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Altered reward learning and hippocampal connectivity following psychosocial stress

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ABSTRACT

Acute stress has a profound influence on learning, as has been demonstrated in verbal learning or fear conditioning. However, its effect on appetitive conditioning is still unclear. Fear conditioning research suggests the possibility of overgeneralization of conditioning to the CS- under acute stress due to its effect on prefrontal and hippocampal processing.

In this study, participants (N = 56 males) were subjected to the *Trier Social Stress Test* or a placebo version. After that, all participants underwent an appetitive conditioning paradigm in the fMRI, in which one neutral cue (CS+) was repeatedly paired with reward, while another (CS-) was not. Importantly, the stress-group revealed overgeneralization of conditioning to the CS- on the behavioral level. On the neural level, stressed participants showed increased connectivity between the hippocampus and amygdala, vACC, and OFC, which maintain specificity of conditioning and also showed reduced differential activation. The results indicate overgeneralization of appetitive conditioning promoted by maladaptive balancing of pattern separation and pattern completion in the hippocampus under acute stress and are discussed with respect to clinical implications.

Introduction

Learning about cues that signal reward is a key element in interactions with our environment. If we repeatedly take a tasty snack out of a blue box, we will soon prefer this blue box over other boxes and our mouth will begin to water as soon as we see it. Previous research showed that this reward learning is altered by acute stress, however, the precise effect of acute stress on reward learning is still unclear (Berker et al., 2016; Lighthall et al., 2013). Reward learning processes can be conceptualized as an appetitive conditioning paradigm, in which a neutral cue (CS+) is repeatedly paired with the chance to win a reward (UCS; e.g. money). Another neutral cue (CS-) is never paired with the UCS. After few pairings, the participants show increased responses to the CS + as compared to the CS- like increased valence and arousal ratings, elevated skin conductance responses (SCRs), and an activation of the reward circuit (Klucken et al., 2015). However, while it is clear that acute stress exerts a profound influence on the reward circuit (Gold et al., 2015; Montoya et al., 2014; Pruessner et al., 2008), its precise effect on appetitive conditioning is still unclear. Studies examining the topic face several difficulties. This includes type and timing of the stressor, as the sympatho-adrenergic response occurs rapidly, while the hypothalamic-pituitary axis (HPA) takes more time to effect the secretion of cortisol (Hermans et al., 2014). Moreover, stress hormones interact with sex hormones and oral contraceptives in females, which often confound effects of gender on emotional learning (Merz et al., 2010; Merz and Wolf, 2017).

The neural circuit underlying reward learning includes the amygdala, the dorsal and ventral striatum, the orbitofrontal cortex (OFC), the anterior insula, as well as the dorsal and ventral anterior cingulate cortex (dACC/vACC) (Haber and Knutson, 2010; Martin-Soelch et al., 2007). Within this circuit, the amygdala is thought to encode the learned CS/UCS-association (Chase et al., 2015). The ventral striatum is assumed to be a key element in the reward circuit, encoding the acquired motivational salience of the cue and CS/UCS contingencies (Klucken et al., 2009). The anterior insula is thought to integrate interoception of emotional reactions with information about the emotional event in reward learning or processing of psychosocial stressors (Kogler et al., 2015; Sescousse et al., 2013). The vACC is thought to play a key role in

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differential conditioning, with a focus on early differentiation between the CS+ and the CS- (Gabriel et al., 2003), while the dACC on the other hand is thought to encode the expected outcome of the CS+ (Alexander and Brown, 2011; Etkin et al., 2011). In addition, the anterior insula has been identified as part of the salience network and is assumed to reflect increased attention towards stimuli associated with reward as well as encoding affective and psychophysiological responses (Chase et al., 2015; Hermans et al., 2014; Kogler et al., 2015).

Previous research on acute stress and conditioning in animals revealed increased generalization of conditioning and impaired goal-directed action under acute stress. In humans, overgeneralization of conditioning from the CS+ to the CS- under stress has previously been discussed in post-traumatic stress disorder (Besnard and Sahay, 2016). In fear conditioning, a network of hippocampus, OFC, and vACC is thought to balance generalization and specificity of conditioning (Xu and Sudhof, 2013). Moreover, this circuit has links to the striatum, amygdala, and midbrain to influence the expression of conditioning. This is in line with research reporting altered functional connectivity of the hippocampus to prefrontal areas as well as the amygdala in fear generalization (Lissek et al., 2014). In this network stress is argued to be an important factor tipping the scales toward generalization of learning (Pedraza et al., 2016). Reduced activation of the vACC, as has also been observed in humans under acute stress (Born et al., 2010; Pruessner et al., 2008), can induce overgeneralization of conditioned responses from the CS+ to the CS- (Cardinal et al., 2003). For the hippocampus, preliminary research suggests that stress impairs pattern separation of different stimuli (Besnard and Sahay, 2016). Structures with ties to the core network mediating specificity of conditioning like amygdala and striatum, which themselves are highly susceptible to stress, are central to the acquisition and expression of conditioning. In a study by Born et al. (2010) participants under acute stress chose more food under stress, while showing reduced activation of amygdala, striatum, hippocampus, and cingulate gyrus toward food cues.

