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Cortisol suppression after memory reactivation impairs later memory performance

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ABSTRACT

Experiencing stressful or traumatic events can result in disabling clinical symptoms of maladaptive emotional memory retrieval, which are only partly addressed by the currently proposed treatments. Cortisol modulation has been shown to affect emotional memory retrieval and potentially reconsolidation, offering an opportunity for developing more efficient treatments for disorders with an emotional memory component. Here, we investigated if cortisol suppression after reactivation of emotional memories weakens later memory thereof. Forty healthy young men were tested in a randomized, placebo controlled, double-blind, and between-subject design, assigned either to a cortisol suppression (metyrapone) group or a placebo group. Participants of both groups, were presented with two emotional stories at an encoding session (Day 1). One of the two stories was later reactivated and followed by metyrapone vs. placebo administration (Day 3). Memory for both stories was tested at a recognition memory session (Day 7). In the group undergoing cortisol suppression after memory reactivation memory performance was weaker compared to the placebo group, tested four days after reactivation. This study shows that cortisol suppression can weaken memory for past events, possibly by altering reconsolidation processes and thus exerting long-lasting weakening effects on the original memory.

1. Introduction

The majority of people will encounter stressful or traumatic events during the course of their life span, such as an accident, an assault, the loss of a partner or a close friend. Exposure to such events can result in disabling mental health problems, such as anxiety disorders or post-traumatic stress disorder (PTSD). At the root of these disorders are strong memories for the emotionally aversive event (de Quervain et al., 2017; Lee et al., 2017; Elsey et al., 2018). While it is primarily adaptive to form a strong memory for an emotionally aversive life event, in individuals who develop mental health disorders, the strong memory becomes maladaptive and leads to clinical symptoms, such as re-experiencing fear reactions (e.g. in anxiety disorders) or uncontrolled recall of the event (e.g. flashback memories in PTSD) (de Quervain et al., 2009). Psychotherapy, such as cognitive-behavioral treatment, is currently the gold standard for treating these disorders, but it reaches its full effectiveness only in a subgroup of patients (50–60%) (Loerinc et al., 2015).

In order to develop more efficient psychotherapeutic treatments, it is vital to understand how strong memories for emotional events are formed in the brain and how they can be changed over time. The finding that memories for emotionally aversive events may be changed when retrieved, offers possibilities to develop novel treatments for disorders with an emotional memory component (Kindt and van Emmerik, 2016). Over the last decade, it has been demonstrated primarily in animal studies, and more recently also in humans, that the process of memory retrieval can reactivate a memory trace and thereby bring it into a labile state, during which the reactivated memory trace is once again sensitive to modifications by environmental or pharmacological manipulations (Schiller et al., 2010; Schiller and Phelps, 2011; Nadel et al., 2012; Agren, 2014; Forcato et al., 2014). Researchers commonly describe that memory is re-stabilized during this post-reactivation phase and therefore that phase is interpreted as reconsolidation of the original memory trace (Schiller and Phelps, 2011;

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Agren, 2014; Lee et al., 2017; Elsey et al., 2018). This reconsolidation window has been considered a unique opportunity to interfere with the process of memory re-stabilization, thereby weakening or even erasing memories for emotional events. Alternatively, changes in memory due to post-reactivation manipulations have been explained by the context/state-dependency of memories: post-reactivation updates memory with a new context/state that gets integrated to the original memory, making it inaccessible without the necessary context/state (Gisquet-Verrier et al., 2015; Gisquet-Verrier and Riccio, 2019).

Recent studies have shown that stress hormones, such as cortisol and noradrenaline, have the capacity to modulate different memory phases, e.g. the process of consolidation, in particular memory extinction, memory retrieval, as well as the process of reconsolidation (Kindt et al., 2009; Coccoz et al., 2011; Schwabe et al., 2012; Akirav and Maroun, 2013; Dongaonkar et al., 2013; Schwabe et al., 2013; Merz et al., 2014; Rimmele et al., 2016; Meir Drexler and Wolf, 2017; Thomas et al., 2017). This suggests that the alteration of levels of the stress hormones could be a potential mean to manipulate consolidation, retrieval and reconsolidation processes and thus weaken memories for emotional events (Lonergan et al., 2013; de Quervain et al., 2017). Importantly, the relationship between cortisol levels and memory performance follows an inverted U-shaped function, with medium levels leading to optimal performance, while increased or lower levels are associated with weakened memory (Diamond et al., 1992; Schilling et al., 2013). To date, experimental protocols have mostly examined ways to weaken memories with increased levels of cortisol, as observed for example under a stressor impairing memory retrieval or enhancing extinction memory of learned material (Bos et al., 2014; de Quervain et al., 2017; Meir Drexler and Wolf, 2017). However, for translation into treatment of psychotherapies it might also be interesting to look at the other side of the inverted-U shaped function and examine how low levels of cortisol could weaken memory, possibly via altering reconsolidation.

