Abelson, 2016) assume fear conditioning and reduced processing and storage of contextual information in the autobiographical memory during and after a traumatic event as relevant processes for the development of intrusions, which are conceptualized as conditioned fear responses (Franke et al., 2021). These processes may explain why PTSD patients are easily triggered by conditioned cues and show conditioned fear responses in safe contexts, which is also demonstrated in context-dependent fear conditioning studies: PTSD patients showed a stronger return of conditioned fear in a safe extinction context (reduced extinction recall), but also a missing up-regulation of conditioned fear (reduced fear renewal) when a dangerous context was presented (Garfinkel et al., 2014; Milad et al., 2009). These results indicate deficits in the contextual modulation of fear because of problems in identifying the context as a safety or danger signal. On the neural level, especially the hippocampus, the ventromedial prefrontal cortex (vmPFC) and the dorsal anterior cingulate cortex (dACC) are crucial brain regions for the context-dependent modulation of conditioned fear expression via the amygdala (Bouton, Westbrook, Corcoran, & Maren, 2006; Hermann, Stark, Milad, & Merz, 2016; Kalisch et al., 2006; Maren, Phan, & Liberzon, 2013). Up to now, it is unclear, if difficulties in the contextual modulation of conditioned fear and underlying neural mechanisms constitute risk factors for the development of PTSD symptoms or rather are the result of traumatic stress or the disorder itself.

Besides longitudinal studies with high risk populations, the trauma film paradigm (TFP) is a valid experimental trauma model to efficiently investigate risk factors for (analog) intrusion development in healthy samples (Holmes & Bourne, 2008; James et al., 2016). In the context of the TFP, healthy participants are exposed to film scenes with stressful or traumatic content. The exposure to the film (analog trauma) elicits intrusive symptoms, which are defined as analog intrusions (James et al., 2016; Weidmann, Conradi, Groger, Fehm, & Fydrich, 2009). They are similar in their characteristics to intrusive memories reported by PTSD patients (Holmes, 2003; Holmes & Bourne, 2008). Although watching 'traumatic' film scenes might not be comparable to experiencing a real traumatic event regarding the intensity of elicited emotional responses, the underlying cognitive information-processing mechanism (e.g. reduced contextualization) are considered to be the same (Holmes, 2003; Holmes & Bourne, 2008; Holmes, Brewin, & Hennessy, 2004; Steel, Fowler, & Holmes, 2005). The TFP is therefore suitable for investigating the development and modulation of posttraumatic stress symptoms and underlying mechanism in a healthy population (Holmes & Bourne, 2008; James et al., 2016). In our study, we were interested in measuring the development of analog intrusions, but also in assessing explicit memory aspects of the analog trauma, since the relationship between involuntary and explicit 'trauma' memories is still unclear (James et al., 2016). People who experienced e.g. sexual violence recall some details about the perpetrator (e.g. 'perpetrator's eyes'), which become conditioned cues signaling danger (Ehlers et al., 2002; Hackmann et al., 2004) and therefore might be better retrieved, while contextual information about the situation seems hardly stored and retrievable (Michael, Ehlers, Halligan, & Clark, 2005). Aspects of the trauma memory (e.g. contextual integration) can also be measured retrospectively in traumatized PTSD populations (Ehring, Kleim, & Ehlers, 2011), but explicit memory contents are difficult to compare when the trauma is not identical across participants. The TFP has the advantage that an analog trauma is standardized across participants, which facilitates the study of explicit memory aspects.

A recent study by Miedl et al. (2020) combined the trauma film with a fear conditioning paradigm by using the aversive film clips as unconditioned stimuli. They showed that stronger activation of the insula and dACC during late extinction learning predicted the development of analog intrusions within the following days. These results validate previous findings (Rattel et al., 2019) which demonstrated that fear acquisition and especially extinction learning were both linked to analog intrusion development. Further prospective fear conditioning studies also found evidence for deficits in extinction learning as a risk factor for PTSD (Guthrie & Bryant, 2006; Lommen, Engelhard, Sijbrandij, van den Hout, & Hermans, 2013; Orr et al., 2012). Besides fear conditioning, dysfunctional context processing is assumed as an additional relevant etiological factor in PTSD (Brewin et al., 2010; Brewin & Holmes, 2003; Ehlers & Clark, 2000; Liberzon & Abelson, 2016), which is however not taken into account in prospective fear conditioning studies with analog samples and PTSD patients so far. Results of cross-sectional studies with PTSD patients (Garfinkel et al., 2014; Milad et al., 2009) using a context-dependent fear conditioning paradigm as in the current study showed consistent evidence for dACC-related extinction deficits, which is also in accordance with the above-mentioned prospective study by Miedl et al. (2020) despite their differences in design and sample characteristics. Moreover, the dACC is a region which is consistently and robustly found to be involved in human fear conditioning (Fullana et al., 2016). In contrast to some others regions of the fear and extinction network, there is also some evidence that hyperactivation of the dACC seem to be a predisposing risk factor for the development of PTSD (Admon, Milad, & Hendler, 2013). The dACC is further regarded as a core region for the detection of intrusions (Crespo-García, Wang, Jiang, Anderson, & Lei, 2022).

This functional magnetic resonance imaging (fMRI) study aims to expand previous findings by investigating the relevance of context-dependent fear conditioning processes including extinction learning, but also delayed extinction recall and fear renewal for the development of analog intrusions in a healthy female sample. Therefore, participants completed a two-day context-dependent differential fear conditioning paradigm during functional magnetic resonance imaging (fMRI) with fear acquisition in context A and extinction training in context B on a first day, as well as extinction recall in the safe extinction context B and fear renewal in a novel context C one day later (see online Supplement). Skin conductance responses (SCRs) and blood oxygen level dependent responses served as main outcome measures. After the conduction of the fear conditioning paradigm, participants underwent the TFP, where they were exposed to film scenes of physical and sexual violence. Extending previous research, we assessed not only short-term analog intrusions (within one week), but also long-term intrusions (after three months) in response to the film. Moreover, we also measured explicit film memory for different content categories (context, perpetrator and victim) by questionnaire.

In addition to stronger conditioned fear responses during fear acquisition in context A, we hypothesized that difficulties in the context-dependent modulation of conditioned fear predict the development of analog intrusions. Difficulties in the context-dependent modulation of fear should be reflected in stronger conditioned fear responses during extinction learning and recall in the safe extinction context B as well as in reduced conditioned fear responses during fear renewal (missing fear renewal) in a novel context C. Stronger conditioned fear responses should be indicated by stronger conditioned SCRs and by activation in brain regions of the fear network (especially stronger activation of the dACC). With regard to the TFP, we also hypothesized that stronger analog intrusions are associated with reduced explicit context memory and a better memory for the perpetrator (which might represent a conditioned cue predicting danger).

Methods and materials

Sample and study procedure

A sample of 94 physically and mentally healthy female students with a mean age of $M = 23.24$ years (S.D. = 2.746, range: 18–31 years) was recruited via mailing lists at the local university and included in the study after screening for study in- and exclusion criteria comprising a structured clinical interview for mental disorders (see online Supplement A). This study was part of a larger project with six study days (see online Supplement B and Supplementary Fig. S1), investigating the relevance of fear

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Table 1. Characteristics and differences between women with (INT) and without (NO-INT) long-term analog intrusions

	INT ($n = 35$) M (S.D.)	NO-INT ($n = 30$) M (S.D.)	Test statistic (two-sided)
Age in years	23.57 (2.893)	22.33 (2.040)	$t(63) = 1.962$, $p = 0.054$
Relationship (yes/no)	0.60 (0.497)	0.53 (0.507)	$\chi^2(1) = 0.293$, $p = 0.588$
Usage of contraceptives (yes/no)	0.34 (0.482)	0.53 (0.507)	$\chi^2(1) = -2.390$, $p = 0.122$
Beck Depression Inventory-II (sum)	3.11 (3.579)	1.73 (3.140)	$t(63) = 1.640$, $p = 0.106$
Global Severity Index of the Symptom Checklist-90-R (sum)	0.18 (0.163)	0.12 (0.124)	$t(63) = 1.541$, $p = 0.128$
State-Trait-Anxiety Inventory (sum)	35.37 (8.303)	33.07 (6.787)	$t(63) = 1.212$, $p = 0.230$
Weeks between study day 6 and online survey	12.84 (0.587)	12.85 (0.889)	$t(63) = -0.059$, $p = 0.953$

conditioning, pattern separation, and emotion regulation for the development of analog intrusions. Data for the current study comprise the diagnostic session (day 1), the context-dependent fear conditioning paradigm (day 4 and 5), the TFP (day 5) with the assessment of analog intrusions, and explicit film memory after one week (day 6) as well as approximately three months after the TFP via an online survey. Six participants dropped out before the completion of the fear conditioning paradigm on study day 4; 14 participants were excluded from fMRI analyses (e.g. due to technical problems or excessive head movements during scanning, see online Supplement C). Three participants did not attend study day 6 for the assessment of short-term intrusions in reaction to the TFP; 1 participant was excluded due to a missing value for short-term intrusions. Regarding long-term intrusions, 65 participants responded to the 3-months-follow-up questionnaires. Therefore, the final sample regarding the prediction of short-term/long-term analog intrusions from neural correlates of context-dependent fear conditioning processes consisted of 70/56 women, respectively. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical review board. Participants gave written informed consent and received 10 Euros/h or course credits for participation.

Trauma film paradigm

During the TFP, participants viewed film clips with a total length of 11:18 min from the movie 'Irreversible' by Gaspar Noé (2002) showing physical and sexual violence. The film clips were successfully used in previous studies to induce analog intrusions (Holz, Lass-Hennemann, & Michael, 2017; Nixon, Cain, Nehmy, & Seymour, 2009; Weidmann et al., 2009). Prior to film viewing, participants were instructed to watch various film scenes within the next 11 min, to concentrate and to watch each scene completely as well as to avoid distracting themselves from the film. Furthermore, they should imagine being a witness of the scene. The audio was played via headphones and individually adjusted beforehand using a neutral audio clip. The Positive and Negative Affect Schedule (PANAS; Krohne, Egloff, Kohlmann, & Tausch, 1996) was conducted immediately before and after the trauma film as a mood manipulation check, in addition to several post-hoc film ratings (see online Supplement D). Analog intrusions and explicit film memory were measured by questionnaires and different tasks (see below and online Supplement D).

Short- and long-term analog intrusions

We used an adapted German version of the intrusion subscale of the Impact of Event Scale-Revised (IES-R; Maercker & Schützwohl, 1998) rather than the number of intrusions as the main outcome measure for short- and long-term analog intrusions, in order to investigate more sustained and potentially clinically relevant intrusion symptoms (see online Supplement D). Higher IES-R scores reflect stronger analog intrusions.

Short-term analog intrusions (assessed one week after the TFP on study day 6) referred to a period of one week following the analog trauma. As indicated by sum scores of the intrusion scale of the IES-R, three participants reported none, all others reported short-term analog intrusions within one week ($M = 8.82$, S.D. $= 6.221$, range: 0–26).

Long-term analog intrusions were assessed three months after study day 6 ($M = 12.84$ weeks, S.D. $= 0.736$) via an online-survey. During this 3-months follow-up assessment, participants retrospectively rated for the last 4 weeks (preceding the 3-months follow-up assessment) whether they had intrusive memories. The distribution of long-term analog intrusions was not well suited for applying a correlative method. The median for long-term analog intrusions (intrusion scale of the IES-R) was $Md = 1.00$, indicating a low occurrence of long-term analog intrusions in the whole sample. Therefore, the data were further analyzed by splitting the participants into two groups. After three months, nearly half of the participants ($n = 30$) reported no analog intrusions in the last 4 weeks and were post-hoc classified as the NO-INT (no intrusions) group. The other participants ($n = 35$) reported the experience of long-term analog intrusions (intrusion scale of the IES-R: $M = 4.43$, S.D. $= 4.279$, range: 1–20) and were post-hoc classified as the INT (intrusion) group. Both groups did not significantly differ in clinical variables, nor relationship status, but the NO-INT group tended to be slightly younger (see Table 1). Therefore, we entered age as a covariate in the analyses when investigating group differences. As shown in Table 1, groups did also not significantly differ in the use of hormonal contraceptives. We evaluated group differences regarding the use of hormonal contraceptives, in order to exclude that group effects in fear conditioning might be the result of the intake of contraceptives influencing sex hormones, which affect fear conditioning processes (Merz, Kinner, & Wolf, 2018; Peyrot, Brouillard, Morand-Beaulieu, & Marin, 2020).

Explicit film memory for context, perpetrator, and victim information

In order to measure the explicit film memory after one week and after three months, we developed a recognition memory questionnaire (see online Supplement E) including ten statements for each content category (context, perpetrator, victim), which should be

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classified as true or false. A sum score (number of correctly classified statements) was calculated for each category. We used correlational analyses according to Pearson (two-sided) to analyze the a priori hypothesized associations between short-term intrusions and explicit film memory. We further conducted univariate analyses of covariance (two-sided) including age as a covariate to assess the a priori hypothesized differences in explicit film memory between the INT and NO-INT group after one week and after three months, using SPSS 27 (IBM Corporation, Armonk, NY, USA).

Context-dependent fear conditioning paradigm

Experimental design

Participants completed a 2-day context-dependent differential fear conditioning paradigm (Hermann et al., 2016; Milad et al., 2007; Milad, Orr, Pitman, & Rauch, 2005) during fMRI, see online Supplementary Fig. S2 and Supplement C for more details. In short, the paradigm consisted of fear acquisition in context A and immediate extinction training in context B on one day. After approximately 24 h, retrieval testing in the extinction context B ('extinction recall') and in the novel context C ('fear renewal') took place. Pictures of different rooms (e.g. office room) served as contexts A, B and C. The lamplight colors (blue, yellow) of a desk lamp presented in each room were used as reinforced conditioned (CS+) or non-reinforced (CS−) stimuli. Electrical stimulation applied via electrodes positioned at the right middle and forefinger served as the unconditioned stimulus (UCS). Fear acquisition included 8 trials per CS type, extinction training 16 trials per CS type. Retrieval testing one day later in the safe context ('extinction recall') and in a novel context ('fear renewal') consisted of 8 trials per CS type. Each trial contained the presentation of a picture of a room (context) with a turned-off desk lamp for 3s, which was followed by the same picture with a turned-on desk lamp, which lit up blue or yellow (CS) for 6s (and was followed by a 500 ms UCS application in 5 out of 8 CS+ trials during fear acquisition).

FMRI data acquisition and analyses

Brain images were acquired with a 3-Tesla whole-body tomograph (Siemens Prisma) with a 64-channel head coil. A T2*-weighted gradient echo-planar imaging sequence (EPI, see online Supplement C) was used for assessing blood oxygen level dependent responses during all experimental phases. For preprocessing and first-level analyses as well as details regarding second-level analyses, see online Supplement C. The CS+ and CS− were contrasted for fear acquisition and for early (first 8 CS+/CS− trials) and late (last 8 CS+/CS− trials) extinction training phase. For retrieval testing in the safe and novel contexts, CS+ and CS− were contrasted for the first 4 CS+/CS− trials of each phase (early extinction/ early fear renewal). Data of 14 participants had to be excluded from fMRI analyses due to technical problems or strong movement (see online Supplement C).

For the analyses of main effects (CS+ minus CS−, $n = 74$) of the fear conditioning paradigm, see online Supplement C. Multiple regression analyses were performed during second-level analyses implemented in SPM12 (r7771) to analyze the relevance of neural activation in our regions of interests (ROI) during context-dependent fear conditioning for the development of short-term analog intrusions ($n = 70$). For the prediction of long-term analog intrusions, differences between the INT and NO-INT group in neural responses (CS+ minus CS−) in our ROIs (covariate of no interest: age) were analyzed ($n = 56$). We defined the dACC (bilaterally) as our primary ROI, as we had strong evidence for its involvement in fear conditioning processes and for its relevance for PTSD (symptom development). We conducted FWE (family-wise error) small volume correction for our primary ROI (dACC). We defined amygdala, insula, vmPFC and hippocampus as secondary ROIs. We conducted FWE small volume correction inside one mask with all secondary ROIs. For all ROI analyses, we used F tests to investigate effects in both directions for all experimental phases. For more information about ROI analyses and masks, see online Supplement C and Supplementary Fig. S5. Peak voxels surviving $p < 0.05$ (FWE, random field theory) were considered significant either for the whole brain or ROIs (small volume correction).