Although the effects of conditioning develop over time, previous research on the effects of acute stress on learning has not taken into account the development of learning in the beginning and in later phases of learning. However, it has been observed that the effects of stress on learning become more pronounced in the late phase. In the dorsal striatum a shift from dorso-medial (caudate) to dorso-lateral (putamen) activation that occurs over time and promotes a shift from goal-directed to habit learning is facilitated under acute stress (Schwabe and Wolf, 2011). It has been suggested that this effect is induced by a deactivation of prefrontal areas, especially the OFC, and a resulting impairment of the executive network (Hermans et al., 2014; Schwabe et al., 2012). In general, under acute stress reduced differential activation of prefrontal and limbic areas has been observed (Dagher et al., 2009; Pruessner et al., 2008).

In the present study, we investigated the altered neural correlates of appetitive conditioning in the fMRI under stress. First, we expected both stressed and non-stressed participants to acquire appetitive conditioning. Second, we expected the stress-group to overgeneralize the acquired conditioning, showing reduced differential neural responses in areas regarding specificity of learning, hippocampus, vACC, OFC, and areas associated with the acquisition and expression of appetitive conditioning, namely the amygdala and the ventral striatum and increased functional connectivity between these structures. In addition, we investigated possible stronger goal-directed activation of the caudate in the control-group during the late phase as compared to the stress-group.

Materials and methods

Participants

A total of 60 male participants (mean age = 23.77 years; SD = 3.03 years) took part in the study. All participants had normal or corrected-to-normal vision and were right-handed, German native speakers with a European background. Exclusion criteria were past or current mental illness, consumption of psychotropic drugs, working in the night shift or travelling across time zones in the past two weeks, and any treatment preventing from entering the magnetic resonance imaging (MRI) scanner. After completion of the experiment, all subjects filled out the German versions of BDI-II (Beck Depression Inventory: Hautzinger, Keller and Kühner, 2009), BIS-15 (Barratt Impulsiveness Scale: Meule, Vögele and Kübler, 2011), and PSS (Perceived Stress Scale: Klein et al., 2016). Prior to the experiment, participants gave written informed consent. After the conclusion of their participation, they received monetary compensation or course credit for their time. Any money they won during the experimental run was paid out directly after participants left the MRI scanner. The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee. Due to technical difficulties data of four participants were excluded from the analysis (3 in the stress-group, 1 in the control-group), leaving 56 participants in the final sample (Table 1).

Procedure

To ensure similar baseline cortisol levels, data acquisition always took place in the afternoon between 1 p.m. and 6 p.m. and participants came into the lab at least 30 min before giving the first saliva sample (Fig. 1). After giving written informed consent, participants performed a training version of the paradigm consisting of different stimuli to familiarize themselves with the task and calculate the speed of their responses in order to adapt the difficulty of the MRI task. Next, participants were prepared for the MRI. Then they gave the first of a total of four saliva samples (Salivette, Sarstedt, Nürnbrecht, Germany), filled out the Positive and Negative Affect Scale (PANAS, Krohne et al., 1996), and were led to a separate room. Here, half the participants (stress-group) took part in the *Trier Social Stress Test* (TSST; Kirschbaum et al., 1993), while the other half (control-group) took part in the placebo version of the TSST (Het et al., 2009). After 20 min, they were led to the MRI, where they gave the second saliva sample and filled out the PANAS a second time. 10 min later they gave a third saliva sample, while in the MRI. The appetitive conditioning paradigm started 10 min after the third sample and a total of 40 min after the beginning of the TSST or Placebo-TSST. This ensured that the appetitive conditioning paradigm would take place after cortisol had been released by the pituitary and reached the brain, which takes about 20 min (Droste et al., 2008). 15 min later the subjects left the MRI, gave the last saliva sample and filled out the PANAS a third time.

TSST/placebo-TSST

The TSST was conducted according to Kirschbaum et al. (1993) in a room with two confederates (one male, one female) in white coats sitting at the head of a conference table. The participants of the stress-group were led in and received written instructions explaining the first task. After 5 min of preparation, one of the confederates instructed the participant to begin. After 5 min, they were given the second task, which again lasted 5 min after which participants could leave the room.

The placebo version was conducted as described by Het et al. (2009) with similar tasks with the same duration as in the TSST, but without elements of uncontrollability or social evaluation. Participants were

Table 1
Descriptive mean (SD) data of stress- and control-group, including age, depression (BDI-II), impulsivity (BIS-15), chronic stress (PSS), sleep duration (hours last night), and total win during the experiment. *p*-values of two-sample-*t*-tests (rightmost column).

	stress-group (n = 27)	control-group (n = 29)	*p*
Age [y]	23.48 (3.30)	23.83 (2.80)	.67
BDI-II	4.59 (4.89)	4.93 (4.50)	.79
BIS-15	33.77 (5.50)	32.51 (5.32)	.40
PSS	13.04 (5.58)	13.19 (4.47)	.92
sleep [h]	7.97 (1.02)	8.05 (0.88)	.76
Win [€]	6.46 (0.13)	6.43 (0.22)	.49