Previous studies have shown that pharmacologically lowering the level of the stress hormone cortisol decreases memory retrieval especially for emotional events (Rimmele et al., 2010; Marin et al., 2011; Rimmele et al., 2015). In particular, administering the cortisol synthesis inhibitor metyrapone and testing memory when the treatment has reached its effectiveness (i.e. under decreased cortisol levels) weakened participants' memories for emotional stimulus material (Rimmele et al., 2010; Marin et al., 2011; Rimmele et al., 2015). Days later, when metyrapone had been cleared from the body and cortisol levels were no longer suppressed, participants still showed lower memory for emotional material (Marin et al., 2011; Rimmele et al., 2015). These findings indicate that recalling an emotional memory under suppressed cortisol levels does not only immediately weaken the memory for the emotional material, but also weakens emotional memories in a long-lasting way. However, the mechanism underlying these effects remains unclear. One possibility is that cortisol suppression alters reconsolidation after retrieval. This possibility has not yet been examined, because in previous studies metyrapone was effective during the time of memory retrieval. As such, in this study we aimed to investigate whether cortisol suppression following a reminder leading to reactivation of an established emotional memory, created in the lab, will weaken the later tested memory.

Specifically, here we examine the impact of cortisol suppression (via oral administration of metyrapone) on weakening memories for emotional events in young healthy adults after their reactivation. During the encoding session, participants were presented with two emotionally arousing stories (Cahill et al., 1994; Rimmele et al., 2003; Kroes et al., 2014). Three days later, memory for one of the two stories was reactivated, by asking a few questions about the first slide of the one story but not the other story (Kroes et al., 2014). Following reactivation of the memory, half of the participants were administered metyrapone and the other half placebo. We hypothesized that metyrapone alters the reconsolidation process of the memory for the reactivated story. As such, we expected participants that received metyrapone (vs. placebo) after labilizing the emotional memory to show weaker memory for the reactivated emotional story in a memory test four days later.

Table 1
Sample characteristics.

	Placebo	Metyrapone	p-value
Age (years)	24.67 ± 4.15	24.88 ± 5.08	.653
BMI (kg/m^2)	23.05 ± 3.13	23.09 ± 2.55	.979
Beck Depression	3.5 ± 3.77	2.27 ± 2.49	.287
Beck Anxiety	2.72 ± 3.18	1.4 ± 1.55	.151
Trait Anxiety (STAI-T)	31.06 ± 5.72	31.33 ± 4.08	.876

There were no differences between the two groups in all sample characteristics (all $p >$ .151).
Values depict means ± standard deviation.

2. Materials and methods

2.1. Participants

Forty healthy males were randomly assigned to the cortisol suppression group (metyrapone) and to the placebo group. The final analysis included 18 participants in the metyrapone group (mean ± SD; age: 25.33 ± 5.04 years; body mass index: 23.09 ± 2.55 kg/m^2; one participant was excluded because of missing data due to software malfunction) and 21 participants in the placebo group (mean ± SD; age: 24.67 ± 4.1 years; body mass index 23.05 ± 3.13 kg/m^2; Table 1). Participants were screened with online questionnaires and a short medical interview and physical exam for their eligibility to participate in the study. There were no differences in age and body mass index, self-reports of anxiety (assessed with the State Trait Anxiety Inventory -Trait Scale, STAI-T: Spielberger, 1983; and the Beck Anxiety Inventory, BDI: Beck and Steer, 1990) and depression (Beck Depression Inventory, BDI: Beck et al., 1979) between the participants in the metyrapone and the placebo group (all $p > .151$; Table 1). Also participants of the two groups did not differ in baseline memory performance in another task, i.e. text recall (see Wagner et al., 2005; Rimmele et al., 2013) administered prior to reactivation and pill administration. All participants were non-smokers, not on any medication, free of neurological and psychiatric disorders, and had a regular sleep-wake rhythm. All participants signed an informed consent form approved by the ethics committee of the canton of Geneva (Commission Cantonal d'Éthique de la Recherche, CCER) and were paid for their participation.