Skin conductance responses and analyses

SCRs were measured with Ag/AgCl electrodes filled with isotonic (0.05 M NaCl) electrolyte paste placed on the hypothenar of the left hand. Data were preprocessed and analyzed via 'trough-to-peak' analyses (Pineles, Orr, & Orr, 2009), which are described in more detail in the online Supplement. Conditioned responses were conceptualized as larger responses to the CS+ compared with CS−. SCR data were analyzed for each experimental phase in parallel to the fMRI data. Statistical analyses were conducted in SPSS 27 (IBM Corporation, Armonk, NY, USA) using non-parametric procedures due to a lack of normality of SCR data. Data of 15 participants were excluded from SCR data analyses (see online Supplement C for details).

For main effect analyses ($n = 59$), we conducted Wilcoxon-tests (see online Supplement C). In order to examine the predictive value of context-dependent fear conditioning for the development of short-term intrusions, correlational analyses according to Spearman's rho (two-sided) were performed ($n = 56$). Wilcoxon-tests (two-sided) were done to investigate group differences (INT *v.* NO-INT group) in conditioned SCRs (CS+ minus CS−) for each experimental phase ($n = 44$; $n = 22$ for each group).

Post hoc ratings

After the fear conditioning paradigm, post-hoc ratings were conducted outside the scanner to measure context recognition and UCS expectancy for the extinction context and the novel context (see online Supplement C for details).

Results

Trauma film paradigm

Mood manipulation check

Participants reported stronger negative affect after ($M = 23.58$, s.d. $= 6.898$) compared to before ($M = 10.75$, s.d. $= 1.164$) film viewing ($t(85) = 17.098$, $p < 0.001$), indicating successful induction of negative affect by the trauma film. The post-hoc film ratings also indicated high levels of concentration, stress, arousal and low positive valence during film watching (see online Supplementary Table S1).

Analog intrusions and explicit film memory

The film successfully induced intrusive symptoms as shown in Fig. 1a and online Supplementary Fig. S3. Stronger short-term intrusions predicted the development of long-term intrusions after three months: The INT group ($M = 10.66$, s.d. $= 6.394$) reported stronger short-term analog intrusions than the NO-INT group ($M = 6.41$, s.d. $= 5.068$), $t(62) = 2.897$, $p = 0.005$).

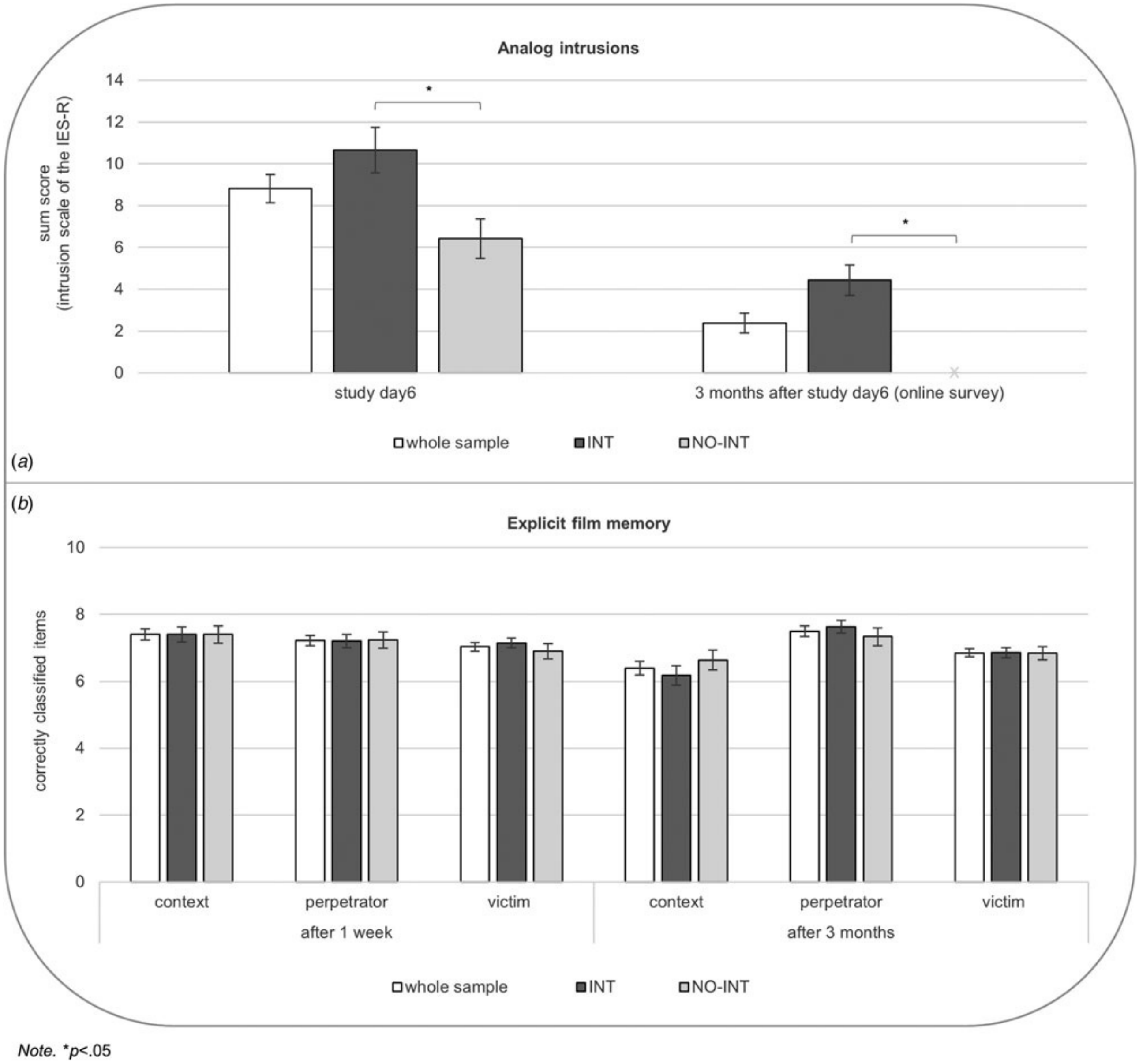

Fig. 1. Trauma film paradigm: analog intrusions and explicit film memory. (a) Analog intrusions [intrusion scale of the Impact of Event Scale-Revised (IES-R)] in response to the trauma film within one week (measured at study day 6) and after three months (measured via online survey) for the whole sample and for each group (INT: women with long-term intrusions; NO-INT: women without long-term intrusions). Error bars depict standard errors of the mean. (b) Explicit film memory (correctly classified items) for context, perpetrator, and victim information one week and three months after the trauma film paradigm for the whole sample and for women with (INT) and women without (NO-INT) long-term intrusions in response to an experimental trauma. Error bars depict standard errors of the mean.

Regarding explicit film memory in the whole sample (Fig. 1b), memory recognition scores for perpetrator, context, and victim information did not significantly differ after one week ($F_{(2,168)}$ = 2.190, $p = 0.115$), but after three months ($F_{(2,128)} = 11.650$, $p < 0.001$). The recognition memory was better for perpetrator in comparison to victim ($t(64) = 3.152$, $p = 0.002$) and in comparison to context information ($t(64) = 4.571$, $p < 0.001$). Information about the victim was also better retrieved than context information (see Fig. 1b), but this difference was not statistically significant, ($t(64) = 1.905$, $p = 0.061$).

With regard to our hypotheses, there was no significant association of short-term analog intrusions with the explicit recognition memory for context, perpetrator, and victim information (see online Supplementary Table S2). Regarding long-term intrusions, groups did not significantly differ in memory scores for context, perpetrator, or victim information after one week and after three months (see online Supplementary Table S2 and Fig. 1b).

Context-dependent fear conditioning and its predictive value for short- and long-term analog intrusions

Analyses of main effects of the fear conditioning paradigm are described and presented in the online Supplement C and Supplementary Table S3.

Short-term analog intrusions and context-dependent fear conditioning

ROI and whole brain analyses (all $p > 0.05$) showed no significant correlations between short-term analog intrusions and neural

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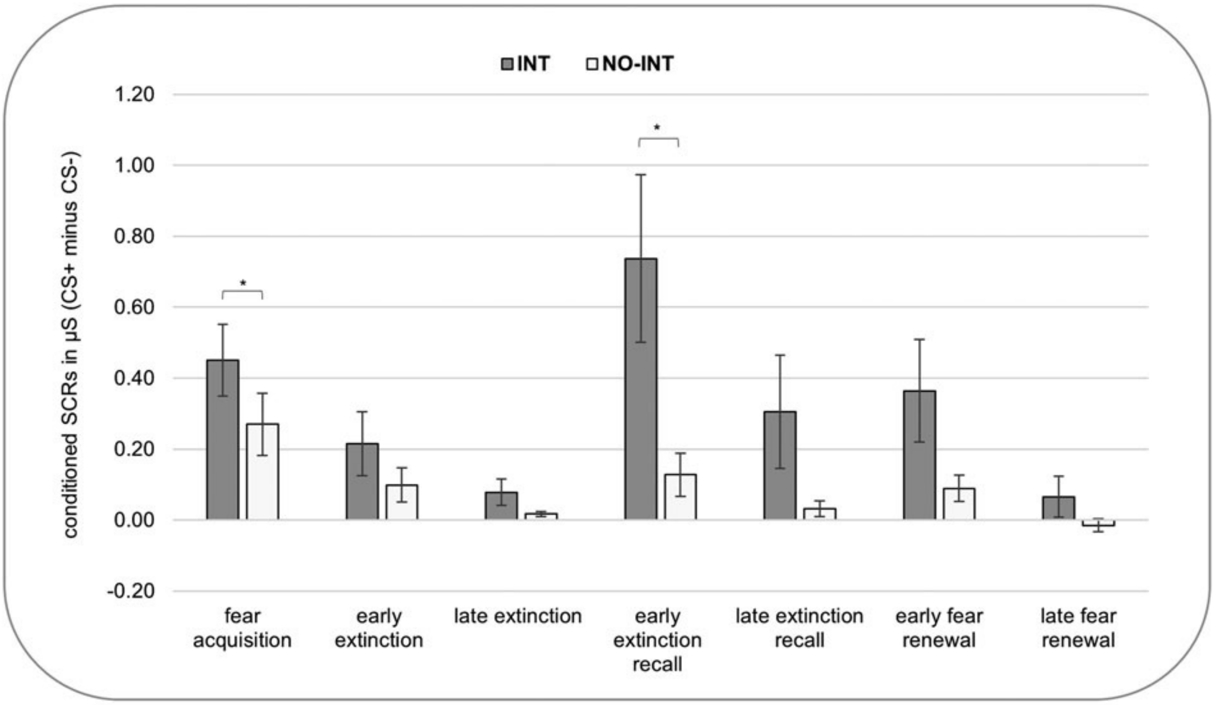

Fig. 2. Conditioned (CS+ minus CS−) skin conductance responses (SCRs) during fear acquisition in context A, (early/late) extinction learning in context B, (early/late) extinction recall in context B and (early/late) fear renewal in context C for women with (INT) and women without (NO-INT) long-term intrusions in response to an experimental trauma. Error bars depict standard errors of the mean.

responses (CS+ minus CS−) during all experimental phases. Moreover, there were no significant correlations between short-term analog intrusions and differential conditioned SCRs during fear acquisition ($r_s = 0.062$, $p = 0.648$), early extinction ($r_s = -0.077$, $p = 0.575$), or late extinction ($r_s = -0.069$, $p = 0.612$) as well as during early extinction recall ($r_s = -0.014$, $p = 0.921$) or early fear renewal ($r_s = -0.132$, $p = 0.334$).

Long-term analog intrusions and context-dependent fear conditioning

In comparison to the NO-INT group, the INT group demonstrated stronger activation of the dACC ($F = 21.11$, $p_{\text{fwecorr}} = 0.024$, MNI: $x = 14$, $y = 12$, $z = 34$) during fear acquisition. The INT group also showed stronger SCRs for CS+ compared with CS− ($z = 2.277$, $p = 0.023$; see Fig. 2). There was no group difference for responses towards the UCS after CS+ compared with the omission response after CS− ($z = 1.338$, $p = 0.181$) during the fear acquisition phase.

During early extinction, the INT group showed stronger activation of the right amygdala ($F = 46.55$, $p_{\text{fwecorr}} < 0.001$, MNI: $x = 20$, $y = -4$, $z = -12$) and the left vmPFC ($F = 26.38$, $p_{\text{fwecorr}} = 0.012$, MNI: $x = -6$, $y = 44$, $z = -6$) for CS+ compared with CS−, but not significantly stronger conditioned SCRs ($z = 1.495$, $p = 0.135$) than the NO-INT group (see Fig. 2 and 3). During late extinction, when context B should be acquired as a safety context, the INT group showed increased conditioned SCRs ($z = 1.800$, $p = 0.072$) than the NO-INT group (see Fig. 2); however, this difference was not statistically significant. There were also no significant group differences in neural activation towards CS+ compared to CS− (all ROI and whole brain analyses: $p > 0.05$).

During early extinction recall in context B, when context B should signal safety, the INT compared to the NO-INT group showed stronger conditioned SCRs ($z = 2.616$, $p = 0.009$) (see Fig. 2). Further SCR analyses revealed a stronger return of fear from late extinction training to early extinction recall for the INT than the NO-INT group ($z = 2.475$, $p = 0.013$). Within-group analyses revealed a significant return of fear on the SCR level only in the INT group ($z = 3.622$, $p < 0.001$), but not in the NO-INT group ($z = 1.758$, $p = 0.079$). On the neural level, the INT group also showed stronger activation of the dACC for the CS+ compared with the CS− than the NO-INT group, but this group difference was not statistically significant ($F = 17.46$, $p_{\text{fwecorr}} = 0.073$, MNI: $x = 0$, $y = 26$, $z = 24$).

Regarding fear renewal in context C, analyses revealed no significant group differences in neural activation (ROI and whole brain analyses, all $p > 0.05$). We could observe stronger conditioned SCRs for the INT than the NO-INT group (see Fig. 2), but this group difference was not significant ($z = 1.748$, $p = 0.080$). Further analyses regarding a stronger return of fear from late extinction recall in context B to early fear renewal in context C also revealed no group differences ($z = 0.455$, $p = 0.649$) on SCR level. Within-group analyses, however, indicated a significant return of conditioned SCRs for the NO-INT group ($z = 2.134$, $p = 0.033$), but not for the INT group ($z = 0.327$, $p = 0.744$).

Groups did not differ in UCS expectancy for context B ($F_{(1,52)} = 2.677$, $p = 0.108$, controlled for age) nor context C ($F_{(1,51)} = 0.025$, $p = 0.874$, controlled for age), as indicated by post-hoc ratings.

