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Acute stress-induced cortisol elevations mediate reward system activity during subconscious processing of sexual stimuli

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Summary Stress is thought to alter motivational processes by increasing dopamine (DA) secretion in the brain's ''reward system'', and its key region, the nucleus accumbens (NAcc). However, stress studies using functional magnetic resonance imaging (fMRI), mainly found evidence for stress-induced decreases in NAcc responsiveness toward reward cues. Results from both animal and human PET studies indicate that the stress hormone cortisol may be crucial in the interaction between stress and dopaminergic actions. In the present study we therefore investigated whether cortisol mediated the effect of stress on DA-related responses to -subliminal-presentation of reward cues using the Trier Social Stress Test (TSST), which is known to reliably enhance cortisol levels.

Young healthy males ($n = 37$) were randomly assigned to the TSST or control condition. After stress induction, brain activation was assessed using fMRI during a backward-masking paradigm in which potentially rewarding (sexual), emotionally negative and neutral stimuli were presented subliminally, masked by pictures of inanimate objects.

A region of interest analysis showed that stress decreased activation in the NAcc in response to masked sexual cues (voxel-corrected, $p < 05$). Furthermore, with mediation analysis it was found that high cortisol levels were related to stronger NAcc activation, showing that cortisol acted as a suppressor variable in the negative relation between stress and NAcc activation.

The present findings indicate that cortisol is crucially involved in the relation between stress and the responsiveness of the reward system. Although generally stress decreases activation in

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the NAcc in response to rewarding stimuli, high stress-induced cortisol levels suppress this relation, and are associated with stronger NAcc activation. Individuals with a high cortisol response to stress might on one hand be protected against reductions in reward sensitivity, which has been linked to anhedonia and depression, but they may ultimately be more vulnerable to increased reward sensitivity, and addictions. Future studies investigating effects of stress on reward sensitivity should take into account the severity of the stressor and the individual cortisol response to stress.

1. Introduction

Stress is widely acknowledged as a risk factor for disorders such as addiction to substances, overeating, and hypersexuality, and is considered a major cause of relapse (Adam and Epel, 2007; Uhart and Wand, 2009; Reid et al., 2012). In patients with stress-related disorders, such as posttraumatic stress-disorder (PTSD), which is characterized by dysfunction of the hypothalamus—pituitary—adrenal (HPA) axis, the incidence of comorbid addiction to substances and obesity is alarmingly high (Cohen et al., 2010; Gielen et al., 2012). Animal studies showed that interactions between stress, glucocorticoids (cortisol in humans) and the dopamine system might be pivotal in determining the individual propensity for vulnerability to addictions (Rouge-Pont et al., 1995; Piazza and Le Moal, 1996; Campioni et al., 2009). However, clear causal relations between stress, cortisol, dopaminergic activity and reward seeking behavior have yet to be established in humans.

Animal and human studies have shown that stress increases dopamine (DA) secretion in the central brain structure of the reward system, the nucleus accumbens (NAcc) (Pruessner et al., 2004; Cabib and Puglisi-Allegra, 2012). NAcc-DA is thought to amplify the incentive salience of stimuli, making these "wanted". "Wanting" refers to the underlying implicit motivational process that drives behavior toward the rewarding target (Berridge and Robinson, 2003). The NAcc responds to primary and higher order rewards, such as food, sex and money (Kringelbach and Berridge, 2009), and stronger NAcc activations in response to food and sexual cues predict weight gain and sexual activity 6 months later (Demos et al., 2012). Even reward cues presented at a subconscious (subliminal) level activate the NAcc (Childress et al., 2008; Gillath and Canterberry, 2012; Oei et al., 2012). This NAcc activation is modulated by DA, with higher activations in response to subliminal reward cues when DA activity is increased, and lower activations when DA activity is decreased (Oei et al., 2012). Moreover, DA modulation of both conscious and subconscious learning processes demonstrates that (i) high DA increases striatal reward prediction error magnitude related to choosing bigger rewards (Pessiglione et al., 2006) and (ii) that high DA causes higher reward seeking, whereas DA decreases cause higher punishment avoidance learning (Palminteri et al., 2009; Bodi et al., 2009). Stress-induced increases in DA secretion in the NAcc are thus thought to explain heightened sensitivity for reward cues or enhanced reward-learning. Nonetheless, this idea is not supported by findings from functional MRI studies using mild stressors, which almost invariably report stress-induced *decreased* NAcc activations or no differences in NAcc-activations to reward cues (Ossewaarde et al., 2011; Porcelli et al., 2012; Lighthall et al., 2012b).

The cortisol response to stress plays a pivotal role in the association between stress and DA secretion in the NAcc (Rouge-Pont et al., 1995; Piazza and Le Moal, 1996; Pruessner et al., 2004; Campioni et al., 2009). Both monkey and human PET studies using stress-induction methods that reliably activate the HPA-axis showed enhanced DA release in the ventral striatum (Pruessner et al., 2004; Wand et al., 2007; Tsukada et al., 2011). The DA-secretion was associated with cortisol elevations. Furthermore, high cortisol after amphetamine administration was found to be associated with increased DA-release in the ventral striatum, and more positive subjective drug effects than with lower cortisol levels (Oswald et al., 2005). In animals, glucocorticoids, both stress-induced and administered, facilitate behavioral responses to drugs (e.g., locomotor activity and self-administration) and promote synaptic plasticity by activating NAcc-DA transmission, whereas these dopaminergic effects are blocked by anti-glucocorticoids (Marinelli and Piazza, 2002; Campioni et al., 2009). In humans, elevated cortisol in the response to stress has, for instance, been associated with faster drop-out of substance abuse treatment (Daughters et al., 2009), and with consuming more calories than low cortisol responders (Epel et al., 2001).

Cortisol, however, is not responsive to every type of laboratory stressor (Dickerson and Kemeny, 2004). It could thus be expected that stressors evoking no or very low cortisol elevations would be associated with decreased NAcc activations in response to reward cues, rather than with increased activation. Indeed, with the cold pressor task, Porcelli and colleagues (2012) found that stress decreased striatal activation during reward processing, and no difference in NAcc activation between a stress and control group was found using an emotion-induction procedure (Ossewaarde et al., 2011). Moreover, no ventral striatal DA-increases were found in a PET study using an arithmetic task as a stressor (Montgomery et al., 2006). Such findings are in contrast to PET studies (Pruessner et al., 2004; Wand et al., 2007) conducted using social-evaluative threat as a stressor, which is known to elicit high cortisol responses, i.e., the Trier Social Stress test (TSST; Kirschbaum et al., 1993). Together, the evidence from PET and behavioral studies suggests that stress-induced cortisol plays an important mediating role in increasing sensitivity to potentially rewarding stimuli through its effects on DA signaling in the NAcc.

In the present study, we first induced acute stress using the TSST, a stress-induction method that reliably raises cortisol levels (Dickerson and Kemeny, 2004). Because the interacting effects of cortisol and DA are most likely dependent on glucocorticoid receptors (GR) (Marinelli and Piazza, 2002; Deroche-Gamonet et al., 2003; van Craenenbroeck et al., 2005), stress was induced in the morning. In the morning, the saturation of mineralocorticoid receptors