2.2. Experimental design and procedure

Participants were tested in a randomized, placebo-controlled, double-blind, between-subject design. In both conditions, participants underwent an encoding session (Day 1), a reactivation session (Day 3), and a recognition memory session (Day 7; Fig. 1A).

At the encoding session (Day 1), participants were presented with two stories. These stories have been used in previous memory experiments. Both contain emotional material, are parallel in structure and presentation but nevertheless distinct from each other (Cahill et al., 1994; Kroes et al., 2014). Each story comprises a sequence of 11 slides presented with an auditory narrative and can be divided into three phases: Phase 1 (four slides), Phase 2 (four slides; considered as emotional), and Phase 3 (three slides). Each slide was presented for 20 s. One story describes the day of a mother with her son going to the hospital (Cahill et al., 1994), and the other is about an evening of two sisters in their 20 s going out (Kroes et al., 2014).

The reactivation session took place two days after the encoding session (Day 3). On that day, only one of the two stories was reactivated with a cue, counterbalanced across participants in both groups, following the procedure described in a previous study and the criteria for

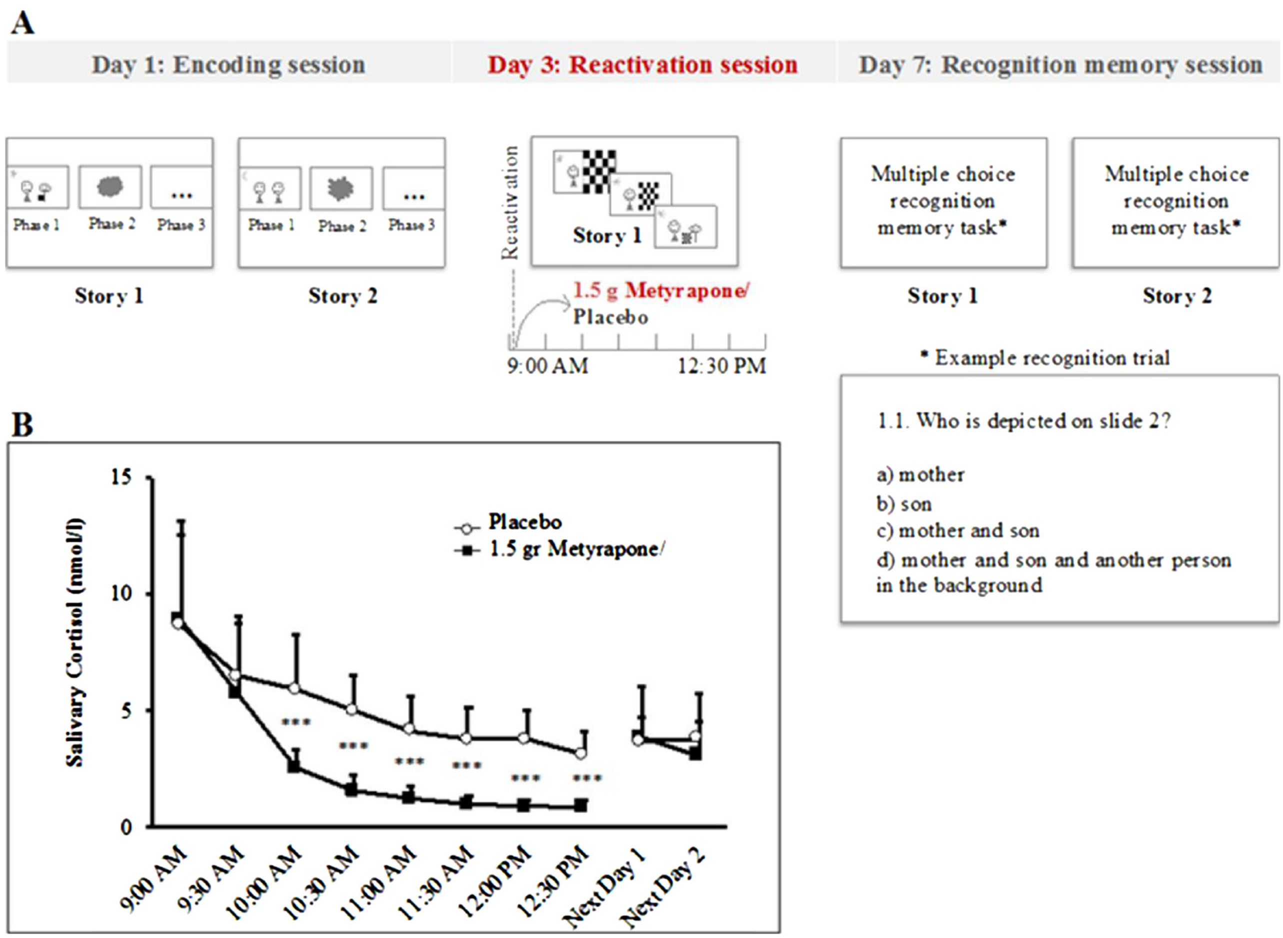

Fig. 1. Experimental procedure (A) and cortisol levels (B).
(A) Participants were randomly assigned to a metyrapone or a placebo group, where they went through three sessions on three different days.
At the encoding session (Day 1), participants were presented two stories.
At the reactivation session (two days later: Day 3), one of the two stories was reactivated, by presenting a reminder cue –the first slide of the story partially masked with a black-and-white checkerboard pattern- and few questions about the story. Following reactivation, participants received either metyrapone or placebo. Salivary cortisol samples were collected just before the reactivation and every 30 min after treatment administration until 12:30 PM.
At the recognition memory session (four days after reactivation: Day 7), participants were tested with a multiple-choice recognition memory task for both the reactivated and the non-reactivated story.
(B) Cortisol levels: Mean ± SE salivary cortisol concentration for Day 3 and the next day (Day 4). Horizontal axis indicates the time-points when saliva samples were collected. Baseline cortisol levels prior to reactivation and treatment administration (at 9:00 AM) as well as 30 min after treatment administration (at 9:30 AM) did not differ between groups. Metyrapone (black squares) suppressed cortisol levels for all the other time-points on Day 3. There was no difference in the cortisol levels tested the next day for a subset of participants.