Discussion

As a main finding of our study, long-term analog intrusions in response to an experimental trauma were not only predicted by

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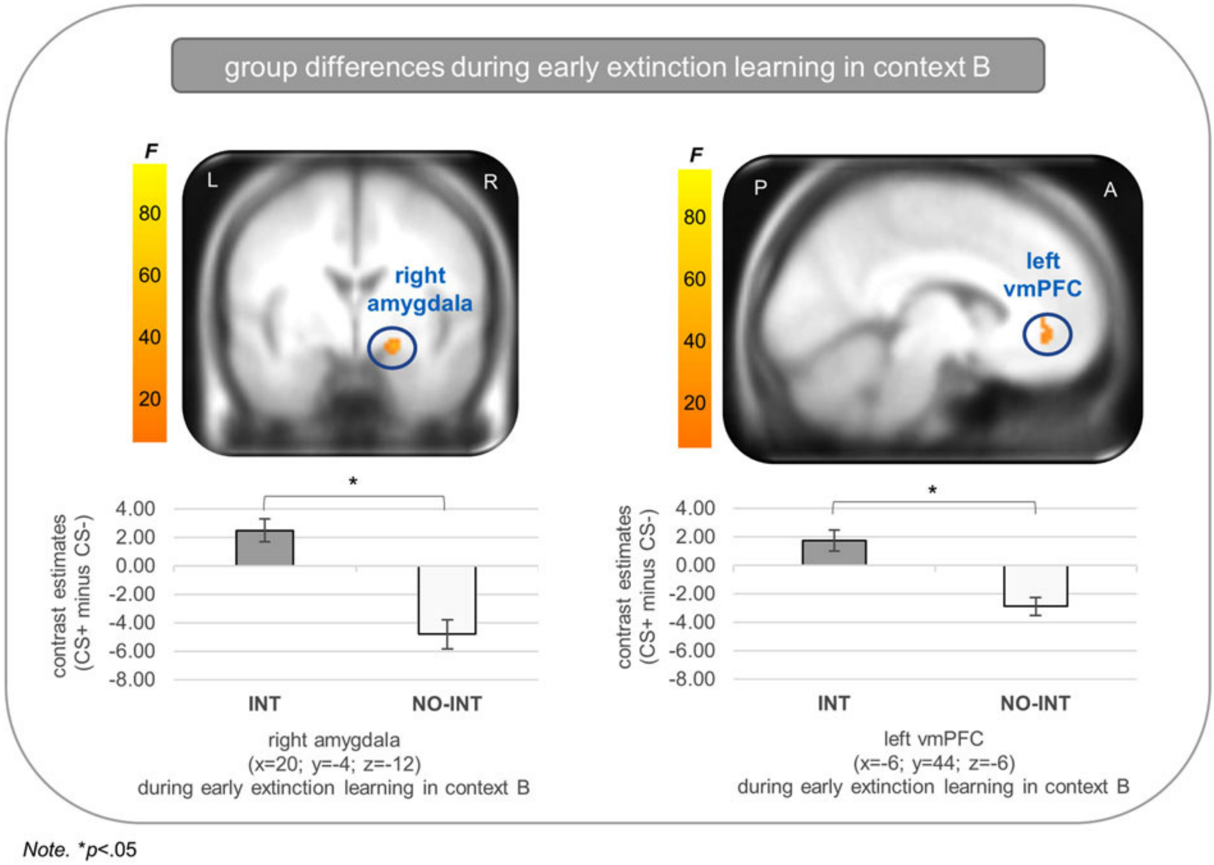

Fig. 3. Stronger activation for CS+ minus CS− in the right amygdala and the left ventromedial prefrontal cortex (vmPFC) during early extinction learning in context B in the INT (INT, women with long-term analog intrusions) compared to the NO-INT (NO-INT, women without long-term analog intrusions) group. Neural activations were superimposed on the MNI305 T1 template. All coordinates (*x*, *y*, *z*) are given in MNI space. The color bar depicts *F* values. A, anterior; *P*, posterior; L, Left; R, Right. Error bars depict standard errors of the mean.

stronger conditioned SCRs in the danger context during fear acquisition, but also in the safe context during extinction recall. Stronger conditioned fear expression, as indicated by stronger SCRs, in danger and safe contexts in women with long-term analog intrusions point to decontextualized fear memories and difficulties in the context-dependent modulation of conditioned fear to be risk factors for the development of analog intrusions. Neural findings support this interpretation, as stronger activation in fear expressing regions (e.g. amygdala, dACC) during fear acquisition in context A and during extinction learning in the safe context predicted the development of long-term analog intrusions. These findings are mainly in line with a meta-analysis, reporting increased fear expression on the neural level during fear acquisition, but also during extinction learning and extinction recall in PTSD patients (Suarez-Jimenez et al., 2019).

Stronger conditioned fear responses in a safe context during extinction learning and recall, as indicated by SCR or neural data, might be due to difficulties in using the context as a safety signal (Jovanovic, Kazama, Bachevalier, & Davis, 2012; Rougemont-Bücking et al., 2011; Sangha, Diehl, Bergstrom, & Drew, 2020). Deficits in using context information for fear modulation are proposed to be etiologically relevant risk factors for PTSD and may explain why patients with PTSD show conditioned fear responses in form of intrusions in safe contexts (Brewin & Holmes, 2003; Ehlers & Clark, 2000; Liberzon & Abelson, 2016). Considering the neural findings, stronger conditioned fear responses in the safe context in the INT compared to the NO-INT group were reflected in increased activation of the amygdala and the vmPFC during extinction learning. The amygdala is a brain region relevant for fear expression (Cheng, Knight, Smith, & Helmstetter, 2006), while the vmPFC is thought to have a modifying influence on the amygdala (Andrewes & Jenkins, 2019; Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2015). Hyperactivity of fear expressing brain regions like the amygdala might enhance the vulnerability for increased fear acquisition and fear retrieval in safe contexts. Neural findings mainly fit the findings of previous context-dependent fear conditioning studies with PTSD patients who showed stronger amygdala activation during early extinction in context B and increased dACC activation, but also hypoactivation of vmPFC and hippocampus, during extinction recall in context B (Garfinkel et al., 2014; Milad et al., 2009). Furthermore, our results of stronger fear responses in safe contexts also point to extinction difficulties as a risk factor for analog intrusions and validates previous findings (Miedl et al., 2020).

Regarding fear renewal in context C, there was no significant group difference in the return of fear, when a novel, potentially dangerous context was presented. However, in within-group analyses the INT group did not show an increase of differential conditioned SCRs from late extinction recall to early fear renewal, indicating reduced or missing fear renewal processes. A significant up-regulation of fear (from late extinction recall to early

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fear renewal) was only found on SCR level within the NO-INT group, reflecting successful context-dependent fear modulation. Reduced fear renewal was previously shown for PTSD patients and might result from problems in identifying a contextual change or in using the context for fear modulation (Garfinkel et al., 2014). Successful fear renewal is linked to stronger hippocampal activation and connectivity with structures of the fear and extinction network (Hermann et al., 2016). Difficulties in fear renewal might rather be associated with dysfunctions in specific brain areas (e.g. hippocampus, vmPFC) as a consequence of traumatic stress and resulting PTSD symptoms than a predisposing factor for the development of PTSD (Admon et al., 2013; Stark et al., 2015) or might be related to other symptoms of PTSD, as PTSD is characterized by multiple symptom clusters (American Psychiatric Association [APA], 2013).

With regard to the TFP, we were able to show that long-term analog intrusions, which rather resemble pathological intrusions known for PTSD, were predicted by short-term intrusions, which are common and not pathological *per se* after a(n) (experimental) trauma (Ehlers & Steil, 1995). This might explain why we did not find significant associations between short-term analog intrusions and electrodermal and neural indicators of context-dependent fear conditioning processes. In addition to analog intrusions, explicit memory scores regarding the trauma film were measured. Scores did not differ in the whole sample after one week, but three months after the TFP. The findings suggest that context information is forgotten more quickly over time or stored less deeply compared to information about the perpetrator in the whole sample. Against our expectations, neither context nor perpetrator information were predictive for the development of short-term nor long-term analog intrusions. Deficits in the storage and retrieval of contextual information of the traumatic situation might therefore be no predisposing factors for the development of (analog) intrusions. However, our results and the interpretation of them are limited as they depend on the quality of the questionnaire, which was newly developed in the context of the current study and has not yet been validated. In general, studying different memory aspects in response to an experimental trauma might help to improve prevention and treatment of memory dysfunctions in PTSD (Al Abed et al., 2020; Desmedt, 2021).

The current study has several limitations: the findings were based on a healthy female sample and cannot be generalized to other genders or clinical populations. Regarding the TFP, the questionnaire for explicit film memory was developed for this study and used for the first time. Furthermore, analyses of main effects of the context-dependent fear conditioning paradigm (see online Supplement C) revealed a significant recall of conditioned fear in the novel, but also in the safe extinction context, which reflects a missing extinction recall in the whole sample. Return of fear in a safe context can be a result of immediate extinction training after fear acquisition, promoting a stronger return of fear (Merz, Hamacher-Dang, & Wolf, 2016).

In sum, the findings of our study indicate that increased conditioned fear responses during extinction learning and recall in a safe context (but also during fear acquisition) are significant predictors for the development of long-term intrusions in response to an experimental trauma. Stronger conditioned fear expression in safe contexts was indicated by stronger SCRs or stronger activation in fear expressing brain regions (e.g. amygdala). Hyperactivation of fear expressing regions is regarded as a risk factor for PTSD (Admon et al., 2013; Stark et al., 2015) and may contribute to decontextualized fear memories and extinction deficits, which are considered as etiologically relevant factors for the development of posttraumatic stress symptoms (Ehlers & Clark, 2000; Liberzon & Abelson, 2016; Miedl et al., 2020). Reduced fear renewal, however, was no significant predictor of intrusion development. Findings of reduced fear renewal in PTSD (Garfinkel et al., 2014) might therefore rather be a consequence of traumatic stress and resulting PTSD symptoms than a precondition of the disorder or might be related to other symptoms of PTSD than intrusions.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723001125

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Authors' contributions. **Marie K. Neudert:** Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Writing – Original Draft, Visualization. **Axel Schäfer:** Software, Formal Analysis, Writing – Review & Editing. **Raphaela I. Zehtner:** Conceptualization, Investigation, Writing – Review & Editing. **Susanne Fricke:** Investigation, Writing – Review & Editing. **Rosa J. Seinsche:** Investigation, Writing – Review & Editing. **Rudolf Stark:** Writing – Review & Editing, Supervision. **Andrea Hermann:** Conceptualization, Methodology, Writing – Review & Editing, Project Administration, Supervision.

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Conflict of interest. The authors declare no conflict of interest.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Supplemental Information

Decontextualized fear memories? Stronger conditioned fear responses during extinction learning and extinction recall in a safe context predict the development of long-term analog intrusions

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Supplementary Materials

A) **Participants: Study in- and exclusion criteria and sample size**
B) **Study Procedure**
C) **Context-dependent fear conditioning paradigm**
D) **Trauma film paradigm**
E) **Questionnaire regarding explicit film memory**

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A) Participants: Study in- and exclusion criteria and sample size

The final sample consisted of 94 right-handed healthy female students who were recruited via the mailing list of the local university and screened via telephone, before they conducted a comprehensive examination appointment on study day 1, in order to check study in- and exclusion criteria. Participants had to be female, between 18 and 35 years old, right-handed as assessed by the Edinburgh Inventory of Handedness (Oldfield, 1971), and had to speak and understand German at a native language level. Further study exclusion criteria were MRI contraindications, the intake of psychoactive or other potentially confounding substances (current and/or regular drug use in the past), color blindness, a current or past psychotherapeutic/psychiatric treatment, or a medical treatment due to an acute or severe chronic physical disease. In order to assess mental health, a trained psychologist conducted the Diagnostic Interview for Mental Disorders (DIPS) for DSM-5 (Margraf, Cwik, Pflug, & Schneider, 2017; Margraf, Cwik, Suppiger, & Schneider, 2017) and the Life-Event-Checklist in combination with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Cwik & Woud, 2015). The DIPS covers the most important and prevalent mental disorders (e.g., affective, anxiety, obsessive-compulsive, somatoform, and eating disorders as well as disorders associated with psychotropic substances and dependent behavior, including screenings for psychoses and suicidal behavior). It does not comprise less prevalent disorders or personality disorders (except borderline personality disorder) (Margraf et al., 2017). Participants were excluded from further study participation, if they fulfilled the diagnosis of a current or past DSM-5 disorder according to the DIPS. Further study exclusion criteria were the experience of a traumatic event within the last four weeks or personal experiences with physical or sexual violence. Participants were informed that they could terminate the study at any point without negative consequences as well as to see a film clip of physical and sexual violence in the context of the study.

The sample size of an a priori conducted power analysis for the main study question regarding analog intrusions and context-dependent fear conditioning (linear regression analysis with one predictor (Power ($1-\beta$)=0.80, α=0.05) with an expected medium effect of

ρ=.3) was N=67. In order to compensate for an estimated drop-out rate of 20% and drop-outs in main outcome measures, the sample size was post-hoc raised to N=94.

B) Study Procedure

The whole project consisted of six study days within four weeks (for an overview see Supplementary Figure 1). On study day 1, each participant underwent an interview with a trained psychologist to screen for mental and physical health and further study in- and exclusion criteria (see ‘Participants’). Participants were further asked about sociodemographic variables and filled in questionnaires regarding clinical variables like depression status (measured with the Beck Depression Inventory-II (BDI-II; Hautzinger, Keller, & Kühner, 2006)) and mental stress (measured with the Global Severity Index (GSI) of the Symptom Checklist-90-R (SCL-90-R; Franke, 1995)). Furthermore, PTSD symptoms in reaction to the most aversive life event and to a traumatic event if existing were assessed by questionnaire.

On study day 2 (1–3 days later), participants conducted the Mnemonic Similarity Task (MST) for objects and scenes (Stark & Stark, 2017; Stark, Yassa, Lacy, & Stark, 2013) as well as a neuropsychological test battery to measure executive functioning. At the end of study day 2, participants’ emotion regulation abilities and personality traits were measured by questionnaire. Trait anxiety, for example, was assessed with the State-Trait-Anxiety Inventory (Spielberger, 1983).

On study day 3 (conducted 7–10 days after study day 1), participants underwent the first part of an emotion regulation paradigm (Hermann, Neudert et al., 2020), while the second part of the emotion regulation paradigm took place at the beginning of study day 4 (6–8 days after day 3). On study day 4, after finishing the emotion regulation paradigm, participants started with the fear conditioning paradigm (see Supplement C for further information). They completed the fear acquisition and the extinction training phase. Approximately 24 hours later (on study day 5), participants conducted the second part of the fear conditioning paradigm including retrieval testing in the safe extinction context B (extinction recall) and in the novel context C (fear renewal). Afterwards, participants filled in several questionnaires and rated items regarding emotional state, stress, emotion regulation, sleep and social empathy as well as social support. Next, the trauma film paradigm was conducted. Analog intrusions and memory aspects with regard to the trauma film were measured daily via an online survey between study day 5 and day 6. After one week, on study 6, (short-term) analog intrusions as well as explicit film memory was assessed by questionnaires and different tasks (see supplement D for further information). At the end of study day 6, participants were informed to be contacted after three months, in order to measure long-term effects of the study via online survey. Finally, they were reimbursed for study participation (10 Euros/h; course credits).

C) Context-dependent fear conditioning paradigm

Experimental design

A 2-day context-dependent differential fear conditioning paradigm adapted from previous studies (Hermann, Stark et al., 2020; Hermann, Stark, Milad, & Merz, 2016; Milad et al., 2007; Milad et al., 2009) was conducted. It consisted of fear acquisition in context A and extinction training in context B on a first day, as well as extinction recall in context B and fear renewal in a novel context (context C) one day later. Pictures of different rooms (office room, conference room, and a room with a shelf) were used as contexts A, B and C. The assignment of contexts to experimental phases was counterbalanced and pseudorandomized across participants. Each room showed the same initially turned-off desk lamp. The desk lamp lit up either in blue or yellow, whereby the lamplight colors served as conditioned stimuli (CS). Via a mirror mounted to the head coil, participants were able to watch the pictures presented on a 32' LCD monitor (NordicNeuroLab Inc., Milwaukee, WI, USA) at the end of the scanner (visual field=28°). Electrical stimulation (1ms pulses with 50Hz for a duration of 500ms) applied via electrodes (Coulbourn Transcutaneous Aversive Finger Stimulator (E13-22)) and positioned at the second and third fingertip of the right hand was used as unconditioned stimuli (UCS). Before the experiment started, the intensity of electrical stimulation was individually adjusted to a level, which was reported as unpleasant but not painful by the participant. The intensity of electrical stimulation was set on average to *M*=1.68mA (*SD*=0.61, range=0.6–4.0mA).

Fear acquisition took place in context A. Each trial began with the presentation of a white fixation cross on a black background (jittered between 0.625 and 2.500s). Then, a picture of a room with a turned-off desk lamp (representing the context) appeared for 3s followed by the same picture with a turned-on desk lamp shining blue or yellow (CS) for 6s. Participants received an electrical stimulation (UCS) after CS+ offset in 62.5% of the trials for a duration of 500ms. The other lamplight color (CS-) was never followed by an electrical stimulation and therefore represented a safety stimulus that should elicit an omission response. The assignment of lamplight color to CS type condition (CS+ or CS-) was pseudorandomized and counterbalanced across individuals. After CS offset, a white fixation cross on a black background appeared up to a total trial duration of 20s. The fear acquisition phase consisted of 16 trials (8 trials for each CS type) arranged in two blocks. Each block comprised half of the CS trials and included the same number of CS+ and CS- trials. The first two and last two trials of the fear acquisition phase consisted of one CS+ and one CS-, respectively. The other CS were presented in a pseudorandomized order (no more than 2 CS+/CS- consecutively). In order to enhance fear learning, the first CS+ during fear acquisition was always reinforced. Additionally, the last CS+ was reinforced, in order to prevent premature extinction learning during the fear acquisition phase. For the fear acquisition phase, participants were instructed about the content and procedures of the trials. Their task was to watch the presentation attentively. They were informed about the possibility to receive an electrical stimulation at the end of each presentation of the turned-on desk lamp or not. They were also told that there might be a relationship such that one color is sometimes followed by an electrical stimulation, while this is not the case for the other desk lamp color. Immediately after the fear acquisition phase, participants were asked via headphones about the discovered relationship between lamplight color and electrical stimulation. Moreover, they were informed about the correct relationship, in order to make all participants aware of CS-UCS contingencies, especially if they could not report the correct relationship (n=4). In addition, they rated how often the electrical stimulation followed after CS+ offset (open answer option: M=6.13, SD=1.61, range: 3–10) and how unpleasant they felt during the first and last electrical stimulation on a 9-point Likert scale with answer options ranging from ‘not unpleasant’ to ‘very unpleasant’ (first stimulation: M=7.54, SD=1.16; last stimulation: M=6.43, SD=1.14).

