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Interaction of noradrenaline and cortisol predicts negative intrusive memories in posttraumatic stress disorder

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ABSTRACT

Recent evidence suggests that an interaction of noradrenaline (NE) and cortisol (CORT) during encoding leads to greater consolidation of emotional memories. Convergent models of posttraumatic stress disorder (PTSD) suggest the release of CORT and NE lead to greater intrusive memories in PTSD. This study examined the effect of NE and CORT during encoding on recall and intrusive memories in PTSD. Fifty-eight participants (18 participants with PTSD, 20 trauma-exposed controls, and 20 non-trauma exposed controls) provided saliva samples of NE (indexed by salivary alpha amylase; sAA) and CORT at (a) baseline and (b) after viewing negative emotional stimuli. Delayed memory recall and number of intrusive memories of negative, neutral and positive stimuli were recorded two days after this initial testing session. The PTSD group had greater NE levels to negative stimuli and reported greater numbers of intrusive memories of negative stimuli than controls. Regression analyses revealed that the interaction of CORT and NE significantly predicted negative intrusive memories in the PTSD group. The trauma-exposed group reported significantly greater recall of negative images compared to controls, but did not differ significantly from the PTSD group. The PTSD group reported greater levels of suppression of negative images during encoding compared to the other groups. Our results confirm that the interaction of NE and CORT significantly predicts greater negative intrusive memories, but this occurs specifically in the PTSD group. This suggests that a level of heightened arousal is required for the relationship between stress hormones and emotional memory to manifest in PTSD.

1. Introduction

A central model of emotional memory is the memory modulation hypothesis which predicts that memories of threatening events are better recalled due to the interaction of noradrenaline (NE) and cortisol (CORT) in the basolateral nucleus of the amygdala (BLA) during encoding (McGaugh, 2004). Emotionally arousing experiences release adrenaline and glucocorticoids from the adrenal gland and induce the release of noradrenaline in the BLA by activating vagal afferents to the nucleus of the solitary tract. Glucocorticoids freely enter the brain and bind directly to glucocorticoid receptors in brainstem noradrenergic neurons to potentiate NE release in the BLA, as well as postsynaptically in BLA neurons to facilitate the NE signalling cascade (Roozendaal, Barsegyan, & Lee, 2008). Lesion and pharmacological challenge studies in animals reveal that the effects of stress hormones in enhancing memory consolidation depend on the integrity of the amygdala noradrenergic system (Roozendaal et al., 2008 for review). The release of NE and CORT is thought to strengthen the memory trace by activating the amygdala, which strengthens the storage of emotionally arousing information via it's modulation of different brain regions involved in learning and memory (including the prefrontal cortex, hippocampus, caudate nucleus and nucleus accumbens (Roozendaal et al., 2008). Roozendaal, Quirarte, and McGaugh (2002) hypothesized that activation of glucocorticoid receptors in the BLA may facilitate memory consolidation by facilitating the noradrenergic signal cascade. Indeed, administration of the noradrenergic antagonist atenolol to rats prior to inhibitory avoidance training prevented the memory enhancing effect of the glucocorticoid agonist RU28362 which was administered immediately post-training (Roozendaal et al., 2002).

There is also recent evidence for these interactive effects in humans. Participants with higher endogenous CORT had increased amygdala response to emotional images compared to participants with lower CORT levels, however administration of propranolol (a noradrenergic antagonist) blocked this CORT-dependent amygdala activation (Van Stegeren, 2008). Kukolja et al. (2008) examined amygdala responses when participants viewed fearful, happy and neutral faces after taking either a placebo, reboxetine (noradrenergic re-uptake inhibitor which increases noradrenergic

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concentration), hydrocortisone (elevating CORT levels), or both reboxetine and hydrocortisone. Increased amygdala activity was found in the reboxetine/cortisol group in response to fearful faces. Using the same design, a subsequent study reported that the simultaneous elevation of CORT and NE enhanced hippocampal activity during encoding of negative images (Kukolja, Klingmuller, Maier, Fink, & Hurlemann, 2012). These studies confirm that the interaction of CORT and NE elevates amygdala and hippocampal function, regions known to be involved in emotional processing and episodic memory. Kukolja et al. (2012) proposed this interaction of NE and CORT may lead to hyperconsolidation of episodic memories of trauma.

This prediction converges with a model of PTSD proposed by Pitman and Delahanty (2005) which suggests that traumatic events cause intense arousal, triggering the release of NE and CORT. This surge of stress hormones results in increased encoding of environmental stimuli at the time of trauma, and an over-consolidation of the trauma memory. Over-consolidated memories are more easily triggered as they are associated with greater arousal, and have a stronger memory trace – these factors lead to greater conditioning and associations with a wider range of stimuli, which leads to greater priming and triggering from stimuli in the environment. These over-consolidated memories lead to the development of the intense (intrusive) memories and reactivity to trauma reminders that are the core symptoms of PTSD (Pitman & Delahanty, 2005). Supporting this model, in a recent analogue study with healthy participants, intrusive memories of previously presented aversive stimuli during administration of a cold pressor stress were predicted in male participants by the increased interaction of NE and CORT following the cold pressor manipulation (Bryant, McGrath, & Felmingham, 2013). No studies have directly examined the relationship between NE and CORT, and emotional memory consolidation in PTSD.

