NeuroImage 171 (2018) 311–322

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

How acute stress may enhance subsequent memory for threat stimuli outside the focus of attention: DLPFC-amygdala decoupling

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ARTICLE INFO

Keywords:
Threat stimuli
Memory
Amygdala
Dorsolateral prefrontal cortex
Functional connectivity
Psychophysiological interaction

ABSTRACT

Stress-related disorders, e.g., anxiety and depression, are characterized by decreased top-down control for distracting information, as well as a memory bias for threatening information. However, it is unclear how acute stress biases mnemonic encoding and leads to prioritized storage of threat-related information even if outside the focus of attention. In the current study, healthy adults (N = 53, all male) were randomly assigned to stress induction using the socially evaluated cold-pressor test (SECPT) or a control condition. Participants performed a task in which they were required to identify a target letter within a string of letters that were either identical to the target and thereby facilitating detection (low distractor load) or mixed with other letters to complicate the search (high load). Either a fearful or neutral face was presented on the background, outside the focus of attention. Twenty-four hours later, participants were asked to perform a surprise recognition memory test for those background faces. Stress induction resulted in increased cortisol and negative subjective mood ratings. Stress did not affect visual search performance, however, participants in the stress group showed stronger memory compared to the control group for fearful faces in the low attentional load condition. Critically, the stress induced memory bias was accompanied by decoupling between amygdala and DLFPC during encoding, which may represent a mechanism for decreased ability to filter task-irrelevant threatening background information. The current study provides a potential neural account for how stress can produce a negative memory bias for threatening information even if presented outside the focus of attention. Despite of an adaptive advantage for survival, such tendencies may ultimately also lead to generalized fear, a possibility requiring additional investigation.

Stress-related disorders, e.g., anxiety disorders and depression, are related to decreased top-down control for distracting information (Bishop, 2009; Bishop et al., 2004a,b; Qi et al., 2014). This decreased control may lead to better memory for emotionally negative information even when this is presented outside the focus of attention (Jenkins et al., 2005). Acute stress in healthy individuals also leads to prioritized storage of emotional compared to neutral information (Finsterwald and Alberini, 2014), and this memory bias appears to contribute to maintain anxiety symptoms (Eysenck and Mogg, 2014). This impact of stress on emotional memory is however not always consistent and appears dependent on a wide range of factors, including time relative to the stressor (Bennion et al., 2013; Schwabe et al., 2012). Moreover, most studies that investigated the impact of stress on emotional memory storage have presented emotional stimuli which are explicitly attended to. Emotional memory formation occurs even if individuals do not intend to remember (Phelps and LeDoux, 2005). Whether acute stress affects emotional memory formation when individuals do not intend to remember, because the emotional information is irrelevant for the current task, is little known. However, this influence is potentially important because many emotional processes have their impact outside our attended awareness (Gainotti, 2012; Jessen and Grossmann, 2015; Stefanics et al., 2012).

Whether information outside the focus of attention is stored or not depends on the attentional load during encoding (Jenkins et al., 2005). Interestingly, the storage of emotionally neutral information outside the focus of attention is better under low attentional load relative to high attentional load tasks (Jenkins et al., 2005), presumably because the

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https://doi.org/10.1016/j.neuroimage.2018.01.010
Received 12 April 2017; Received in revised form 20 December 2017; Accepted 7 January 2018
Available online 9 January 2018

off-focus information captures more attentional resources in a low load condition compared to a high load condition. Likewise, recent studies have shown that interference by emotional distractors also depends on attentional resources. For example, threat distractors disrupt task performance in a low attentional load condition, whereas this detrimental effect is diminished under high load (Fox et al., 2010, 2012; Yates et al., 2010). A recent study shows that also non-conscious processing of emotional information (fearful faces) depends on attentional load (Wang et al., 2016). However, it is unclear whether acute stress enhances memory for threatening stimuli when presented outside the focus of attention, and if so, whether such effects depend on attentional load. Answering this question would help develop mechanistic insight concerning the impact of stress on behavior.

The current study further aimed to delineate neural mechanisms of the impact of acute stress on memory for unattended emotional information. Previous studies showed that the presentation of emotional distractors leads to reduced prefrontal cortex (PFC) activity and increased amygdala activity (Ansari and Derakshan, 2011; Bishop, 2009). The amygdala, as a core emotion processing structure, is involved in information selection for further analysis (Pessoa, 2014), while the dorsal lateral prefrontal cortex (DLPFC) is one of the core regions of the goal-directed attention system (Eysenck and Derakshan, 2011; Eysenck et al., 2007). Successful suppression of distractor processing is thought to require down-regulation of amygdala activity through increased PFC activity. Recent neural models indeed suggest that amygdala-prefrontal connectivity is engaged in attentional filtering of task irrelevant information (Pessoa, 2014). Animal models show that this prefrontal-subcortical pathway mediates rapid and goal-directed attentional filtering at the earliest stages of sensory processing (Phillips et al., 2016). Moreover, in human data the ability to regulate the impact of negative stimuli is correlated with the connectivity between amygdala and DLPFC (Rohr et al., 2015). Also, connectivity between amygdala and DLPFC is increased when participants' attentional control ability significantly increased (Cohen et al., 2016). Finally, a recent study showed that crowds of fearful distractor faces reduce subsequent target processing, by narrowing attention via amygdala mediated down regulation of perceptual processing regions (Schulte Holthausen et al., 2016). Together these studies suggest that connectivity from the amygdala and DLPFC is critical in filtering out negatively valenced information.