During extinction training in context B, the CS were presented 32 times (16 trials for each CS type) in two blocks without subsequent UCS, in order to extinguish the conditioned fear response. Each block contained half of the CS trials and included the same number of CS+ and CS- trials. The CS were again presented in a pseudorandomized order (no more than 2 CS+/ CS- consecutively) except the first two CS trials of the extinction training phase that consisted of one CS+ and one CS-, respectively. In order to avoid the idea of reversal of CS contingencies, the instruction was given that the relationship between lamplight color and electrical stimulation was going to be stable over the experiment, meaning that if a lamplight color was safe (not followed by an electrical stimulation), it would always be safe. If the lamplight color was sometimes followed by electrical stimulation, it might or might not be followed by electrical stimulation.

One day later (approximately 24 hours), extinction recall in context B and fear renewal in a novel context (context C) took place (each phase: 8 trials for each CS type). The trials for extinction recall and fear renewal were each arranged in two blocks, each consisted of four CS+ and four CS- trials, which were presented in a pseudorandomized order (no more than 2 CS+/ CS- consecutively) except the first two CS trials of each phase that included the presentation of one CS+ and one CS-, respectively. Participants received the same instruction as for the extinction training phase. The finger electrodes were again positioned at the fingertip and they were instructed that if they receive electrical stimulation today, the intensity will be identical to the day before.

FMRI data acquisition and analyses

Functional and anatomical images were acquired using a 3-Tesla whole-body tomograph (Siemens Prisma) with a 64-channel head coil. In order to receive information for unwarping of B0 distortions, a gradient echo field map sequence was conducted before the functional runs on each day. Functional image acquisition consisted of 152 volumes for fear acquisition, 280 volumes for extinction training as well as 280 volumes for extinction recall and fear renewal using a T2*-weighted gradient echo-planar imaging sequence (EPI) with 42 slices covering the whole brain (slice thickness =3mm; 0.75mm gap; descending slice order; TE=30ms; TR=2.5s; flip angle=81°; field of view=220×220mm; matrix size =110×110; PAT mode GRAPPA, acceleration factor PE 2). The first three volumes were excluded from analyses because of an incomplete steady state of magnetization. For structural imaging, T1-weighted sagittal images were registered (MPRAGE: 0.94mm slice thickness) which were needed for the normalization procedure. All neuroimaging data were analyzed using

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Statistical Parametric Mapping (SPM12, r7771, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (R2019a; Mathworks Inc., Sherborn, MA, USA). Preprocessing of the data consisted of unwarping and realignment (b-Spline interpolation), slice time correction, co-registration of functional data to each participant's anatomical image, segmentation of the anatomical image into different tissue types and normalization to the standard space of the Montreal Neurological Institute (MNI) brain. Furthermore, smoothing with an isotropic three-dimensional Gaussian filter with a full-width at half maximum (FWHM) of 6mm was conducted. Five participants were excluded from data analyses due to a framewise displacement (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012) of more than 0.5mm in at least 15% of the volumes of one scanning session (fear acquisition, extinction training, retrieval testing). After preprocessing, first level models were generated separately for fear acquisition, extinction training and retrieval testing (extinction recall and fear renewal). For fear acquisition, the first level model included the following regressors: context alone, blocks of eight trials for CS+ and CS- and blocks of UCS and UCS omission-trials (noUCS-trials). For extinction learning, the regressors consisted of context alone and blocks of eight trials of CS+ and CS- for early/late extinction training. For retrieval testing the model contained the regressor context alone as well as blocks of four trials of CS+ and CS- as regressors for early/late extinction recall and for the early/late renewal phase. The six movement parameters from the realignment step as well as one regressor for each volume with a framewise displacement >0.5mm (Power et al., 2012) were added as regressors of no interest in the first-level models. All regressors of interest were modelled based on a stick function convolved with the canonical hemodynamic response function in the general linear model, without specifically modeling the durations of the different events (i.e. event-related design). Furthermore, a high-pass filter of 128s was used for filtering voxel-based time series and autocorrelation of errors was controlled by an AR(1) process. Contrasts between the CS+ and CS- were calculated on an individual level for fear acquisition, for extinction training (first 8 compared with last 8 CS trials), as well as for early extinction recall and early renewal (first 4 CS trials, respectively). Due to early study drop-out (*n*=6), 88 participants conducted the fear conditioning paradigm. Data of *n*=14 participants were excluded from fMRI analyses because of technical problems during scanning or artifacts (*n*=9) or strong head movement during scanning (*n*=5), resulting in a sample size of *n*=74 for analyses of main effects.

For the analyses of main effects (CS+ minus CS-) of the fear conditioning paradigm, *F*-Tests were performed for each experimental phase during second-level analyses implemented in SPM 12 (r7771). For main effect analyses, we conducted FWE small volume correction for a combined mask of all regions of interest (ROI) to correct for multiple testing. ROIs for the analyses of main effects (CS+ minus CS-) were amygdala, dACC, hippocampus, insula, and vmPFC. Probability masks for amygdala, insula, and hippocampus were taken from the current 'Harvard-Oxford Cortical and Subcortical Structural Atlases' provided by the Harvard Center for Morphometric Analysis (http://www.cma.mgh.harvard.edu/) with a probability threshold of 0.5 included in the FSL software package (http://www.fmrib.ox.ac.uk/fsl/). Masks for the dACC and vmPFC were constructed with the MARINA software package (Walter, 2002) and used in previous fear conditioning studies (Hermann et al., 2016; Hermann, Stark et al., 2020). For exploratory whole brain analyses, the significance threshold was set to $p=.05$ on voxel-level corrected for multiple testing (family-wise error (FWE) correction); the minimal cluster size (k) for exploratory whole brain analyses was set to 10 voxels. The peak voxels of the whole brain (WB) analyses were labeled based on the Harvard-Oxford Cortical (Lateralized) and Subcortical Structural Atlas and the Automated Anatomical Labeling Atlas 3.

Skin conductance responses and analyses

SCRs were measured during all experimental phases using Ag/AgCl electrodes filled with isotonic (0.05M NaCl) electrolyte medium positioned hypothenar at the left hand. Data were recorded with a sampling rate of 1000Hz. For preprocessing and data analyses Ledalab 3.4.4 written in MATLAB was used, which is available online (www.ledalab.de). The raw skin conductance data were down sampled with a sampling rate of 10Hz, and smoothed with a Gaussian kernel of 32mm. For checking data quality, a manual data inspection was conducted. If technical artifacts were visible in data, the affected data section was corrected via the manual interpolation of Ledalab. The data were analyzed via ‘trough-to-peak’-analyses (Pineles, Orr, & Orr, 2009). The entire interval response (EIR) was defined as the largest difference between a minimum within a defined time window and the directly following maximum. For CS responses, the time window was set to 0.8–6s after CS onset, while for UCS responses it was set to 0.8–2.5s after UCS onset. Conditioned responses were defined as larger response magnitudes in reaction to the CS+ than to the CS-.

Participants excluded from fMRI analyses were also excluded from the main SCR data analyses, but not vice versa. SCR data had to be discarded because of non-responding during fear acquisition (less than two SCRs >0.02µs in reaction to the UCS after CS+ (*n*=12)), technical problems during measurement (*n*=1), or missing data (*n*=2), reducing the sample size of *n*=74 to *n*=59 for SCR analyses of the main effects of the fear conditioning paradigm.

Post-hoc ratings

After the experimental phases, a post-hoc rating was conducted outside the scanner to measure context recognition and UCS expectancy for the extinction context and the novel context. The memory for the contexts (=rooms) was tested by presenting the participants pictures of six different rooms. They had to report which room(s) they saw ‘only yesterday’ (≙ acquisition context A), ‘today and yesterday’ (≙ extinction context B), or ‘only today’ (≙ novel context C) and were further asked in which room(s) they had ever received an electrical stimulation after CS offset. For measuring context recognition, a recognition score was calculated for the acquisition, extinction and novel context as well as for false rooms, and an overall sum score for correct context assignment was calculated. The majority of individuals (*n*=62) were able to correctly classify all presented context pictures.

After the memory test, participants saw pictures of the three rooms (context A, B, C) presented during the experimental phases. They had to rate valence, arousal and fear (not reported here) when the desk lamp was turned off (no CS condition), and when shining blue and yellow (CS condition) for each room on a 9-point Likert scale. To examine UCS expectancy in the different contexts, they also rated how certain they had been that an electrical stimulation immediately appeared in the extinction (context B) and in the novel context (context C) on a 9-point Likert scale (answer options ranging from 'sure' to 'unsure that the electrical stimulation followed'), respectively.

Main effects of the context-dependent fear conditioning paradigm

Fear acquisition in context A

During fear acquisition individuals showed stronger SCRs to the CS+ compared with CS- (z=6.487, p<.001) as well as to the UCS after CS+ compared with the omission response after CS- (z=6.680, p<.001), indicating successful fear conditioning. On the neural level, fear acquisition (CS+ minus CS-) in context A resulted in increased activation in bilateral insula, left amygdala, left dACC, and bilateral vmPFC (see Supplementary Table 3). Moreover, whole brain analyses revealed stronger differential conditioned activation in the caudate and left supplementary motor area as well as in the right thalamus and right cerebellum during fear acquisition. In addition, stronger differential conditioned neural activation was found in the frontal and central opercular cortex regions, in the precuneus as well as in the pre- and postcentral and supramarginal gyrus (see Supplementary Table 3).

Extinction learning in context B

There was a decrease in differential conditioned SCRs from early to late extinction training (z=3.248, p=.001), indicating successful extinction learning. Stronger SCRs for CS+ compared with CS- were found during early (z=4.014, p<.001), as well as during late extinction (z=3.740, p<.001), pointing towards conditioned fear expression even during late extinction learning (see Supplementary Figure 4). However, a further post-hoc test comparing the last CS+ and the last CS- trial of the extinction training phase revealed no significant differences in SCRs (z=1.207, p=.227). On the neural level, there was no significant de- or increase of differential conditioned activation from early to late extinction training in either whole brain or ROI analyses (see Supplementary Table 3).

Extinction recall in context B

Analyses showed stronger SCRs for CS+ compared with CS- during early extinction recall (z=4.613, p<.001, see Supplementary Figure 4) and an increase in differential conditioned SCRs from late extinction to early recall (z=3.934, p<.001), reflecting spontaneous recovery in the safe extinction context. Extinction recall in context B (CS+ minus CS-) was associated with stronger activation in the bilateral insula and left dACC (ROI; see Supplementary Table 3). Moreover, exploratory whole brain analyses showed stronger activation in the brain-stem, in the left caudate and right thalamus as well as in the left central opercular cortex towards CS+ compared with CS-. Reduced activation towards CS+ compared with CS- was exhibited in the right precentral gyrus during extinction recall for exploratory whole brain analyses (see Supplementary Table 3).

Renewal in context C

During early fear renewal, stronger SCRs were found for the CS+ compared with the CS- (z=4.799, p<.001). There was on trend level an increase in differential conditioned SCRs from late extinction recall to early renewal (z=1.769, p=.077), indicating a return of fear in the novel context (see Supplementary Figure 4). Early fear renewal (CS+ minus CS-) resulted in increased activation in the bilateral insula and the left dACC and in reduced activation in the left vmPFC (ROI; see Supplementary Table 3). Exploratory whole brain analyses revealed stronger activation in the frontal opercular cortex towards CS+ compared with CS- during fear renewal (see Supplementary Table 3).

D) Trauma film paradigm

During the paradigm, 88 participants (study dropout, *n*=6) were exposed to aversive film clips of the movie 'Irreversible' by Gaspar Noé with explicit depiction of scenes of physical and sexual violence. Respiration, heart rate variability and electrodermal responses were recorded during film viewing and during a resting state period prior to film viewing. As a mood manipulation check, the Positive and Negative Affect Schedule (PANAS; Krohne, Egloff, Kohlmann, & Tausch, 1996) was immediately completed before and after film viewing. Participants also conducted a post-hoc film rating (results are presented in Supplementary Table 1). It also showed that none of the participants knew the film. After the post-hoc film rating, participants conducted a monitoring task to assess intrusive memories shortly after film watching. Participants had to close their eyes and to press a button on a key board with their right index finger every time they experienced an intrusive film memory. The button should be pressed as long as the intrusion lasted. In order to get an impression about the development of analog PTSD symptoms within the following week, participants were asked at the end of study day 5 to complete an online survey every evening from 6 pm until midnight of the respective day between study day 5 and 6 (results are presented in Supplementary Figure 3). They received the links for the online survey via email. Intrusive symptoms were measured with an adapted version of the intrusion scale of the Impact of Event-Scale Revised (IES-R; Maercker & Schützwohl, 1998). The instruction part and items of the intrusion subscale of the IES-R were adapted to the analog trauma and consisted of seven items (e.g. 'Even without intending it, I had to think about the film clips.'). Answers could be given on a 4-level scale (*not at all '0', seldom '1', sometimes '3', often '5'*). A sum score was calculated. Furthermore, the number of analog intrusions were assessed by an open question ('How many film intrusions did you have today in total? *Intrusions are sudden, spontaneously occurring, and uninitiated memories of the film scenes from the study, which can be very vivid and consist of images, sounds, words, phrases, or thoughts and feelings (you had during the film) or a combination thereof.'*). The Memory Characteristics Questionnaire (MCQ; Hagenaars, van Minnen, Hoogduin, & Verbraak, 2009) was also used to measure characteristics (re-experiencing and disorganization) of the film memory. Beside analog PTSD symptoms, emotional state, sleep (quality and hours) and the number of social contacts were also assessed each day by single items. In addition, participants who reported intrusions were asked about the content of the intrusion(s) (open answer) as well as the emotional state (valence, arousal, stress) during intrusive memories.

After one week (study day 6), 85 participants returned to the laboratory and again rated analog intrusion symptoms (IES-R, number of intrusions) and memory aspects (MCQ) within the last week, in order to have standardized measures and values for short-term analog PTSD symptoms for each participant. The degree of distress through the film during the last week was also rated (rating scale: 0 to 100 percent). Participants were also asked about emotion regulation, emotional state, sleep characteristics, social contacts during the last week by questionnaire or single items. Afterwards, participants underwent the intrusion monitoring task in the same setting and manner as on study day 5. Afterwards, participants completed the recognition memory questionnaire regarding explicit film memory (described in the method section of the article; see supplement E) as well as a questionnaire regarding disorganization of the film (chronical order of film actions) which included ten sentences. Participants should arrange the 10 sentences chronologically according to the sequence of actions in the film. Afterwards, participants also completed a recognition memory task for film scenes developed in analogy to the test phase of the MST (Stark et al., 2013), in order to measure patten separation/completion processes with regard to the film. Participants were informed to see pictures of film scenes which should be categorized as ‘old’, ‘similar’ or ‘new’ to the film clips they saw during the trauma film paradigm. Study day 6 ended with a short open talk to check impairments in daily life functioning and to offer psychological assistance in the case of high distress due to the film, which was not required by any participant who attended study day 6 (N=85). Two participants (*n*=2) had quit the study during the trauma film paradigm on study day 5 due to high distress. An appointment was made with those participants to check the level of distress through the film and to offer psychological assistance, which was also not required by them. One participant (*n*=1) was not able to attend study day 6 due to another appointment. Data of one participant (*n*=1) had further to be excluded from analyses regarding short-term intrusions due to a missing value in the IES-R. Thus, data regarding short-term intrusions was available from 84 participants. At the end of study day 6, participants were also informed to be contacted after three months for a further online survey to investigate long-term effects of the study. The online survey after 3 months was completed by 65 participants. It included the above-mentioned items and questionnaires for the assessment of analog PTSD symptoms within the last four weeks. Moreover, the questionnaires regarding explicit film memory and film disorganization which were already assessed at study day 6 were also included in the survey as a follow-up assessment. Furthermore, participants filled in a questionnaire regarding emotion regulation during the last four weeks and were asked some questions about stimuli or experimental conditions of paradigms used in the study. Participants who had completed the online surveys each day within one week between study day 5 and day 6 as well as after three months entered the drawing for cash vouchers (20 euros; 10 percent chance of winning).

SUPPLEMENTAL INFORMATION

E) Questionnaire regarding explicit film memory (English translation)

For each statement, please tick whether it is 'true' or 'false' with regard to the content of the film. If you are unsure, please choose the answer option you think is most likely to be true.

The first part of the statements relates to the woman who was the victim of rape in the film.