reconsolidation paradigms (Kroes et al., 2014). Participants were presented with the first slide of one of the two encoded stories, partially masked by a black-and-white checkerboard pattern, and tested for their memory of that slide with three questions. They were first asked about the covered part of the scene and after their response, they were presented with the same scene again but with a smaller mask; i.e., with every of the three questions the covered part was progressively made more visible allowing answering the question. If the participant could not freely recall the response, the experimenter gave two alternative answers for the participant to choose from. Immediately after reactivation, participants orally received either placebo or metyrapone (1.5 g, HRA Pharma) with a light snack (yogurt). Metyrapone is a cortisol synthesis inhibitor and it has been previously shown that a dose of 1.5 g can sufficiently lower cortisol levels within an hour and up to six hours after administration, i.e. the proposed duration of the reconsolidation window (Maheu et al., 2004; Marin et al., 2011; Schiller and Phelps, 2011; Rimmele et al., 2015).

The recognition memory test (Day 7) was four days after the reactivation session and seven days after the encoding session. Participants were asked to complete a computerized multiple-choice recognition memory task for the two stories they had seen on Day 1. For each question, four verbal response options were provided. To test participants' memory for the reactivated and the non-reactivated story, they were asked 3–5 questions per slide (39 questions in total), presented in the order of the scenes in the original slide shows (Kroes et al., 2014).

2.3. Hormonal measures

During the reactivation session, salivary cortisol samples were collected with Sarstedt salivette tubes (Sarstedt, Rommelsdorf Germany) at 9:00 AM (just before treatment administration) and then every 30 min for four hours, i.e. at 9:30, 10:00, 10:30, 11:00, 11:30 AM, 12:00, and 12:30 PM (Fig. 1A & 1B). For a subset of participants (9 for each group), two more salivary samples were taken the next day (31 h after administration) as a control measure for the cortisol levels (as Next Day 1 & 2 on Fig. 1B).

Saliva samples were stored at -25 C until their analysis. Cortisol levels were assessed with the use of a luminescence immunoassay for the in vitro diagnostic quantitative determination of cortisol in human saliva (IBL International). Inter- and intra-assay coefficients of variation for cortisol were below 8.5%.

