



## Retrieval-induced forgetting under psychosocial stress: No reduction by delayed stress and beta-adrenergic blockade



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### ABSTRACT

Retrieval-induced forgetting (RIF) is the phenomenon that 'retrieval-practice', the repeated retrieval of a subset of initially learned material, can impair the recall of episodically related memories. Previous studies showed that RIF is eliminated when retrieval-practice is carried out under psycho-social stress, anxiety, or in negative mood. However, pharmacological manipulation by hydrocortisone did not eliminate the effect. This study investigated the effect of beta-adrenergic blockade on stress-induced modulations of RIF, addressing possible interactive effects of the glucocorticoid and sympatho-adrenomedullary systems. Participants learned categorized word lists and then received either 60 mg propranolol or a placebo. After 90 min they were exposed to the TSST. A third group did not receive any medication and performed a non-stressful control task with the same timing as the other two groups. Finally, all participants underwent retrieval-practice and final recall. Both TSST groups exhibited a stress-induced increase in cortisol-levels, and the placebo group also exhibited large increases in markers of sympathetic nervous system activity and more psychological distress at the time of retrieval-practice. Although, overall recall was poorer under stress, an overall RIF effect emerged irrespective of group and showed no clear modulation by stress with or without beta-adrenergic blockade. In previous demonstrations of RIF elimination by negative emotion, state induction and retrieval-practice followed very briefly after initial learning. Given that both the previous study of hydrocortisone effects on RIF and the present study used longer delays between learning and retrieval-practice, the possibility that stress effects on retrieval-practice eliminate RIF only relatively briefly after learning is discussed.

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### 1. Introduction

Stress can have profound cognitive and physiological effects. The physiological stress response is mediated by two partially interacting pathways, the sympathetic branch of the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis. Activation of the sympathetic nervous system (SNS) results in increased secretion of adrenaline and noradrenaline as well as increases in blood pressure and heart rate (Ulrich-Lai & Herman, 2009). Stress-induced activation of the HPA axis ultimately leads to increased secretion of glucocorticoids from the adrenal cortex. In

addition, circulating glucocorticoids potentiate many sympathetically mediated effects.

Regarding cognition, particularly stress-induced memory modulation has been investigated, with the classic findings that glucocorticoids enhance memory consolidation and impair memory retrieval (e.g., Wolf, 2009). Moreover, noradrenergic activity, primarily in the basolateral complex of the amygdala (BLA), appears to play an important role in mediating the influences of cortisol and other hormones or neurotransmitters on memory (for review see McGaugh & Roozendaal, 2008).

Recent research (Koessler, Engler, Riether, & Kissler, 2009) indicates that psychosocial stress can also affect memory control processes like retrieval-induced forgetting (RIF), i.e. forgetting that is caused by the repeated retrieval of a subset of previously studied material. RIF is generally seen as an adaptive mechanism promoting successful selection and retrieval of target memories by temporarily inhibiting related but irrelevant information (e.g., MacLeod, Saunders, & Chalmers, 2010). It is studied using the retrieval-practice paradigm (Anderson, Bjork, & Bjork, 1994), where participants

*Abbreviations:* ANS, autonomic nervous system; BLA, basolateral amygdala; BMI, body-mass index; BP, blood pressure; HPA (-axis), hypothalamic-pituitary adrenal (axis); RIF, retrieval-induced forgetting; sAA, salivary alpha-amylase; SNS, sympathetic nervous system; TSST, Trier Social Stress Test; VAS, visual analogue scale.

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learn a list of category–exemplar pairs (e.g., fruit – strawberry, spice – ginger, fruit – apricot) and then are repeatedly cued to retrieve half of the items from some of the categories (e.g., fruit–ap\_\_\_\_). In a subsequent memory test, this typically leads to impaired recall of the nonpracticed items (e.g., strawberry) from practiced categories (e.g., fruit) relative to recall of items from totally unpracticed categories (e.g., spice). The RIF effect is commonly attributed to an inhibitory process acting during retrieval–practice: the category name that is presented as a retrieval cue activates all exemplars associated with the cue which then compete for retrieval. This causes interference, which is thought to be resolved by active inhibition of the currently irrelevant items, whose recall in a later memory test is consequently impaired (Anderson & Spellman, 1995; Anderson et al., 1994; for non-inhibitory accounts see Raaijmakers & Jakab, 2012; Williams & Zacks, 2001). The active inhibition is thought to primarily act at the level of the unpracticed items' memory representation itself, possibly by reducing in-trial feature binding (Bäuml, Pastötter, & Hanslmayr, 2010). Factors that influence the RIF effect are the level of integration of the studied material, i.e. forming inter-relations between items that share a common retrieval cue, and the affective state experienced during retrieval–practice. Highly integrated material produces less interference during retrieval–practice. Therefore, less inhibition is needed which reduces or even reverses the RIF effect (Anderson & McCulloch, 1999; Chan, 2009). Recent findings suggest that RIF can also be reduced or even eliminated by negative mood (Bäuml & Kuhbandner, 2007), high state anxiety (Koessler, Steidle, Engler, & Kissler, 2013; Law, Groome, Thorn, Potts, & Buchanan, 2012) or psychosocial stress (Koessler et al., 2009). It has been suggested that the experience of such negative affective states during retrieval–practice induces a switch in processing style towards a greater focus on a target item's features and distinctive qualities (Bäuml & Kuhbandner, 2007) which in turn reduces interference from unpracticed memories bound to the same retrieval cue. Therefore, inhibition becomes less necessary and the RIF effect is reduced. Interestingly, integration and negative mood can have interactive effects that lead to a restoration of the RIF effect even though they individually reduce RIF: The protective effect of integrated material against RIF can be reduced by negative mood (Kuhbandner & Pekrun, 2013).