1.	The woman was wearing a dress.	**TRUE**	FALSE
2.	The woman had her hair tied in a braid.	**TRUE**	FALSE
3.	The woman had dark hair.	**TRUE**	FALSE
4.	The woman was carrying a handbag.	**TRUE**	FALSE
5.	The woman had a tattoo.	TRUE	**FALSE**
6.	The woman was wearing sneakers.	TRUE	**FALSE**
7.	The woman had a jacket with her.	**TRUE**	FALSE
8.	The woman was wearing a necklace.	TRUE	**FALSE**
9.	The woman had a ring on her finger.	TRUE	**FALSE**
10.	The woman was wearing earrings.	TRUE	**FALSE**

The second part of the statements relates to the man who raped the woman in the film.

1.	The man was wearing a black shirt.	TRUE	**FALSE**
2.	The man had dark hair.	**TRUE**	FALSE
3.	The man was wearing sneakers.	TRUE	**FALSE**
4.	The man was alone in the underpass at the beginning.	TRUE	**FALSE**
5.	The man was wearing a suit.	**TRUE**	FALSE
6.	The man had an earring on one ear.	TRUE	**FALSE**
7.	The man was wearing a bracelet.	**TRUE**	FALSE
8.	The man had a tattoo.	TRUE	**FALSE**
9.	The man had a ring on his finger.	**TRUE**	FALSE
10.	The man was wearing glasses.	TRUE	**FALSE**

The third part of the statements relates to spatial and temporal details of the film.

1.	The light in the underpass flickered.	**TRUE**	FALSE
2.	The illuminated sign shown said 'underpass'.	TRUE	**FALSE**
3.	There was trash on the ground in the underpass.	**TRUE**	FALSE
4.	Two people entered the underpass together during the rape and left it unnoticed.	TRUE	**FALSE**
5.	The walls in the underpass were painted in a shade of blue.	TRUE	**FALSE**
6.	Graffiti was partially present on the ceiling of the underpass.	**TRUE**	FALSE
7.	The underpass was accessible from two sides.	**TRUE**	FALSE
8.	There was a trash can in the underpass.	TRUE	**FALSE**
9.	An information sign hung at the exit of the underpass.	TRUE	**FALSE**
10.	Rails of a train station could be seen above the underpass.	TRUE	**FALSE**

Note: The correct answer is presented in bold type for each item.

SUPPLEMENTAL INFORMATION

GERMAN VERSION

Bitte kreuzen Sie für jede Aussage an, ob diese in Bezug auf den Inhalt des Films „wahr“ oder „falsch“ ist. Wenn Sie sich unsicher sind, entscheiden Sie sich bitte für die Antwortoption, die Sie für am wahrscheinlichsten halten.

Der erste Teil der Aussagen bezieht sich auf die Frau, die im Film Opfer einer Vergewaltigung wurde.

1.	Die Frau trug ein Kleid.	WAHR	FALSCH
2.	Die Frau hatte ihre Haare zu einem Zopf gebunden.	WAHR	FALSCH
3.	Die Frau hatte dunkle Haare.	WAHR	FALSCH
4.	Die Frau hatte eine Handtasche dabei.	WAHR	FALSCH
5.	Die Frau hatte ein Tattoo.	WAHR	FALSCH
6.	Die Frau hatte Turnschuhe an.	WAHR	FALSCH
7.	Die Frau hatte ein Jäckchen dabei.	WAHR	FALSCH
8.	Die Frau trug eine Halskette.	WAHR	FALSCH
9.	Die Frau hatte einen Ring am Finger.	WAHR	FALSCH
10.	Die Frau trug Ohrringe.	WAHR	FALSCH

Der zweite Teil der Aussagen bezieht sich auf den Mann, der im Film die Frau vergewaltigte.

1.	Der Mann trug ein schwarzes Hemd.	WAHR	FALSCH
2.	Der Mann hatte dunkle Haare.	WAHR	FALSCH
3.	Der Mann hatte Turnschuhe an.	WAHR	FALSCH
4.	Der Mann war zu Beginn alleine in der Unterführung.	WAHR	FALSCH
5.	Der Mann trug einen Anzug.	WAHR	FALSCH
6.	Der Mann hatte einen Ohrring an einem Ohr.	WAHR	FALSCH
7.	Der Mann trug ein Armband.	WAHR	FALSCH
8.	Der Mann hatte ein Tattoo.	WAHR	FALSCH
9.	Der Mann hatte einen Ring am Finger.	WAHR	FALSCH
10.	Der Mann trug eine Brille.	WAHR	FALSCH

Der dritte Teil der Aussagen bezieht sich auf räumliche und zeitliche Details des Films.

1.	Das Licht in der Unterführung flackerte.	WAHR	FALSCH
2.	Auf dem gezeigten Leuchtschild stand „underpass“.	WAHR	FALSCH
3.	In der Unterführung lag Müll am Boden.	WAHR	FALSCH
4.	Zwei Personen betraten gemeinsam die Unterführung während der Vergewaltigung und verließen diese unbemerkt wieder.	WAHR	FALSCH
5.	Die Wände in der Unterführung waren in einem Blauton gestrichen.	WAHR	FALSCH
6.	An der Decke der Unterführung waren Graffitis teilweise vorhanden.	WAHR	FALSCH
7.	Die Unterführung war von zwei Seiten begehbar.	WAHR	FALSCH
8.	Ein Mülleimer befand sich in der Unterführung.	WAHR	FALSCH
9.	Ein Informationsschild hing am Ausgang der Unterführung.	WAHR	FALSCH
10.	Oberhalb der Unterführung sah man Schienen eines Bahnhofs.	WAHR	FALSCH

SUPPLEMENTAL INFORMATION

Supplementary Table 1

Post-hoc film rating: Affective and behavorial responses during film viewing

	whole sample (*n*=85)	group differences		
		INT (*n*=30)	NO-INT (*n*=35)	*test statistics* (*two-sided*)
	M (SD)	*M (SD)*	*M (SD)*	
How well were you able to concentrate on the film scenes? “not at all” (1) to “very well” (9)	7.96 (1.107)	8.00 (1.029)	8.23 (0.817)	*t(63)*=-1.000, *p*=.321
How often did you look away or close your eyes while watching the film? (number)	2.55 (2.937)	2.36 (2.525)	2.30 (2.277)	*t(63)*=0.095, *p*=.925
Please indicate your emotional state while film viewing:				
- Valence: "feeling uncomfortable" (1) to "feeling comfortable" (9)	1.55 (0.838)	1.57 (0.884)	1.63 (0.850)	*t(63)*=-0.286, *p*=.775
- Arousal: "feeling calm" (1) to "feeling excited" (9)	7.65 (1.270)	7.74 (1.120)	7.53 (1.224)	*t(63)*=0.720, *p*=.474
- Stress: “not at all” to “very strong” (9)	6.89 (1.793)	7.31 (1.586)	6.67 (1.788)	*t(63)*=1.548, *p*=.127
How strongly did you identify with the female victim? “not at all” (1) to “very strong” (9)	6.02 (2.127)	5.66 (1.984)	6.33 (2.106)	*t(63)*=-1.331, *p*=.188
How strongly did you commiserate with the female victim? “not at all” (1) to “very strong” (9)	8.00 (1.528)	7.97 (1.543)	8.00 (1.390)	*t(63)*=-0.078, *p*=.938

Note. Data are presented for the whole sample and for each group separately (INT=intrusion group: women with long-term intrusions in response to an experimental trauma; NO-INT: women without long-term intrusions).

SUPPLEMENTAL INFORMATION

Supplementary Table 2

Explicit film memory and analog intrusions. Pearson's r correlations between short-term analog intrusions and explicit film memory as well as group differences in explicit film memory (controlled for age) between women with (INT) and without long-term intrusions (NO-INT) in response to an experimental trauma

			short-term analog intrusions (n=84)	long-term analog intrusions		
				INT (n=30)	NO-INT (n=35)	test statistics (two-sided)
explicit film memory	after 1 week	context	r=-.062, p=.576	M=7.400 SD=1.376	M=7.400, SD=1.380	F(1,62)= 0.211, p=.648
		perpetrator	r=-.049, p=.657	M=7.200, SD=1.183	M=7.233, SD=1.305	F(1,62)= 0.263, p=.610
		victim	r=.034, p=.760	M=7.143 SD=0.845	M=6.900, SD=1.242	F(1,62)= 1.172, p=.283
	after 3 months	context	r=-.126, p=.321	M=6.171, SD=1.671	M=6.633, SD=1.608	F(1,62)= 1.388, p=.243
		perpetrator	r=.102, p=.424	M=7.629, SD=1.114	M=7.333 SD=1.470	F(1,62)= 1.071, p=.305
		victim	r=-.133, p=.296	M=6.857, SD=0.879	M=6.833, SD=1.085	F(1,62)= 0.054, p=.816

SUPPLEMENTAL INFORMATION

Supplementary Table 3

Main effects of the fear conditioning paradigm: Neural activation differences for CS+ minus CS- during fear acquisition in context A (A), during extinction learning in context B (B), during early extinction recall in context B (C) and during early fear renewal in context C (D)

Brain structure	***x***	***y***	***z***	***F***	p_{corr}
A) fear acquisition					
CS+ minus CS-					
L amygdala (ROI)	-16	-4	-14	30.93	.002
R insula (ROI)	32	20	6	31.65	.002
L insula (ROI)	-30	26	4	54.30	<.001
L dACC (ROI)	-4	8	38	59.94	<.001
R vmPFC (ROI)	20	12	-14	43.67	<.001
L vmPFC (ROI)	-20	12	-14	31.62	.002
L caudate (WB)	-8	8	0	89.96	<.001
L supplementary motor area (WB)	-8	-4	64	89.04	<.001
R caudate (WB)	10	10	-2	81.25	<.001
L frontal opercular cortex (WB)	-34	16	10	64.48	<.001
L precentral gyrus (WB)	-14	-22	40	46.12	<.001
L amygdala (WB)	-14	-2	-12	44.69	.001
L supramarginal gyrus (WB)	-58	-24	20	43.21	.001
R thalamus (WB)	6	-6	-2	42.45	.001
L postcentral gyrus (WB)	-24	-40	68	41.19	.002
L precuneus cortex (WB)	-4	-46	56	40.78	.002
R cerebellum (WB)	32	-48	-30	37.43	.006
R central opercular cortex (WB)	54	0	8	37.06	.007
R precentral gyrus (WB)	50	2	50	35.19	.011
L supramarginal gyrus, anterior division (WB)	-66	-38	30	35.12	.012
L precuneus cortex (WB)	-14	-64	30	33.87	.017
CS- minus CS+					
		no significant results			
B) extinction learning					
decrease in CS+E minus CS-		no significant results			
increase in CS+E minus CS-		no significant results			
C) early extinction recall					
CS+E minus CS-					
R insula (ROI)	32	24	4	49.08	<.001
L insula (ROI)	-30	26	2	64.18	<.001
L dACC (ROI)	-2	28	22	35.06	.001
L insular cortex (WB)	-30	26	2	64.18	<.001

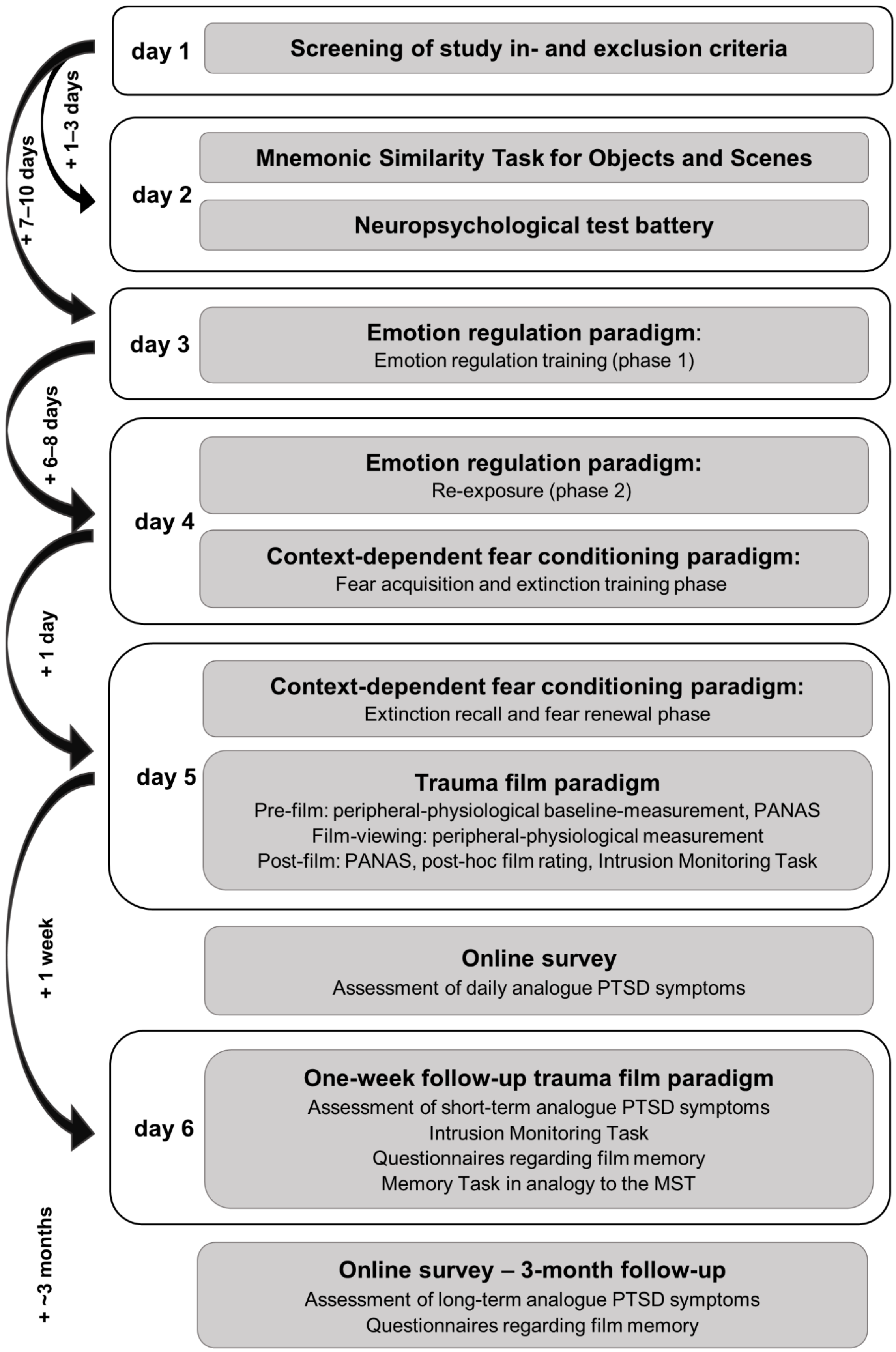
brain-stem (WB)	8	-28	-12	59.72	<.001
R insular cortex (WB)	30	26	6	58.05	<.001
L caudate (WB)	-8	8	0	40.02	.003
R thalamus (WB)	12	0	6	39.56	.003
L central opercular cortex (WB)	-44	8	0	38.20	.005
CS- minus CS+E					
R precentral gyrus (WB)	34	-22	50	35.84	.009
D) early fear renewal					
CS+E minus CS-					
R insula (ROI)	32	24	4	28.16	.004
L insula (ROI)	-30	20	8	32.68	.001
L dACC (ROI)	-6	6	42	29.90	.003
R frontal opercular cortex (WB)	36	26	8	37.21	.006
CS- minus CS+E					
L vmPFC (ROI)	-6	62	-2	21.54	.042

Note. The significance threshold was set to $p \leq .05$ (FWE-corrected). The peak voxels of the whole brain (WB) analyses were labeled based on the Harvard-Oxford Cortical (Lateralized) and Subcortical Structural Atlas and the Automated Anatomical Labeling Atlas 3. For main effect analyses, we conducted FWE small volume correction for a combined mask of all regions of interest (ROIs) to correct for multiple testing. Results from ROI analyses are indicated with (ROI). All coordinates (x, y, z) are given in MNI space. L=left, R=right.

