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Emotional memory can be persistently weakened by suppressing cortisol during retrieval

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ABSTRACT

Cortisol's effects on memory follow an inverted U-shaped function such that memory retrieval is impaired with very low concentrations, presumably due to insufficient activation of high-affine mineralocorticoid receptors (MR), or with very high concentrations, due to predominant low-affine glucocorticoid receptor (GR) activation. Through corresponding changes in re-encoding, the retrieval effect of cortisol might translate into a persistent change of the retrieved memory. We tested whether partial suppression of morning cortisol synthesis by metyrapone, leading to intermediate, circadian nadir-like levels with presumed predominant MR activation, improves retrieval, particularly of emotional memory, and persistently changes the memory. In a randomized, placebo-controlled, double-blind, within-subject cross-over design, 18 men were orally administered metyrapone (1 g) vs. placebo at 4:00 AM to suppress the morning cortisol rise. Retrieval of emotional and neutral texts and pictures (learned 3 days earlier) was assessed 4 h after substance administration and a second time one week later. Metyrapone suppressed endogenous cortisol release to circadian nadir-equivalent levels at the time of retrieval testing. Contrary to our expectations, metyrapone significantly impaired free recall of emotional texts ($p < .05$), whereas retrieval of neutral texts or pictures remained unaffected. One week later, participants still showed lower memory for emotional texts in the metyrapone than placebo condition ($p < .05$). Our finding that suppressing morning cortisol to nadir-like concentrations not only impairs acute retrieval, but also persistently weakens emotional memories corroborates the concept that retrieval effects of cortisol produce persistent memory changes, possibly by affecting re-encoding.

1. Introduction

Cortisol is a potent modulator of memory, which differentially affects processes of encoding, consolidation, and retrieval (de Quervain, Aerni, Schelling, & Roozendaal, 2009; Kelemen, Bahrendt, Born, & Inostroza, 2014; Schwabe, Joels, Roozendaal, Wolf, & Oitzl, 2011). Generally, it enhances encoding of information, but impairs memory retrieval, especially of negative material. Of note, memory retrieval is not only impaired at strongly elevated cortisol levels (de Quervain, Roozendaal, & McGaugh, 1998; de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Domes, Rothfischer, Reichwald, & Hautzinger, 2005; Kuhlmann, Piel, & Wolf, 2005), but also at minimum levels after suppression of cortisol synthesis by metyrapone (Marin, Hupbach, Maheu, Nader, & Lupien, 2011; Rimmele, Meier, Lange, & Born, 2010), suggesting an inverted U-shaped function that describes the relationship between memory retrieval and cortisol concentrations (Schilling, Kolsch, Larra, Zech, Blumenthal, Frings, & Schachinger, 2013). The inverted U-shaped response function has been linked to an imbalance in mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) activation with both enhanced GR activation at high cortisol levels and reduced MR activation at very low cortisol levels mediating impairing effects on retrieval. In line with this notion, administration of metyrapone at a dose of 3 g almost completely suppressed endogenous cortisol release, and this was accompanied by a significantly impaired free recall of texts and pictures, in particular when emotional (Rimmele et al., 2010). Thus, optimal memory retrieval is expected when MRs are occupied to a great extent, but not GRs, i.e. conditions presumably

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achieved during the circadian nadir of cortisol release (de Kloet, Oitzl, & Joels, 1999; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007).

Besides an acutely impairing effect on retrieval, there is first evidence that the impairing effect of metyrapone on memory retrieval persists beyond the acute period of cortisol suppression and is still present at a second retrieval test 4 days later (Marin et al., 2011). That study showed a persisting decrease of emotional, but not neutral memories for pictures with 1.5 g of metyrapone, but not with 0.75 g of metyrapone given before the first retrieval of the test materials. Salivary cortisol measures indicated that a significant suppression of cortisol was achieved only after the 1.5 g dosis.

Here, we tested the effect of metyrapone-induced cortisol inhibition during the morning hours on acute retrieval and the persistence of this effect over an even longer 1-week interval. Adopting the framework of an MR/GR activation balance that determines the direction of glucocorticoid effects, we chose a dose of 1 g metyrapone. Based on pilot studies and our previous work (Rimmele et al., 2010), this dose was expected to only partially block cortisol release and to induce cortisol levels comparable with those during the circadian nadir of pituitary-adrenal activity where MRs are estimated to be occupied by 50–70%, in the absence of substantial GR occupation (Kalman & Spencer, 2002; Reul & de Kloet, 1985; Spencer, Miller, Moday, Stein, & McEwen, 1993). We expected that such predominance of MR over GR occupation would acutely enhance memory retrieval. Assuming that the effect on retrieval goes along with a parallel effect on re-encoding, we further expected that the acute enhancement in retrieval after metyrapone would persist during a second retrieval test 1 week later.

2. Methods

2.1. Participants

Eighteen healthy native German-speaking men (mean age 22.17 ± 2.50 years; mean body mass index 22.92 ± 1.65 kg/m^2) participated in the double-blind, within-subject cross-over study, which was approved by the local ethics committee. Subjects provided informed consent and were paid for participation.