This study provides the first examination to our knowledge of the relationship between NE and CORT during encoding of negative images and subsequent recall and intrusive memories in participants with PTSD. To control for the relative effects of trauma exposure, we compared PTSD participants with trauma-exposed controls as well as non-trauma exposed controls. We hypothesized that compared to controls, the PTSD group would display greater levels of CORT and NE. Given that memory recall reflects the strength of memory consolidation, we predicted that the PTSD group would display greater recall of negative images than the control groups. In addition, models of PTSD propose that greater arousal results in greater intrusive memories, therefore, we predicted that the PTSD group would display greater numbers of negative intrusive memories than the control groups. Finally, in line with existing models, we hypothesized that the interaction of CORT and NE would predict negative recall and intrusions, and this relationship would be particularly evident in the PTSD group.

2. Materials and methods

2.1. Participants

Fifty-eight participants were recruited from advertising at the University of Tasmania and in local clinical psychology private practices. Twenty participants (12 women, 8 men, age $M = 21.80$ years, $SD = 5.72$) were classified as controls as they reported never being exposed to a Criterion A traumatic event as determined by the Traumatic Events Questionnaire (TEQ: Vrana & Lauterbach, 1994) and reported minimal symptoms on the PTSD Checklist (PCL: Foa, Cashman, Jaycox, & Perry, 1997). Twenty participants (14 women, 6 men, age $M = 29.0$, $SD = 11.46$) were classified as trauma-exposed controls (TE) having experienced a Criterion A traumatic event but did not meet DSM-IV-TR diagnostic criteria for PTSD or subclinical PTSD (one or two symptoms below the diagnostic criteria) according to the PCL (Foa et al., 1997). Eighteen participants were classified as PTSD (13 women, five men, age $M = 30.72$, $SD = 13.42$) having experienced a Criterion A traumatic event and reported symptoms consistent with DSM-IV-TR diagnostic criteria for PTSD on the PCL (Foa et al., 1997). In the TE group, 11 participants reported experiencing interpersonal or sexual assault, 3 reported natural disasters, and 6 reported motor vehicle accidents (MVA). In the PTSD group, 4 participants were combat/war veterans, 11 experienced interpersonal or sexual assault and 3 reported MVAs. The average time post-trauma was 10.2 years (SD 10.1) for the TE group, and 13.2 years ($SD = 14.1$) for the PTSD group. Anyone reporting neurological damage or head injury (greater than 5 min loss of consciousness) was excluded and all participants were under 65 years to control for potential memory confounds. Participants in the control group were not taking any medication and had no reported psychiatric history. Two participants in the TE group and 7 in the PTSD group were taking anti-anxiety or anti-depressant medications.

2.2. Procedure

2.2.1. Encoding session (testing session 1)

Participants completed two testing sessions two days apart. Due to circadian variation in CORT and noradrenergic responses (and in particular, morning elevations of CORT and sAA), all testing sessions were conducted between 12 pm and 6 pm (Andreano, Arjomandi, & Cahill, 2008). Participants were also asked to refrain from eating, nicotine, and caffeine for 3 h prior to the study, and to avoid alcohol or excessive exercise for 24 h prior to the study to control for potential confounds in sAA/CORT responses according to methodological recommendations (Segal & Cahill, 2009). In the first session, informed consent was obtained and participants were habituated to the test environment for 10 min during which time a dummy saliva sample was taken (to reduce anticipatory arousal). The depression, anxiety and stress scale (DASS: Lovibond & Lovibond, 1995) was administered to examine participants' mood on the day of testing. A baseline saliva sample was then taken to extract baseline NE (using salivary alpha amylase: sAA) and CORT.

Participants were then instructed to view a series of images on a computer screen. Sixty images were presented from the IAPS (Lang, Bradley, & Cuthbert, 2008), 20 negative (mean valence: 2.30, arousal: 6.18), 20 neutral (mean valence: 4.99, arousal: 2.75) and 20 positive (mean valence: 7.49, arousal: 4.42). Images were displayed for six seconds each in block format (20 negative, 20 neutral, 20 positive) the order of which was randomized across participants.

sAA levels respond immediately to threatening stimuli (Nater & Rohleder, 2009), therefore a second saliva sample was taken immediately after presentation of the negative image block to measure the sAA response to threat. The latency of CORT peak response to threat is 20 min post stimulus (Kirschbaum & Hellhammer, 1994), therefore a third saliva sample to measure CORT response was taken 20 min after the negative image block presentation. To get an index of whether the PTSD participants suppressed or avoided processing the images during encoding, during this 20 min period, participants were asked about their thought processes whilst encoding the images. Specifically, they were asked to provide a rating on a 9-point Likert scale (1 = *not at all*, 9 = *extremely*) to indicate how much they were trying to suppress (block the processing) of the negative images. Participants were then instructed to return for further testing in two days time. To prevent image rehearsal or priming, participants were not told they would complete a memory test at that time.