SUPPLEMENTAL INFORMATION

Supplementary Figure 1

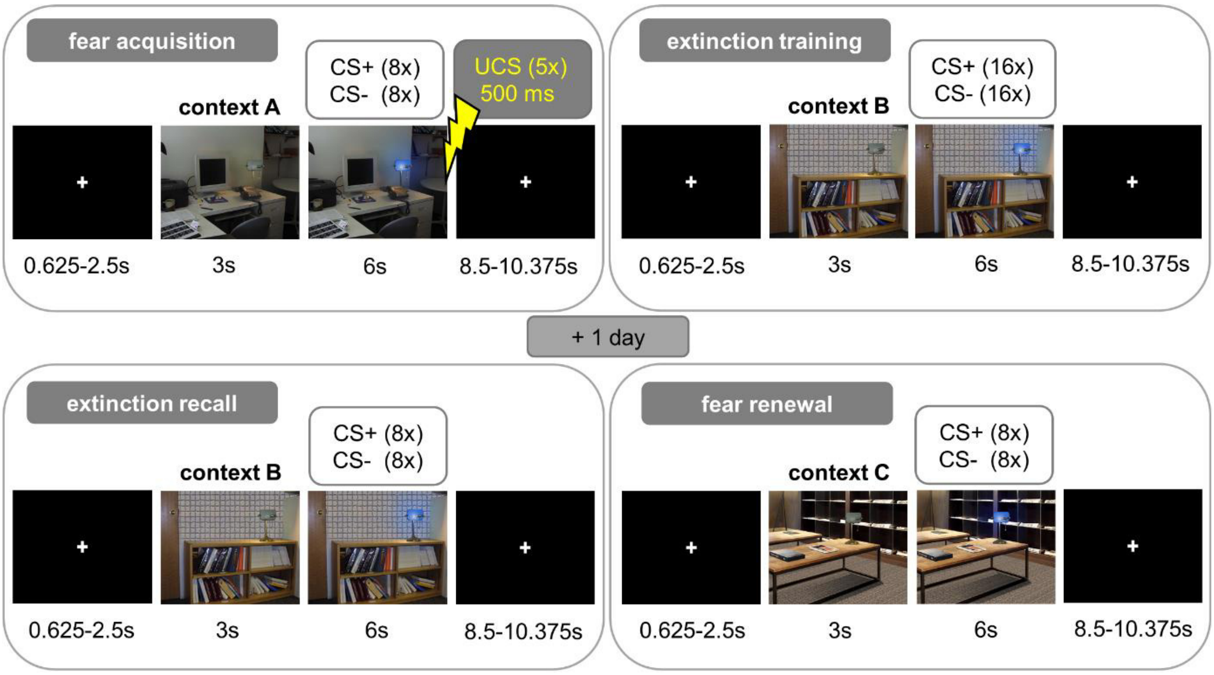
Overview of study days: Main procedures and variables.



SUPPLEMENTAL INFORMATION

Supplementary Figure 2

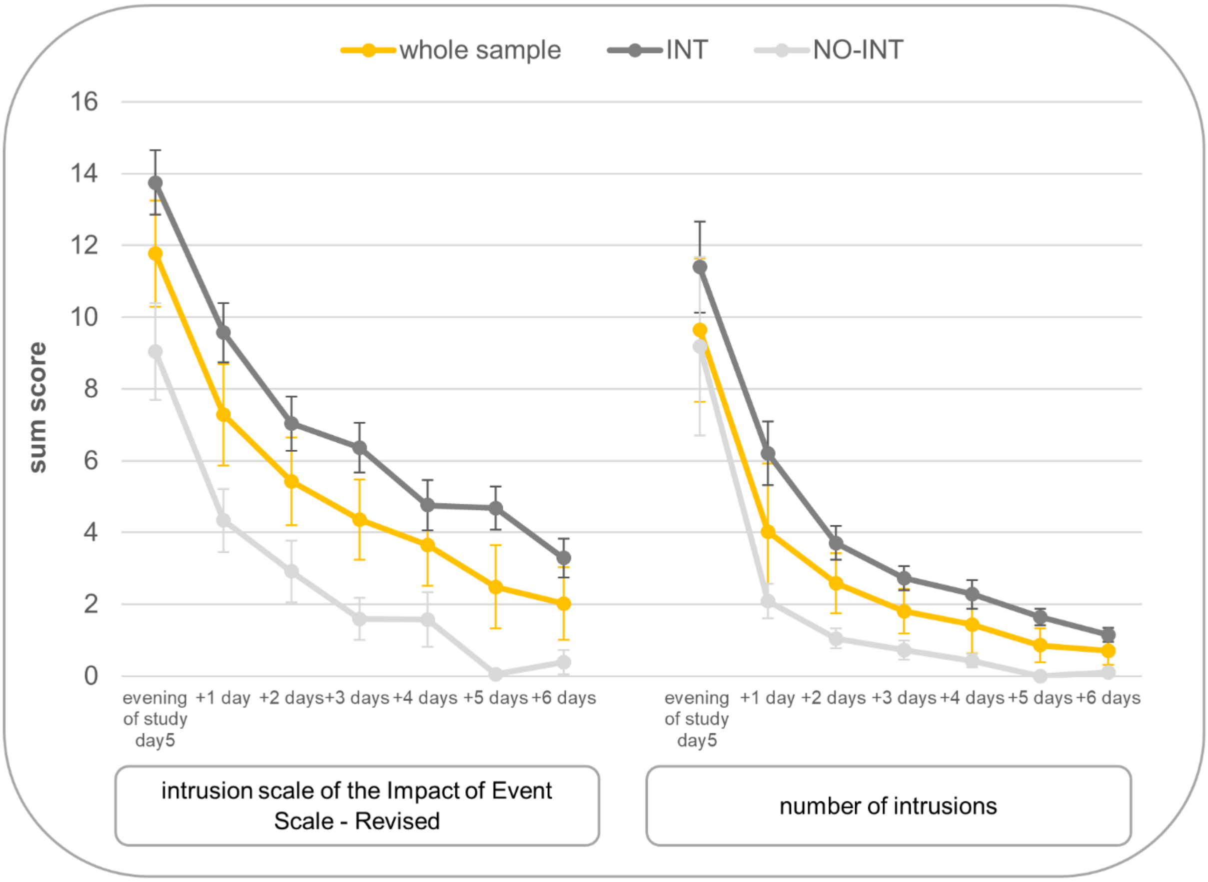
Schematic representation of the fear conditioning design



SUPPLEMENTAL INFORMATION

Supplementary Figure 3

Development of daily rated analog intrusive symptoms in response to the trauma film between study day 5 and study day 6 (starting at the evening of study day 5)

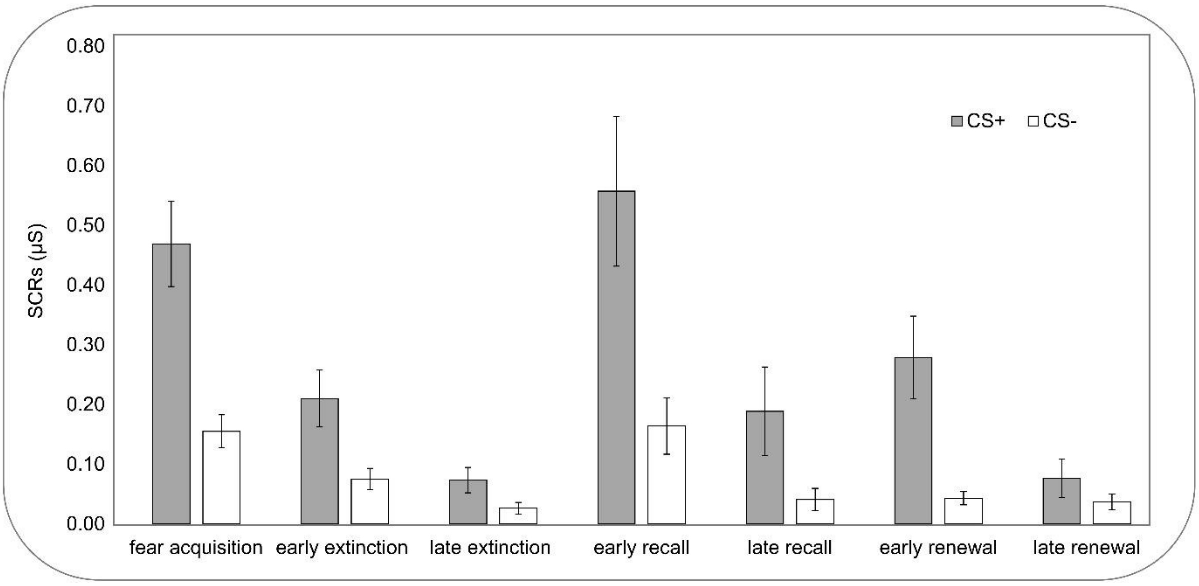


Note. Data are presented for the whole sample and for each group separately (INT=intrusion group: women with long-term intrusions in response to an experimental trauma; NO-INT: women without long-term intrusions). Sample size varies (*n*=59–68) due to missing data or data exclusion due to incorrect conduction of the survey (*n*=15). Error bars depict standard errors of the mean.

SUPPLEMENTAL INFORMATION

Supplementary Figure 4

Skin conductance responses (SCRs) towards the CS+ and the CS- during fear acquisition in context A, (early/late) extinction training in context B, (early/late) extinction recall in context B and (early/late) renewal in context C

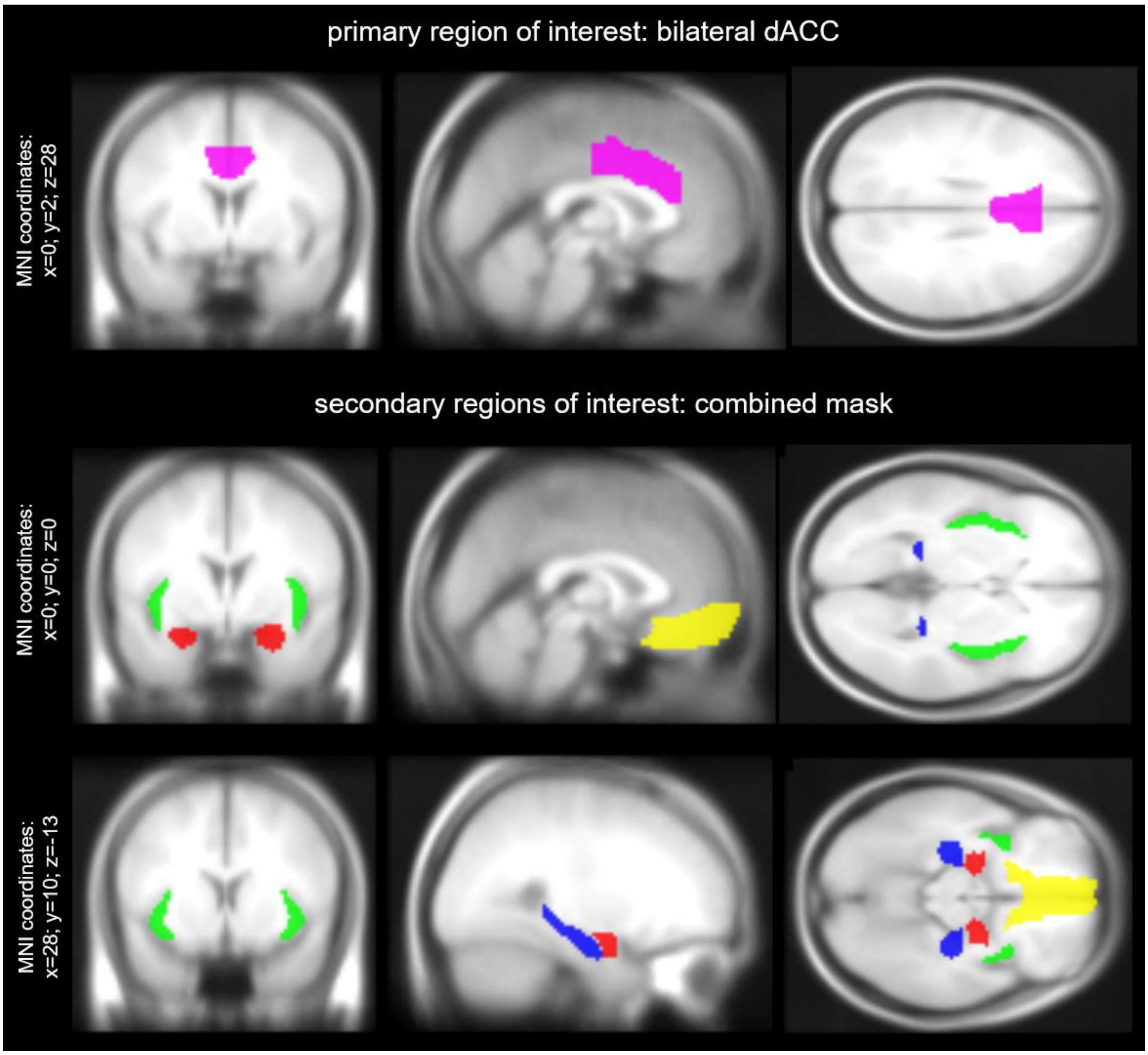


Note. Error bars depict standard errors of the mean.

SUPPLEMENTAL INFORMATION

Supplementary Figure 5

Mask for the bilateral dorsal anterior cingulate cortex (first row). Combined mask (second and third row) with all secondary regions of interest (insula=green; amygdala=red; vmPFC=yellow; hippocampus=blue). Coordinates (x, y, z) are given in MNI space.



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Behavioral pattern separation is associated with neural and electrodermal correlates of context-dependent fear conditioning

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Hippocampus-dependent pattern separation is considered as a relevant factor for context discrimination and might therefore impact the contextual modulation of conditioned fear. However, the association between pattern separation and context-dependent fear conditioning has not been investigated so far. In the current study, 72 healthy female students completed the Mnemonic Similarity Task, a measure of behavioral pattern separation, in addition to a context-dependent fear conditioning paradigm during functional magnetic resonance imaging. The paradigm included fear acquisition in context A and extinction training in context B on a first day, as well as retrieval testing of the fear and extinction memories in the safe context B (extinction recall) and a novel context C (fear renewal) one day later. Main outcome measures comprised skin conductance responses (SCRs) and blood oxygen level-dependent responses in brain regions of the fear and extinction circuit. Regarding retrieval testing, pattern separation did not correlate with extinction recall, but with stronger dorsal anterior cingulate cortex activation and conditioned SCRs (trend) during fear renewal, indicating a stronger retrieval of the fear memory trace. Our findings suggest that behavioral pattern separation ability seems to be important for context-dependent fear modulation, which is impaired in patients with posttraumatic stress disorder.

The occurrence of conditioned fear in safe contexts is a main characteristic of anxiety disorders and posttraumatic stress disorder (PTSD)[1,2]. Conditioned stimuli can activate a fear memory trace that elicits a fear response even in safe contexts because of deficits in using contextual information for fear modulation[3–5]. The context-dependent modulation of conditioned fear is therefore of clinical relevance and can be studied with context-dependent fear conditioning paradigms[3,6–8]: A fear memory trace is acquired during fear learning in context A. During extinction training in context B, an extinction memory trace is formed that inhibits, but does not erase the fear memory trace[10,11]. After extinction learning, retrieval of the competing memory traces can be tested in different contexts. Retrieval testing in the safe extinction context ('extinction recall') leads to a stronger activation of the extinction memory[9], while the fear memory is activated more strongly during the presence of conditioned cues in the acquisition context or a novel and potentially dangerous context ('fear renewal')[7,10]. The hippocampus is important for context-dependent retrieval of fear and extinction memories[7,11–13] by modulating the fear response via direct and indirect projections through the dorsal anterior cingulate cortex (dACC) and the ventromedial prefrontal cortex (vmPFC) to the amygdala[3].

For adaptive context-dependent responding, contexts must be checked for (dis)similarity to already stored contexts, in order to prepare the organism for a fear response in the presence of conditioned cues in novel, potentially dangerous contexts (e.g., novel context C) or to relax in the case of safe contexts (e.g., extinction context B)[5]. Pattern separation is discussed to be involved in context discrimination[14] and in memory formation and retrieval processes by storing the diversity of experiences[15]. It extracts the dissimilarity of an input stimulus

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(e.g., today's parking lot in a parking garage) that shares similarity to already stored stimuli (e.g., different parking lot yesterday in the same parking garage)[16]. Thus, pattern separation is responsible for encoding a stimulus or event as a dissimilar, non-overlapping memory representation despite its similarity to other stimuli or events (e.g., enables to find the right parking lot each day)[16]. Behavioral pattern separation performance can be measured with the Mnemonic Similarity Task (MST)[17, 18] and is linked to activity in the dentate gyrus (DG) and CA3 (cornu ammonis) regions of the hippocampus[19, 20]. More recent findings show evidence for the exclusive role of the DG in pattern separation[21].

Following the neural model of classically conditioned fear generalization in humans[22, 23], pattern separation processes in the hippocampus should activate structures of the fear- and extinction network including the vmPFC, the dACC, the insula and the amygdala in the case of similarity of a new stimulus/situation with already stored stimuli/situations. For example, if a novel context (e.g., context B or C) shares or includes features of a dangerous context (e.g., context A), pattern separation should initiate and prepare the individual for a fear response by activating the dACC, insula and amygdala, brain regions that are involved in fear excitation and processing[22, 23], but have different functions. Neurons of the amygdala are involved in the encoding and retrieval of fear memories[3]. The amygdala is considered as a gate keeper, which detects and sends information about emotional stimuli into different processing channels[24]. The insula provides information how salient stimuli affect the body state and is important for interoceptive processes[25, 26]. The dACC is a key region for fear expression[9] and also involved in the storage of contextual memories[27, 28]. Pattern separation should moreover activate the ventromedial prefrontal cortex, a region known for fear inhibition[29], in the presence of conditioned safety signals[22, 23].