2.2. Procedure and memory tasks

Each participant was tested in two conditions (metyrapone vs. placebo), separated by an interval of at least 12 days, with the order of conditions balanced across subjects. Each condition included a learning session and two retrieval sessions (Fig. 1A). In the learning session (9:00–11:00 AM), participants memorized emotional and neutral texts (Wagner, Degirmenci, Drosopoulos, Perras, & Born, 2005) and pictures (Lang, 1999). Substance administration took place at 4:00 AM before the first retrieval session (between 7:45 AM and 9:00 AM, 3 days after the learning session). To this end, subjects slept in the laboratory (lights off at 11:00 PM) and were shortly awakened for oral administration of either metyrapone (1 g, Novartis Pharma, Switzerland, half life in plasma 20–120 min) or placebo. Retrieval of the texts took place between 7:45 AM and 8:30 AM, and retrieval of the pictures between 8:30 AM and 9:00 AM. Cortisol, ACTH, epinephrine and norepinephrine levels were assessed repeatedly in blood sampled at 2:00 AM and 3:30 AM, and following substance administration every 30 min from 4:30 AM until 10:00 AM. The second retrieval session took place one week later in the afternoon (2:00–4:00 PM).

For assessment of text memories in each of the two learning sessions, participants were instructed to read one emotional and one neutral text, which were printed on a sheet of paper, thoroughly within 4 min (abundant time to complete the readings) and to memorize as many details as possible for later recall. The order of the experimental texts within a session and the order of parallel versions on the subject's two test occasions were balanced across subjects. Immediately after learning, participants wrote down the previously read text as exactly as possible in order to obtain a measure of the original encoding level. Free recall was assessed in the same way in the first retrieval session 3 days (after pill administration) as well as in the second retrieval session 10 days (without any pill administration) after learning. Assessment of memory performance was based on the number of correctly recalled content words. Validity of this measure has been confirmed in previous experiments (Schuerer-Necker, 1994).

For assessment of picture memory in the learning session, participants were instructed to memorize 50 negative and 50 neutral pictures. Following the presentation of each picture for 4 s, using the Self Assessment Manikin (1, highly positive; 9, highly negative; 1, very much arousing; 9, not at all arousing) (Bradley, Greenwald, Petry, & Lang, 1992; Lang, 1999), emotional and neutral pictures were rated significantly different on valence (average rating – emotional 5.92 ± .26; neutral 4.27 ± .18; $t(14) = 6.24$, $p < .001$) and arousal (emotional 5.10 ± .46; neutral 6.79 ± .34; $t(14) = 5.89$, $p < .001$). Arousal and valence ratings did not differ between the parallel versions (all $p > .19$). The two sets were counterbalanced across the metyrapone and placebo condition. Immediately after encoding, during the first retrieval session 3 days (after receiving placebo or metyrapone) and the second retrieval session 10 days after learning (without pill administration), participants' free recall was assessed by asking them to list, for each picture recalled, as many details as they could remember with no time constraint.

2.3. Psychological control variables

At the beginning of the retrieval sessions, attention, mood, calmness, wakefulness, and working memory were assessed using the d2 letter cancellation test (Brickenkamp & Zillmer, 1998), the Positive and Negative Affect Scale (PANAS) (Watson, Clark, & Tellegen, 1988), the Multidimensional Mood Questionnaire (Steyer, Schwenkmezger, Notz, & Eid, 1997), and the Digit Span subtest (forward, backward) of the Wechsler Adult Intelligence Scale (Wechsler, 1981). Additionally at the end of the retrieval sessions, working memory was assessed with the Sternberg task as previously described (Lupien, Gillin, & Hauger, 1999).

2.4. Hormonal measures

Blood samples were immediately centrifuged and stored at −80 °C until assay. Cortisol and ACTH concentrations were assessed using Immulite (Siemens Medical Solutions Diagnostics, Los Angeles, CA; sensitivity .2 μg/dl for cortisol, 9 pg/ml for ACTH). Plasma epinephrine (E) and norepinephrine (NE) were assessed with standard high-performance liquid chromatography (ChromSystems, Munich, Germany; sensitivity 15 pg/mL for E and NE). Interassay coefficients of variation for all assays were <10%. E levels were mostly below detection threshold and are not reported.

2.5. Data analyses

Two independent raters, blind to treatment, quantified written free recall. Statistical analysis was based on analyses of variance (ANOVA) with repeated-measures factors for 'treatment' (metyrapone vs. placebo) and 'session' ('learning session vs. 1st retrieval session, and 1st vs. 2nd retrieval session, respectively) and for the memory variables, the additional factor 'emotionality' (neutral vs. emotional). For hormone levels, analyses included repeated-measures factors 'treatment' and 'time of measurement'. Where appropriate, Greenhouse–Geisser corrections of degrees of freedom were used. Significant ANOVA effects were specified by