Possible neuroendocrine mechanisms underlying state-related eliminations of RIF are largely unexplored. Structurally and functionally, medial-temporal lobe structures like the hippocampus as well as prefrontal cortical regions seem to be involved in the processes generating the RIF effect (Conway & Fthenaki, 2003; Johansson, Aslan, Bäuml, Gäbel, & Mecklinger, 2007; Kuhl, Dudukovic, Kahn, & Wagner, 2007; Kuhl, Kahn, Dudukovic, & Wagner, 2008; Wimber, Rutschmann, Greenlee, & Bäuml, 2009; Wimber et al., 2008). The hippocampus is a key structure for forming and retrieving associations between different elements of an episodic memory representation (binding) whereas the prefrontal cortex is associated with the monitoring and control of encoding and retrieval processes (Ghetti & Bunge, 2012) and is thought to exert the inhibition of irrelevant information (e.g., Kuhl et al., 2007). These structures also have many glucocorticoid receptors (McEwen, Weiss, & Schwartz, 1969; Perlman, Webster, Herman, Kleinman, & Weickert, 2007) and can be impaired in their function by stress or glucocorticoids (Arnsten, 2009; McEwen & Magarinos, 2001). This allows for possible modulating influences of stress hormones on the RIF effect. So far, two studies have investigated the role of glucocorticoids in the elimination of RIF by stress (Koessler et al., 2009, 2013), but no study has specifically addressed the role of the SNS. Koessler et al. (2009) exposed participants to the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993; Kudielka, Hellhammer, & Kirschbaum, 2007) briefly after learning, immediately before the retrieval–practice phase and found that

psychosocial stress eliminates RIF. The stress-induced rise in salivary cortisol levels was negatively correlated with the amount of RIF, suggesting that cortisol may be involved in this process, possibly by disrupting episodic binding in the hippocampus and promoting item-specific processing. However, hydrocortisone administration could neither eliminate nor reduce RIF (Koessler et al., 2013). Nevertheless, the later study provided evidence for an effect of state anxiety on RIF: participants with high levels of state anxiety during retrieval–practice showed reduced RIF and this effect was more pronounced in the hydrocortisone group. A role of state anxiety in the elimination of RIF is also supported by Law et al. (2012), who found an inverse correlation between state anxiety scores and RIF. As state anxiety is associated with ANS activation (e.g., Spielberger & Reheisser, 2009), Koessler et al.'s finding (2013) suggests that some degree of emotional activation, possibly reflecting activity of the sympatho–adrenomedullary axis, might either be necessary to enable cortisol effects on RIF, via an interaction of noradrenergic and glucocorticoid actions in the basolateral amygdala modulating memory processes in the hippocampus and prefrontal cortex (for a review see Roozendaal & McGaugh, 2011), or might have been the primary mediator of the stress-induced elimination of RIF observed by Koessler et al. (2009). Indeed, the TSST induces not only activation of the HPA axis but also of the ANS, as indexed by increases in emotional arousal and state anxiety (e.g., Federenko, Nagamine, Hellhammer, Wadhwa, & Wüst, 2004), blood pressure (BP), heart rate, salivary alpha-amylase (sAA) activity and the release of adrenaline and noradrenaline (e.g., Nater et al., 2006; for a review see Kudielka et al., 2007). Therefore in the Koessler et al. (2009) study an interaction of the HPA axis and the ANS could have mediated the elimination of RIF in the TSST condition, but ANS activation was not assessed.

The present study aimed at investigating whether psychosocial stress effects on RIF can be blocked via administration of the  $\beta$ -adrenoceptor antagonist propranolol. By blocking the sympatho–adrenomedullary axis with propranolol, the roles of the HPA axis and the SNS in stress effects on RIF are examined. Three groups of participants learned a list of category–exemplar pairs and then two of them received either placebo or 60 mg of propranolol prior to being exposed to the TSST. To allow for the propranolol to take effect before the TSST started, the retrieval–practice paradigm had to be adapted and the delay between learning and retrieval–practice was extended to just under 2 h. However, since there is evidence that longer delays between study and retrieval–practice can reduce the RIF effect (Macleod & Macrae, 2001), a no-stress control group was included in order to examine whether RIF would still be present with a delay of about 2 h between study and retrieval–practice. This third group did not receive any drug and instead of the TSST performed a non-stressful control task as used by Koessler et al. (2009). Retrieval–practice followed immediately and in the same context as the TSST or control task to assure that in the two stress groups participants' stress levels remained high during retrieval–practice. We hypothesized that, if stress-related elimination of RIF depends on the interaction of heightened levels of cortisol with concurrent noradrenergic activation during retrieval practice, then RIF should be absent in the placebo + TSST condition, but present in the no-stress condition and under propranolol, where the interaction is pharmacologically blocked.

## 2. Methods

### 2.1. Participants

Seventy-three healthy participants, recruited by advertisements at the University of Konstanz, were included in this study. They were extensively screened for acute and chronic health problems

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