Given its role in the integration and differentiation of old and new events[16, 30], pattern separation may therefore be involved in the context-dependent retrieval of fear and extinction memories. Contextual modulation of conditioned fear requires the discrimination of different, more or less similar contexts in the presence of identical/similar conditioned or generalization stimuli. However, to date, there are no studies investigating the association between behavorial pattern separation and the context-dependent retrieval of fear and extinction memories. Previous studies focused on the association between behavioral pattern separation performance and stronger fear learning and generalization over stimuli[31–33]. Reduced pattern separation performance was associated with a less steep fear generalization gradient and with lower fear inhibition in frontal brain regions and stronger threat expectancies to stimuli that were similar to the conditioned cue[31, 32], but not with differential fear learning in general[33].

Expanding previous research, we investigated the association between behavorial pattern separation performance and the context-dependent retrieval of fear and extinction memories in a sample of 72 healthy female participants. The MST[17] was conducted for assessing behavioral pattern separation performance. Furthermore, participants completed a 2-day context-dependent differential fear conditioning paradigm (adapted from previous studies[2, 6, 7, 13]) during functional magnetic resonance imaging (fMRI). The paradigm included fear acquisition in context A and extinction training in context B on a first day, as well as retrieval testing in context B (extinction recall) and in a novel context C (fear renewal) approximately 24 h later. Neural activation in regions of the fear and extinction network and skin conductance responses (SCRs) were used as dependent variables.

Pattern separation –relevant for processing the (dis)similarity between contexts– is hypothesized to contribute to a better contextual modulation of conditioned fear. During extinction learning, higher pattern separation performance should be associated with a stronger activation increase in the hippocampus and in the vmPFC as well as with an activation decrease in fear-related structures (amygdala, insula, dACC) and with a reduction of conditioned SCRs. With regard to retrieval testing, we further assume that higher pattern separation performance is associated with stronger activation of the hippocampus and with reduced conditioned fear expression during early extinction recall (context B) and stronger conditioned fear expression during early fear renewal (context C). A stronger conditioned fear response should be reflected in enhanced conditioned SCRs and increased activation of fear expressing regions (amygdala, insula, dACC) as well as reduced activation of the vmPFC.

Methods

Study procedure. This study belongs to a larger project that investigates the prediction of analog intrusions using the trauma film paradigm based on pattern separation, emotion regulation and context-dependent fear conditioning processes. The whole project consisted of six study days within four weeks and contained clinical interviews, different experimental paradigms and a neuropsychological test battery. For this study, only the relevant paradigms are described below, which were the MST[17] for assessing behavioral pattern separation (study day 2), the Block-Tapping-Test[34] as a measure of visuo-spatial memory span from the neuropsychological test battery (study day 2), and the context-dependent fear conditioning paradigm (study days 4 and 5) to assess the context-dependent learning and retrieval of fear and extinction memories. All study procedures were in accordance with the Declaration of Helsinki and approved by the local ethical review board of the Faculty of Psychology and Sports Science at the Justus Liebig University Giessen, Germany.

Sample. Ninety-four healthy female students recruited via mailing lists at the local university were eligible to participate in this study. All interested students underwent a screening for study in- and exclusion criteria (study day 1), including the Diagnostic Interview for Mental Disorders for DSM-5 (DIPS)[35, 36] and the Life-Event-Checklist in combination with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[37]. Participants were excluded if they fulfilled the diagnosis of a current or past DSM-5 disorder according to the DIPS/CAPS or reported the experience of a traumatic event within the last four weeks. Participants had to be female and had to report no personal experiences with physical or sexual violence, as we used film scenes during the trauma film paradigm, showing e.g., how a female person was raped by a male perpetrator. Further study exclusion criteria were current and/or regular drug use in the past, color blindness, left-handedness, fMRI contraindications, current or past psychotherapeutic or psychiatric treatment, or medical treatment due to an acute or chronic physical disease.

An a priori power analysis resulted in a minimum sample size of $N = 67$ for a linear regression analysis with one predictor (Power $(1 - \beta) = 0.80$, $\alpha = 0.05$) with an expected medium effect of $\rho = 0.3$. Compensating for a drop-out rate of 20% and further drop-outs in main outcome measures (e.g., SCRs), the final sample consisted of $N = 94$ participants. Twenty-two participants had to be discarded from analyses for the following reasons: early study termination ($n = 5$), technical problems ($n = 9$) or excessive head movements during scanning ($n = 5$) (see below), neurological abnormalities ($n = 1$), technical problems ($n = 1$) or an outlier value in the MST ($n = 1$), leaving a final sample of 72 participants (age: $M = 23.00$ yrs, $SD = 2.51$ yrs, range: 18–31yrs) for analyses regarding the association between pattern separation and context-dependent fear conditioning. The Beck Depression Inventory-II (BDI-II)[38] as a measure of depressive symptoms and the Symptoms Checklist-90-R (SCL-90-R)[39] with the Global Severity Index (GSI) as a measure of mental stress indicated low mean scores (BDI-II: $M = 2.50$, $SD = 3.57$, range:0–15; GSI: $M = 0.15$, $SD = 0.16$, range: 0–0.74).

Mnemonic similarity task. For measuring behavioral pattern separation performance, all participants conducted the MST for objects[17] (picture set 1) and for scenes[18] (picture set C), always starting with the MST for objects. The results for the MST for scenes are not reported here. The MST for objects[17] consists of two phases, the encoding and the following test phase. During the encoding phase, participants viewed 128 pictures of objects for 2 s on a white background presented on a monitor of a laptop (15.6 inches). Participants should indicate via button press on the keyboard if the object is an 'indoor' or 'outdoor' item (a note card was given as a reminder for the answering options). If they did not give an answer during picture presentation, a white background was presented to avoid differences in picture presentation times within the sample. The next picture was presented on the screen with an inter-stimulus-interval (ISI) of 500 ms, after an answer (forced choice, no time-limitation) was given by button press (no missing responses possible). Immediately after the encoding phase, participants were told that the following test phase is a memory test for the items they had just seen before. During the test phase, 64 pictures of objects presented during the encoding phase (condition: 'old'), 64 pictures of new objects (condition: 'foils'), and 64 pictures showing similar but not identical items they had seen during the encoding phase (condition: 'lure'), were presented for 2 s in a randomized order. For each picture, participants should decide if the presented picture is an 'old', a 'new' or a 'similar' item. After picture presentation, a white background appeared until an answer (forced choice, no time-limitation) was given by button press (no missing responses possible).

The overview of responses for each stimulus and response type of the MST for objects is presented in Table 1. The response distribution of the MST for objects is similar to previous findings in young and healthy samples[31, 40]. Behavioral pattern separation performance was calculated by the 'Lure Discrimination Index (LDI)'. It is composed of the number of 'similar' responses given to lure items (correctly classified lure objects) minus the number of 'similar' responses given to foils to correct for a general bias to respond with 'similar'[41]. Higher behavioral pattern separation performance, as measured with the LDI, represents a better identification of similar items. As described above, two participants were excluded from analyses due to technical problems during the conduction of the MST ($n = 1$) or an outlier value in the number of correctly classified lure items (score > or < 3 × interquartile range, $n = 1$).

Block-tapping-test (BTT). After the conduction of both MST on study day 2, a neuropsychological test battery (not reported here) including the BTT[34] was carried out. The BTT was used as a covariate in correlational analyses between behavioral pattern separation performance and context-dependent fear conditioning, in order to control for visuo-spatial working memory performance. There was no significant correlation between pattern separation performance and the sum score of the BTT ($r = 0.175$, $p = 0.143$).

Context-dependent fear conditioning paradigm. *Experimental design.* A 2-day context-dependent differential fear conditioning paradigm was adapted from previous studies[7, 13, 42, 43]. It consisted of different experimental phases: a fear acquisition phase in context A and an extinction training phase in context B on a first day, as well as a retrieval testing phase in context B (extinction recall) and in a novel context C (fear renewal) one day later.

Pictures of different rooms (office room, conference room, and a room with a shelf) served as contexts A, B and C. Each room included the same initially turned off desk lamp. The lamplight colors were used as conditioned stimuli (CS), electrical stimulation as the unconditioned stimulus (UCS). The intensity of the UCS was adjusted in advance to a level, which participants perceived as unpleasant but not painful. The assignment of contexts to

	Old	Lure	Foil
Response: Old	55.31 (4.81)	24.00 (8.47)	1.10 (1.49)
Response: Similar	6.72 (4.11)	34.19 (9.87)	7.31 (4.97)
Response: New	1.96 (2.72)	5.81 (4.72)	55.60 (5.17)

Table 1. Responses (mean score (maximum = 64) and standard deviations) for each stimulus and response type of the Mnemonic Similarity Task for objects ($n = 72$).

experimental phases and the assignment of lamplight colors to CS type condition (CS + /CS −) was counterbalanced and pseudorandomized across participants.

Each trial of each experimental phase started with the presentation of a white fixation cross on a black background (jittered between 0.625 and 2.500 s). Afterwards, a picture of a room with a turned off desk lamp (= context) appeared for 3 s. After three seconds, the desk lamp lit up either blue or yellow for a duration of 6 s. During the fear acquisition phase, one lamplight color (CS +) was followed by an electrical stimulation (UCS) with a duration of 500 ms in 62.5% of the trials; the other lamplight color (CS −) was never followed by the UCS, representing a safety stimulus that should elicit an omission response. In the other experimental phases, the UCS was not administered after CS + or CS − presentation. After CS offset, a white fixation cross on a black background appeared up to a total trial duration of 20 s.

The fear acquisition phase consisted of 8 trials, the extinction training phase of 16 trials, and the extinction recall and the fear renewal phase (retrieval phase) each of 8 trials for each CS type, respectively. Trials were arranged in blocks. Each experimental phase consisted of two blocks. Each block comprised half of the CS trials and contained the same number of CS + and CS − trials. The first two and last two trials of each phase consisted of one CS + and one CS − , respectively. The other CSs were presented in a pseudorandomized order (no more than 2 CS + /CS − in succession). The first CS + was always reinforced during fear acquisition to enhance fear learning. In addition, the last CS + was reinforced to avoid premature extinction learning during fear acquisition.

Participants were informed about the trial structure and content. Before each experimental phase, they were instructed to attentively watch the presentation. They were also informed about the possibility of receiving electrical stimulation after the desk lamp lit up either blue or yellow. They were further instructed that there is a relationship between lamplight color and electrical stimulation. After the fear acquisition phase, participants were asked and informed about the relationship between lamplight color and electrical stimulation, in order to make participants aware of CS-UCS contingencies. We provided information about of CS-UCS contingencies (one lamplight color (CS +) was sometimes followed by electrical stimulation; the other lamplight color (CS −) was never followed by stimulation), to avoid differences in fear and extinction-related processes due to awareness issues[44–47]. Before the extinction training phase started, participants received the instruction that the relationship between light color and electrical stimulation will remain stable over the experiment. This information was given to avoid the idea that CS-UCS contingencies might change over the course of the experiment. It was explicitly stated that the lamplight color that was not followed by stimulation will always be safe and will never be followed by stimulation. The other light color may or may not be followed by electrical stimulation.

FMRI data acquisition and analyses. A 3-Tesla whole-body tomograph (Siemens Prisma) with a 64-channel standard head coil was used for image acquisition. We used a T2*-weighted gradient echo-planar imaging sequence (EPI) with 42 slices covering the whole brain (slice thickness = 3 mm; 0.75 mm gap; descending slice order; TE = 30 ms; TR = 2.5 s; flip angle = 81°; field of view = 220 × 220 mm; matrix size = 110 × 110; PAT mode GRAPPA, acceleration factor PE 2) for functional image acquisition (152 volumes for fear acquisition, 280 volumes for extinction training as well as 280 volumes for extinction recall and fear renewal). The first three volumes were excluded from analyses because the magnetization was not yet completely stable. T1-weighted sagittal images were registered (MPRAGE: 0.94 mm slice thickness) and used for normalization procedure. Neuroimaging data were analyzed with Statistical Parametric Mapping (SPM12, r7219, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (R2019a; Mathworks Inc., Sherborn, MA, USA). Preprocessing of the data consisted of the following steps: unwarping and realignment (b-Spline interpolation), slice time correction, co-registration of functional data to each participant's anatomical image, segmentation of the anatomical image into different tissue types and normalization to the standard space of the Montreal Neurological Institute (MNI) brain. For data smoothing, an isotropic three-dimensional Gaussian filter with a full-width at half maximum (FWHM) of 6 mm was used. Participants ($n = 5$) who showed a framewise displacement[48] of more than 0.5 mm in at least 15% of the volumes of one scanning session (fear acquisition, extinction training, retrieval testing) were excluded from data analyses.

After preprocessing, first level models were generated separately for fear acquisition, extinction training and retrieval testing (extinction recall and fear renewal). The first level model for the fear acquisition phase contained the regressors context alone, blocks of eight trials for CS + and CS − and blocks of UCS and UCS omission-trials (noUCS-trials). For extinction learning, the regressors context alone and blocks of eight trials of CS + and CS − for early and for late extinction training were included in the model. The first level model for the retrieval testing phase consisted of the regressor context alone as well as of blocks of four trials of CS + and CS − as regressors for early and late extinction recall and for the early and late renewal phase. All first level models also included six movement parameters from the realignment step in addition to one regressor for each volume with a framewise displacement > 0.5 mm[48]. All regressors of interest were modelled based on a stick function convolved with the canonical hemodynamic response function in the general linear model, without specifically modeling the durations of the different events (i.e., event-related design). In addition, we used a high-pass filter of 128 s for filtering voxel-based time series. Autocorrelation of errors was controlled by an AR(1) process. Contrasts between the CS + and CS − were calculated on an individual level for fear acquisition (comparison of the eight CS + and CS − trials), for extinction training (activation decrease from early to late extinction: comparison of the first 8 CS minus last 8 CS trials), as well as for early extinction recall and early fear renewal (comparison of the first four CS + and CS − trials).

The main effects of the context-dependent fear conditioning paradigm are reported in detail elsewhere. In short, neural and SCR data indicated successful fear acquisition in context A. SCRs also indicated successful extinction learning in context B (decrease in SCRs from early to late extinction training). Neural and SCR data showed a return of fear not only during fear renewal in context C (which was expected), but also during extinction recall in context B, when context B should be used as a safety signal. A stronger fear response during extinction recall in the whole sample might be a result of immediate extinction training after fear acquisition[49]. Nevertheless, it still permitted to investigate our research question if differences in pattern separation performance are associated with indices of context-dependent fear conditioning processes.

For analyzing the association between behavioral pattern separation performance and neural correlates of context-dependent fear conditioning processes, multiple regression analyses during second-level analyses implemented in SPM12 were conducted. In a further step, to control for visuo-spatial working memory performance, the multiple regression analyses were repeated adding the sum score of the BTT as a covariate of no interest in the model. Amygdala, dACC, insula, vmPFC and hippocampus, regions of the fear and extinction network[3, 24, 50], were defined as regions of interests (ROIs). For amygdala, insula, and hippocampus maximum probability masks were taken from the current "Harvard–Oxford Cortical and Subcortical Structural Atlases" provided by the Harvard Center for Morphometric Analysis (http://www.cma.mgh.harvard.edu/) with a probability threshold of 0.50 included in the FSL software package (http://www.fmrib.ox.ac.uk/fsl/). Masks for the left and right dACC and vmPFC were constructed with the MARINA software package[51] and were used in previous studies[43, 52]. The vmPFC mask consisted of the bilateral medial orbital area of the frontal cortex and the gyrus rectus according to the parcellation of Tzourio-Mazoyer[53]. The dACC mask was defined as the anterior and mid cingulate cortex from the AAL parcellation[53] in the range of $y = -17$ mm to $y = 32$ mm, $z >= 12$ mm (MNI coordinates). For ROI analyses, the significance threshold was set to $\alpha \leq 0.05$ on voxel-level, corrected for multiple testing within each ROI (family-wise error (FWE) correction; using the small volume correction option of SPM12; intensity threshold: $p \leq 0.05$ uncorrected). Each ROI was tested bilaterally, as we had no hypotheses about laterality. Results with a trend towards significance are reported up to $p \leq 0.10$. For exploratory whole brain analyses, the significance threshold was set to $\alpha \leq 0.05$ on voxel-level corrected for multiple testing for the whole brain (FWE-correction); the minimal cluster size (k) for exploratory whole brain analyses was 10 voxels.