2.4. Data analysis

To assess recognition memory performance, we computed the percentage of correct answers out of the number of questions per phase, which included 11 questions for Phase 1 (excluding questions for the first slide), 14 questions for Phase 2, and 9 questions for Phase 3. Memory performance for the first slide of both the reactivated and the non-reactivated story was not taken into account for all memory scores. Memory performance was analyzed with a 2 (reactivated/non-reactivated story) mixed-design analysis of variance (ANOVA) with metyrapone/placebo group as between-subject factor "treatment" (see Supplementary for results including the phase of each story as a factor). Greenhouse-Geisser corrections of degrees of freedom were used when suitable. In order to explain the observed effects, planned comparisons were performed with separate t-tests between the groups for the reactivated and the non-reactivated stories (all two-tailed and considered significant when $p \leq .05$).

Cortisol levels were analysed with mixed-design analyses of variance (ANOVA) with treatment, i.e. metyrapone/placebo group, as a between-subject factor and the 8 time-points of saliva samples on Day 3 (and separately the two cortisol measures on the next day) as repeated-measures factor "time". Greenhouse-Geisser corrections of degrees of freedom were used when appropriate and follow-up t-tests were employed to specify the observed effects (all two-tailed and considered significant when $p \leq .05$). One participant in the metyrapone group was excluded from the cortisol level analysis, due to missing data of the cortisol measures (as the output of the analyses of the memory performance was not affected by this participant's exclusion, this participant was included in the memory analyses).

3. Results

3.1. Hormonal measures

At the reactivation session (Day 3), salivary cortisol levels were lower after metyrapone vs. placebo administration [main effect of treatment: $F(1,35) = 24.84$, $p < .001$, $\eta^2 = .415$; main effect of time: $F(1.591,55.669) = 78.357$, $p < .001$, $\eta^2 = .691$; treatment by time interaction: $F(1.591,55.669) = 6.72$, $p < .01$, $\eta^2 = .161$]. Baseline cortisol levels did not differ between placebo and metyrapone condition prior to treatment administration [at 9:00 AM: $M_{PL} = 8.64$, $SE = .85$ nmol/l vs. $M_M = 8.89$, $SE = 1.03$ nmol/l; $p = .856$] and 30 min after treatment administration [at 9:30 AM: $M_{PL} = 6.48$, $SE = .56$ nmol/l vs. $M_M = 6.03$, $SE = .68$ nmol/l; $p = .609$]. For all the other time points on Day 3 (from 10:00 to 12:30), cortisol levels were significantly suppressed after metyrapone (all $p < .001$; see Fig. 1B).

There was no difference in the cortisol levels tested the next day for a subset of participants (N = 9 for each group; all $p > .364$; see Fig. 1B).

3.2. Memory

Metyrapone administration just after the reactivation of a memory weakened overall performance in the multiple-choice memory task, administered four days later [main effect of treatment: $F(1,37) = 4.674$, $p = .037$, $\eta^2 = .112$; $M_M = .466$, $SE = .028$ vs. $M_{PL} = .548$, $SE = .026$]. Planned comparisons between groups showed that metyrapone vs. placebo administration decreased overall memory performance for the reactivated story [$M_M = .443$, $SE = .038$ vs. $M_{PL} = .552$, $SE = .031$; $t(37) = -2.281$, $p = .028$, d = .75; Fig. 2]. There was no difference in memory performance for the non-reactivated story between the two groups [$M_M = .490$, $SE = .029$ vs. $M_{PL} = .544$, $SE = .028$; $p = .191$; Fig. 2].

No other effects were significant [main effect of reactivation: $F(1,37) = .723$, $p = .401$, $\eta^2 = .019$; treatment by reactivation interaction: $F(1,37) = 1.368$, $p = .250$, $\eta^2 = .036$].

4. Discussion

With this study, we investigated whether memories for emotional events can become weaker when cortisol levels are pharmacologically suppressed during the time of reconsolidation. Firstly, metyrapone administered just after reactivating the memory of an emotional story decreased cortisol levels after treatment administration compared to the placebo group. Secondly, a multiple-choice memory test showed that metyrapone vs. placebo administration before the reactivation of an emotional memory weakened overall memory performance four days later.