This filtering mechanism appears to depend on attentional load and recent studies indicate that increasing attentional load can reduce the processing of distractors through increased connectivity between amygdala and DLPFC (Mothes-Lasch et al., 2013). Several studies have shown that the amygdala response to task-irrelevant fearful cues is modulated by task demands (e.g. Pessoa et al., 2002; Bishop et al., 2007). Furthermore, a study showed that increased amygdala response to task-irrelevant fearful stimuli in a low load condition was accompanied by increased functional coupling with DLPFC (Sebastian et al., 2017). Moreover, this study suggested that increased functional coupling of amygdala with prefrontal cortex might be instrumental to filter task-irrelevant emotional information depending on attentional load, although the effect of stress and subsequent impact on memory remain unknown.

Acute stress impairs attention selection and increases emotional processing by affecting the DLFPC and amygdala responses in diverse tasks (Lupien et al., 2009). For example, acute stress impairs attentional allocation and enhances stimulus-driven selection, leading to a stronger distractibility by salient stimuli, and this effect may be driven by the prefrontal cortex based executive control (Sanger et al., 2014). Also acute stress has previously been shown to increase amygdala activation in response to emotional pictures (Dedovic et al., 2009; van Marle et al., 2010; van Stegeren et al., 2007). On a network level, acute stress can change the balance between a neural executive control network and a salience network (Hermans et al., 2011; Hermans et al., 2014; Young et al., 2017), and disrupts the connectivity between amygdala and DLPFC (Arnsten, 2015; Maier et al., 2015; Sladky et al., 2015). Greater amygdala-DLPFC connectivity has been associated with threat-induced anxiety (Gold et al., 2015). However, anxious participants show less amygdala-DLPFC connectivity while viewing fearful faces (MacNamara et al., 2016). Together, these studies suggest that acute stress may disrupt the connectivity between a threat processing network including the amygdala and the attention control network including the DLPFC.

To investigate whether a stress-related change in this neural circuitry might underlie the encoding of emotionally salient information outside the focus of attention, a factorial design was employed with between subject factor stress (stress, control) and within subject factors perceptual load (high, low), as well as distractor valence (fearful face, neutral face). A surprise recognition memory test for the facial distractor was performed approximately 24 h later. According to the perceptual load theory (Lavie, 2005) and reports of acute stress facilitation of fear memory (Roozendaal et al., 2009; Schwabe et al., 2012), we hypothesized that acute stress would facilitate negative emotional memory formation of fearful faces presented outside the focus of attention comparing to neutral stimuli, depending on attentional load. We expected that this memory effect would be accompanied by disruptions in the amygdala–DLPFC circuit.

Methods and materials

Participants

A total of fifty-three right-handed healthy male participants with normal or corrected-to-normal vision were tested for this study. Participants were screened before their participation and reported no psychiatric, neurological, cardiovascular or endocrine disease, head surgery, history of or current endocrine treatment, epilepsy, irregular sleep/wake rhythm, habitual smoking (>1 package weekly and unable to cease smoking for 24 h prior to testing), alcohol consumption (>21 beverages weekly), use of recreational drugs (>weekly), psychotropic medication, and cardiovascular impairments. Subjects were asked to refrain from any medication other than paracetamol for acute pain and recreational drugs for 72 h, alcohol for 24 h, and coffee for 2 h before testing. Participants' mean age was 22.22 ± 2.89 years, ranging from 18 to 30 years, with no significant difference between the stress (21.96) and control (22.67) group ($t(51) = -0.86$, $p = .39$). Previous experience with being in an MR scanner, which can affect cortisol responses (Peters et al., 2011; Tessner et al., 2010; Vogel et al., 2015), was also not different between two groups, $\chi^2 = 0.458$, $p = .498$. Given the influence of menstrual cycle on the stress response (Fernández et al., 2003; Kirschbaum et al., 1999; Ossewaarde et al., 2013) and because we did not have resources to include sufficient female participants from different cycle phases, we restricted our study to male participants. All participants reported to be free of neurological or psychiatric disorders and gave written informed consent before the experiment. The study was approved by the local Medical-Ethical Board.

Experimental design

A full factorial $2 \times 2 \times 2$ mixed design was used, with stress (stress, control) as a between-subject factor and perceptual load (high, low) and distractor valence (fearful, neutral) as within-subject factors manipulated in the experiment (see task details below). Participants were randomly assigned to the stress ($n = 27$) or control group ($n = 26$).

General procedure

The experiment was conducted between 12:00 and 19:00 to ensure relatively stable levels of endogenous cortisol. After arrival, the subjects were taken to the behavioral laboratory by two experimenters dressed in white laboratory coats acting in a reserved manner (stress group) or friendly experimenters wearing normal casual clothing (control group). Next, participants rested for 5 min and completed a demographics