Skin conductance responses and analyses. SCRs were recorded with a sampling rate of 1000 Hz during all experimental phases using Ag/AgCl electrodes filled with isotonic (0.05 M NaCl) electrolyte medium. The electrodes were positioned hypothenar at the left hand. We used Ledalab 3.4.4 written in MATLAB for preprocessing and data analyses. In a first step, data was downsampled with a sampling rate of 10 Hz and smoothed with a 32 mm Gaussian kernel. A manual data check was performed to check data quality. If technical artifacts were detected in the data, the affected data section was corrected by manual interpolation in Ledalab.

Data were analyzed via 'trough-to-peak'-analyses[54]. The entire interval response (EIR) was defined as the largest difference between a minimum within a defined time window and the directly following maximum. For CS responses, the time window was set to 0.8–6 s after CS onset, while for UCS responses it was set to 0.8–2.5 s after UCS onset. Contrasts between CS+ and CS− (conditioned response) were calculated in parallel with the fMRI analyses. From the final sample of $N = 72$ participants, data of $n = 15$ participants had to be discarded from SCR analyses because of non-responding during fear acquisition (less than two SCRs > 0.02 µs in reaction to the UCS after CS+ ($n = 12$)), technical problems during measurement ($n = 1$), or missing data ($n = 2$), leaving a final sample of $n = 57$ for SCR analyses. In order to examine the relationship between context-dependent fear conditioning processes and behavioral pattern separation performance, correlational analyses according to Spearman's rho (r_s) were conducted (due to the violation of normal distribution of the SCR data) in IBM SPSS 27 (IBM Corporation, Armonk, USA). We repeated the analyses and added the raw scores of the BTT as a covariate of no interest to the analyses to control for visuo-spatial memory performance.

Post-hoc ratings and analyses. After the context-dependent fear conditioning paradigm, post-hoc ratings were conducted outside the scanner to measure context recognition and UCS expectancy for the extinction and novel context. Participants had to decide which of the 6 presented rooms (3 unknown rooms) were used during the paradigm. They should further indicate which room(s) they saw 'only yesterday' (≙ the acquisition context), 'today and yesterday' (≙ extinction context), or 'only today' (≙ the novel context C) and were further asked in which room(s) they had ever received an electrical stimulation after CS offset. For measuring context recognition, a recognition score (overall sum score for correctly classified context assignments) was calculated. After the memory test, participants saw the pictures of the rooms (context A, B, C) which were used during the experimental phases. Valence, arousal and fear were rated on a 9-point Likert scale for each room when the desk lamp was turned off (context alone; no CS condition) or shining blue or yellow (CS condition) (not reported here). To examine UCS expectancy in the different contexts, they also rated how certain they had been that an electrical stimulation immediately appeared after CS offset in the extinction and novel context on a 9-point Likert scale (answer options ranging from 'sure' to 'unsure that the electrical stimulation followed'), respectively. Correlation analyses were conducted to investigate the association between pattern separation performance and post-hoc context recognition and UCS expectancy for the extinction and novel contexts using IBM SPSS 27 (IBM Corporation, Armonk, USA). We repeated the analyses and added the raw scores of the BTT as a covariate of no interest to the analyses to control for visuo-spatial memory performance.

Consent to participate. All participants spoke German fluently and gave written informed consent. We informed participants that they could terminate the study at any time without negative consequences for them. They were reimbursed for their participation (10 Euro/h or course credits).

Results

The results of this study show that pattern separation was associated with neural correlates of fear acquisition in context A. Higher pattern separation performance (LDI) was associated with reduced activation in the dACC ($T_{max} = 3.99$, $p_{fwe} = 0.046$, $k = 270$, MNI: x = −2; y = 32; z = 30) and on trend level with reduced activation in the insula ($T_{max} = 3.73$, $p_{fwe} = 0.091$, $k = 517$, MNI: x = 36; y = −12; z = 10) and hippocampus ($T_{max} = 3.64$, $p_{fwe} = 0.075$, $k = 172$, MNI: x = 34; y = −12; z = −18) for CS + compared with CS − during fear acquisition in context A. After controlling for visuo-spatial memory performance, the dACC result remained significant ($p_{fwe} = 0.046$), the insula result on trend level ($p_{fwe} = 0.089$), but the hippocampus result did not reach significance any more ($p_{fwe} = 0.138$). In contrast to neural findings, there was no significant association between pattern separation performance and conditioned SCRs during fear acquisition (Spearman's rho (r_s) correlation coefficient: $r_s = 0.089$, $p = 0.510$). Pattern separation performance was also not correlated with SCRs towards the UCS after CS + compared with the omission response after CS − ($r_s = 0.024$, $p = 0.857$) during fear acquisition.

Higher pattern separation performance was not associated with neural (all ROI analyses: $p_{fwe} > 0.10$), but with electrodermal indicators of extinction learning in context B, when the extinction memory trace should be established. Higher pattern separation performance was correlated with a stronger decrease in conditioned SCRs ($r_s = 0.333$, $p = 0.011$; controlled for visuo-spatial memory performance: $r_s = 0.299$, $p = 0.025$) from early to late extinction training. Regarding retrieval testing in different contexts after approximately 24 hours, behavioral pattern separation performance was neither correlated with conditioned SCRs ($r_s = 0.111$, $p = 0.409$) nor neural correlates (all ROI analyses: $p_{fwe} > 0.10$) of extinction recall in context B. During early fear renewal in context C, higher pattern separation performance correlated with stronger conditioned SCRs (trend: $r_s = 0.233$, $p = 0.081$; controlled for visuo-spatial memory performance: $r_s = 0.259$, $p = 0.054$) and with stronger activation in the dACC ($T_{max} = 4.03$, $p_{fwe} = 0.040$, $k = 694$, MNI: x = 0; y = 32; z = 30) and on trend level in the insula ($T_{max} = 3.79$, $p_{fwe} = 0.075$, $k = 184$, MNI: x = 34; y = 20; z = −8,) for CS + compared with CS − (see Fig. 1). DACC results remain significant ($p_{fwe} = 0.014$), but insula results ($p_{fwe} = 0.150$) did not reach significance after controlling for visuo-spatial memory performance. Exploratory whole brain analyses showed no significant associations between pattern separation performance and indicators of context-dependent fear conditioning.

Analyses of post-hoc ratings revealed no association between pattern separation performance and post-hoc UCS expectancy ratings for the safe extinction context ($r = 0.136$, $p = 0.261$), nor for the novel context C ($r = -0.184$, $p = 0.128$), also when controlled for visuo-spatial memory performance (all $p > 0.189$). Higher pattern separation performance was associated with a better post-hoc overall context assignment to experimental phases ($r_s = 0.352$, $p = 0.003$; controlled for visuo-spatial memory performance: $r_s = 0.350$, $p = 0.007$). However, the results for context assignment are limited in power, since the majority of individuals ($n = 62$) were able to correctly classify all presented context pictures.

Discussion

The main goal of this study was to investigate the relevance of behavioral pattern separation for context-dependent learning and retrieval of fear and extinction memories. As expected, better behavioral pattern separation performance was associated with electrodermal (SCRs) indicators of stronger extinction learning in context B and electrodermal (trend) and neural indicators of stronger fear renewal in context C, but in contrast to our assumptions not with indicators of stronger extinction recall in context B.

Higher pattern separation performance was related to a stronger decrease of conditioned SCRs from early to late extinction training in context B, when the extinction memory should be acquired. Our results therefore indicate better extinction learning in individuals with higher pattern separation performance. But this interpretation is limited, as neural indicators of extinction learning show no significant association with pattern separation performance. Extinction learning is regarded as a main mechanism for fear reduction during exposure therapy[55]. Pattern separation might be required during extinction learning in context B for encoding the extinction memory as dissimilar from the fear memory trace despite the sharing of identical features. Accordingly, higher pattern separation performance might therefore also explain better post-hoc recognition of the contexts.

In contrast to our expectations, we did not find an association between behavioral pattern separation performance and early extinction recall neither on the neural level nor in conditioned SCRs. It is possible that the retrieval of the extinction memory in a safe context might more likely require pattern recognition, the ability to remember known stimuli, rather than pattern separation which focuses on stimulus dissimilarity[17,56]. Regarding retrieval testing in the novel context ('fear renewal'), higher pattern separation performance was associated with stronger conditioned SCRs (trend) and stronger activation in the dACC, a structure relevant for the expression of learned fear[9]. These results might therefore reflect a stronger recall of the fear memory trace in women with higher behavioral pattern separation performance. The return of fear in the presence of conditioned cues in a novel, potentially dangerous context is adaptive by preparing an individual for a potential threat. Impaired pattern separation processes might therefore contribute to difficulties in fear renewal processes which are known for example for patients with PTSD[2].

Taking a closer look at the neural level, former work on fear renewal emphasizes the interplay between the dACC and the hippocampus. For example, fear renewal was associated with dACC and hippocampus activation and stronger structural connectivity between these regions[7,57]. In general, the dACC sends input to subregions of the hippocampus which regulate the retrieval of contextual fear memories[28] and in turn receives input from subregions of the hippocampus important for initiating the fear response[3]. Contrary to our hypotheses, pattern separation was not significantly correlated with activation of the hippocampus during fear renewal. This is in line with findings, showing no association between behavioral pattern separation abilities and hippocampus activation during fear generalization[31], although the differentiation of stimuli that resemble the CS + are considered to require pattern separation by the hippocampus which then initiates activation of fear- and extinction-related

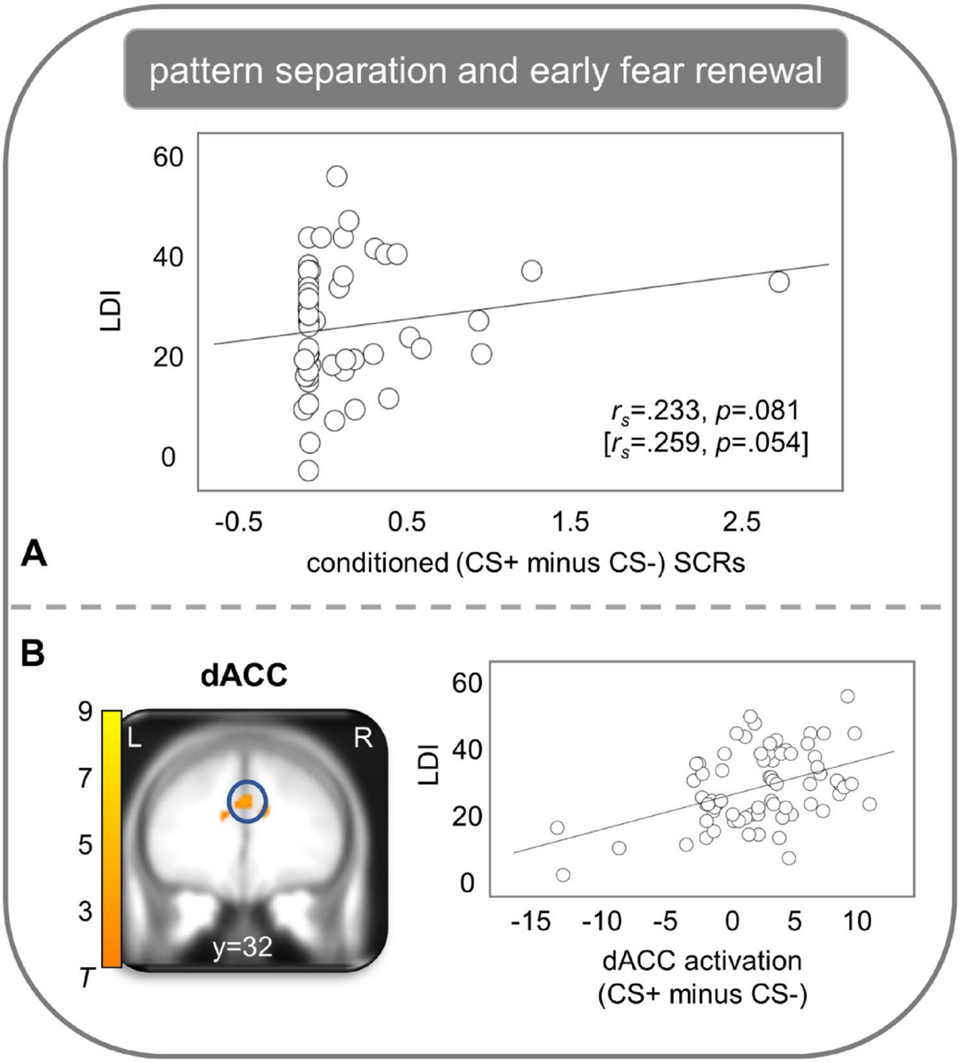

Figure 1. Association between pattern separation performance (LDI: Lure discrimination index) of the Mnemonic Similarity Task for objects and (**A**) conditioned (CS + minus CS −) skin conductance responses (SCRs) using Spearman's rho correlation coefficient (r_s) as well as (**B**) neural activation (CS + minus CS −) in the dorsal anterior cingulate cortex (dACC; contrast estimates of peak voxels) during early fear renewal in context C. Results of the control analyses (controlled for visuo-spatial working memory (sum scores of digit span of the Block-Tapping-Test)) are presented in square brackets. Neural activations were superimposed on the MNI305 T1 template. All coordinates (x, y, z) are given in MNI space. The color bar depicts *T* values. L: left, R: right.

brain regions[22, 23, 58]. The missing hippocampus activation in association with pattern separation in our and previous studies might be related to methodological issues, as e.g., limited resolution of imaging data, preventing the investigation of hippocampal subregions (e.g., dentate gyrus) especially relevant for pattern separation[21] as well as for encoding and retrieval of memories[59].

Given the findings of our study, pattern separation may particularly play an important role in the processing of novel stimuli. Context B during extinction learning as well as context C during fear renewal represented unknown contexts for the participants. New contexts need to be checked for (dis)similarities to other already stored contexts, which should require pattern separation. In line with that idea, novelty processing is impaired in Alzheimer's disease[60], which on the other hand is associated with reduced pattern separation performance[61]. Kesner and colleagues[62] also reported the relevance of the DG for novelty detection. From mice studies it is known that suppression or lesions of the DG impaired contextual fear extinction[59, 63, 64] and that its inactivation reduced context-dependent fear renewal[65]. Although we did not investigate neural activation specifically in the DG region of the hippocampus and did not find significant results for the entire hippocampus region of interest, our study also emphasizes the relevance of behavioral pattern separation ability for context-dependent extinction learning and early fear renewal.

The findings of the current study also showed that pattern separation was associated with neural correlates (dACC, insula (trend)) of fear acquisition in context A, when the fear memory trace should be acquired. During the fear acquisition phase, pattern separation might be less required, because context A cannot be compared to a previous context. This could lead to reduced activation in both structures, which are considered to be involved in the retrieval of contextual fear memories and recognition memory[28,66], in persons with higher pattern separation performance. These neural findings could also point to less fear expression during fear acquisition, as the dACC and the insula are also fear-related brain regions[9,24], to be associated with pattern separation performance. However, the results cannot be interpreted unambiguously and should be treated with caution, because the insula results were only significant on trend level and because there were no correlations with conditioned SCRs. A previous study using SCRs as the main outcome measure for fear learning did also not find an association between pattern separation performance and conditioned SCRs during fear acquisition[33]. However, this was the first study investigating the association between pattern separation and context-dependent learning and retrieval of fear and extinction memories in a female sample which makes comparability to previous findings difficult.

There are further study limitations, which might affect the results. The current findings were based on a young and healthy female sample and cannot be generalized to older individuals, others genders or clinical populations. Additionally, the results should be treated with caution since we did not control for hormonal status and menstrual cycle, which are known to affect emotional learning processes[67,68].

Conclusions

In conclusion, our study shows first evidence for a link between behavioral pattern separation performance and context-dependent learning and retrieval of fear and extinction memories. The findings particularly highlight the relevance of pattern separation performance and underlying neural and electrodermal correlates for early fear renewal. Our data are mainly in line with previous assumptions which consider reduced pattern separation performance as a relevant factor for reduced context discrimination[14]. The current findings further support the idea that maladaptive pattern separation may contribute to deficits in the contextual modulation of fear and the inflexibility of adaptive fear up- and down-regulation known for anxiety disorders and PTSD[2,5]. However, in order to close the gap between pattern separation, fear conditioning and psychopathology, future studies should investigate the association between pattern separation performance and context-dependent fear conditioning in clinical samples.

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Data availability

The data of this study are available on request from the authors and are not publicly available, as the study also comprises very sensitive clinical information.

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Competing interests

The authors declare no competing interests.

Additional information

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