Our finding that metyrapone administration in the present study suppressed cortisol levels in comparison to the placebo group is in accordance with robust previous findings (Lupien et al., 1995, 2002; Maheu et al., 2004; Rimmele et al., 2010; Hermans et al., 2011; Marin et al., 2011; Rimmele et al., 2015; Antypa et al., 2018). The cortisol suppression was effective one hour after the administration of 1.5 g of metyrapone. At the latest measurement point (3.5 h after treatment administration) cortisol levels were still suppressed. The level of cortisol that participants reached after metyrapone corresponds to relatively low levels of cortisol, comparable to the circadian nadir (Rimmele et al., 2015). These effects of metyrapone administration have been observed to last for four to six hours after treatment administration for similar doses in previous protocols (Maheu et al., 2004; Marin et al., 2011; Rimmele et al., 2015). Importantly, in our study cortisol levels were comparable again between the two groups 31 h after treatment administration showing that the medication had been washed out and as such was unlikely to affect performance in the recognition test four days later. Overall, our study confirms that administration of 1.5 g of metyrapone can lower cortisol to levels similar to the circadian nadir for a definite period of time when compared to a placebo group.

Interestingly, metyrapone administration just after memory reactivation resulted in weaker overall memory performance in the metyrapone vs. placebo group, when tested four days after the reactivation session. This finding extends previous findings showing that free recall during suppressed cortisol levels weakens emotional memories immediately and days later (Marin et al., 2011; Rimmele et al., 2015). In particular, our findings suggest that the mere reactivation rather than full recall of an emotional memory –a story for this paradigm- followed by cortisol suppression suffices to observe weaker memory performance for the event in a long-lasting way, when compared to the placebo group. This finding indicates that cortisol suppression after memory reactivation exerts a long-lasting effect of weakening the original memory in comparison to a placebo group, possibly through an alteration of reconsolidation processes or a memory update by a new context/state.

Nevertheless, the specificity of the metyrapone effects depending on reactivation of the memory should be taken into consideration. Even though planned comparisons showed that cortisol suppression weakened memory for the reactivated but not the non-reactivated story; overall, there was a main effect of treatment, indicating a more generalized memory effect. Such an effect could be explained by the impact of one or more elements of our design, which have been proposed crucial for reconsolidation processes. Firstly, reconsolidation has been described as highly context-dependent (Hupbach et al., 2008). As both stories were encoded in the same room and the reactivation room was the same as the room in which the encoding took place, the reactivation of one story might also have reactivated the memory for the other story. Secondly, consolidation and reconsolidation have been proposed to concern mnemonic episodes rather than distinct elements of an episode (Staresina and Davachi, 2009; Deuker et al., 2016; Milivojevic et al.,

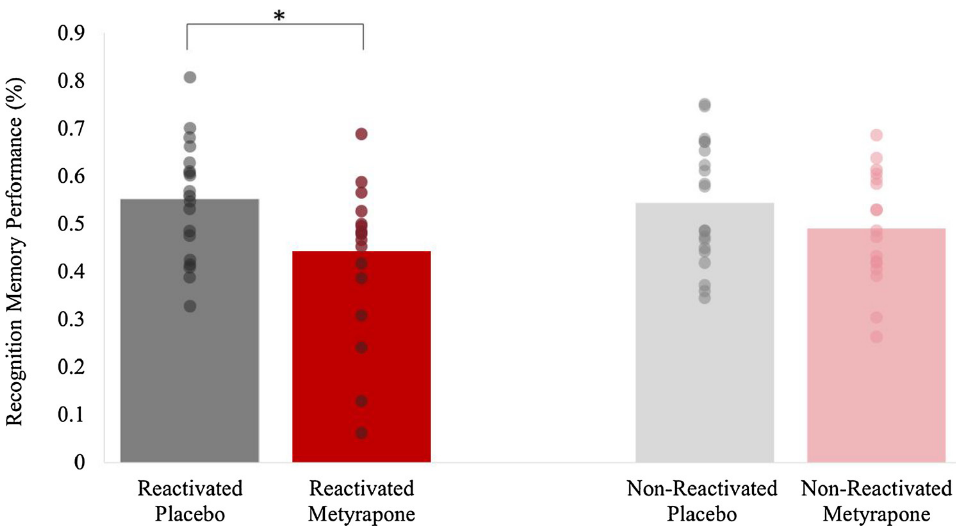

Fig. 2. Memory performance for reactivated and non-reactivated stories in the placebo and the metyrapone group.
Pharmacologically suppressing cortisol levels after memory reactivation decreased memory performance tested four days later [main effect of treatment: $F(1,37) = 4.674$, $p = .037$, $\eta^2 = .112$]. Planned comparisons revealed that metyrapone impaired memory for the reactivated story.
Error bars indicate SE and * $p < .05$.

2016). By encoding two stories, which may be distinctive but nevertheless presented shortly after each other on the computer in the same way, in the same room, and by the same experimenter, participants may have encoded the two stories as a whole episode (such as “an experiment in the lab”) and therefore a future reminder of only one story may have led to the reactivation of both stories. In order to better understand the specifics of metyrapone effects on memory reconsolidation, future studies could adopt a between-subject design also for the reactivation variable, i.e. presenting only one story followed by reactivation in one group and a group without reactivation. If metyrapone specifically alters reconsolidation, the group receiving metyrapone after re-activation should show different memory than the placebo group with re-activation or the metyrapone group without reactivation. Additionally, particularly addressing the premises of a context/state-dependency account future studies should include a condition where later recall will be tested under cortisol suppression.

Notably, this study addressed the effects of cortisol suppression on the reconsolidation of memories for emotional events in a group of healthy male participants. The inclusion of only male participants has been common practice for the study of cortisol and cortisol suppression effects on emotional memory (Lupien et al., 2002; Maheu et al., 2005; Rimmele et al., 2010; Marin et al., 2011; Drexler et al., 2015; Rimmele et al., 2015; Antypa et al., 2018), because of the known interaction of female sex hormones with stress and cortisol reactivity affecting emotional learning and memory (Merz et al., 2012, 2013; Merz and Wolf, 2017; Shields et al., 2017). Nevertheless, this common practice restricts the generalizability of these findings to women. Future studies are needed to investigate if cortisol suppression can similarly affect reconsolidation of memories for emotional events in women.

While our findings suggest that cortisol suppression affects reconsolidation and therefore weakens memories for emotional events in a long-lasting way, the exact neurobiological mechanism is still unknown. Evidence from animal research indicates that cortisol modulation directly affects the involvement of amygdala in emotional memory, as well as its impact on other memory-related brain regions, such as the hippocampus (Roozendaal et al., 2009; Roozendaal and McGaugh, 2011). Future studies need to address how cortisol suppression affects the engagement of brain regions related to emotional memory in the human brain as well as examine whether cortisol suppression could alter the representations of emotional memories in the human brain. Thereby, future studies should also examine different ways of metyrapone could modulate memory. Metyrapone inhibits synthesis of cortisol via blockade of 11-hydroxylase at the level of the adrenal glands, resulting in an increase of hypothalamic corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH) and accumulation of 11-deoxycorticosterone (11-DOC) (Fiad et al., 1994; Otte et al., 2007). Crucially CRF as well as mineralocorticoid receptor agonist such as 11-DOC play a role in memory formation (Pitts et al., 2009; Wingenfeld and Otte, 2018) and may as such may be a means through which metyrapone exerts its effects.

5. Conclusions

In sum, this study shows that a group undergoing cortisol suppression after reactivation can have weaker memory for emotional events, in comparison to a placebo group, possibly because of distinct processing in the reconsolidation of reactivated memories or updating original memories with a new internal context/state. This interesting finding can have useful implications for clinical practice and, particularly, the treatment of anxiety disorders and PTSD, i.e. fear-related disorders for which researchers have started to examine cortisol-based interventions (Soravia et al., 2006; de Quervain and Margraf, 2008; de Quervain et al., 2009, 2011; Soravia et al., 2014; de Quervain et al., 2017). In agreement with previous studies showing that increased cortisol levels can modulate reconsolidation processes (Marin et al., 2010; Schwabe and Wolf, 2010; Drexler et al., 2015), here we show that metyrapone administration leading to reduced cortisol levels after reactivation likewise seems to affect reconsolidation. Because reconsolidation of an emotionally aversive event requires only reactivation instead of retrieving or potentially re-experiencing the original memory, the effectiveness of cortisol suppression on weakening emotional memories upon reconsolidation suggests a well-suited candidate for future studies aiming to address traumatic memories and to establish more efficient psychotherapeutic treatments. In this regard, studying the effects of cortisol suppression on the reconsolidation of reactivated autobiographic memories for individuals suffering from anxiety disorders or PTSD in a safe psychotherapeutic context could be the next step.

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Declarations of interest

None.

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