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# The effects of glucocorticoids on the inhibition of emotional information: A dose–response study

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ABSTRACT

There is evidence that cortisol influences cognitive and affective processes such as selective attention and memory for emotional events, yet the effects of glucocorticoids on attentional inhibition in humans remain unknown. Consequently, this double-blind study examined dose-dependent effects of exogenous glucocorticoids on the inhibition of emotional information. Sixty-three university students (14 male, 49 female) ingested either a placebo pill or hydrocortisone (10 mg or 40 mg), and completed a negative priming task assessing the inhibition of pictures depicting angry, sad, and happy faces. The 10 mg, but not the 40 mg hydrocortisone dose elicited increased inhibition for angry faces relative to placebo. Thus, moderate glucocorticoid elevations may have adaptive effects on emotional information processing, whereas high glucocorticoid elevations appear to attenuate this effect, consistent with the view that there are dose-dependent effects of glucocorticoids on cognition.



## 1. Introduction

The steroid hormone cortisol, the principal human glucocorticoid, is released from the adrenal cortex into blood circulation in response to an internal or external challenge, and acts in the periphery by contributing to the breakdown of glucose and the mobilization of energy (Munck and Holbrook, 1984). It crosses the blood–brain barrier and binds to several target receptors in the prefrontal cortex as well as subcortical structures (amygdala, hypothalamus, and hippocampus) in areas that are relevant to cognition and emotion (Lovallo et al., 2010). Through their effects on these target structures in the brain, glucocorticoids (GCs) are believed to influence a wide variety of cognitive and affective processes in ways that presumably promote adaptation to environmental challenges (de Kloet et al., 2005; for review, see Lupien and McEwen, 1997). Nevertheless, there still remains much to uncover on the complex ways in which cortisol affects cognitive and affective processes. Because the interactions between GCs and cognitive-affective functions in the brain may have considerable implications for stress-related disorders including post-traumatic stress disorder and major depression (Kaufman et al., 2000), it is essential to better understand the complex dynamics operating between these systems.

It is well known that GCs influence different aspects of memory (Lupien and McEwen, 1997). Most importantly, the acute administration of GCs facilitates memory consolidation and disrupts memory retrieval (Abercrombie et al., 2003; de Quervain et al., 1998; Het et al., 2005; Kirschbaum et al., 1996; Roozendaal, 2002). The effects of GCs on the consolidation of memory are particularly evident for emotional stimuli: GCs appear to facilitate long-term recall of emotional relative to neutral information (Buchanan and Lovallo, 2001; Kuhlmann and Wolf, 2006; Putman et al., 2004). This suggests that the release of GCs and norepinephrine during stress promotes the consolidation of memories that are important for future survival, particularly memory of emotionally arousing events (Ferry et al., 1999; Buchanan and Lovallo, 2001; Putman et al., 2004). With respect to working memory, both stress-related increases in cortisol (Schoofs and Wolf, 2009; Schoofs et al., 2009) and the intravenous administration of hydrocortisone (Lupien et al., 1999) worsen performance, with some exceptions (Oei et al., 2009). Interestingly, the relationship between memory function and GCs is often non-linear and dose-dependent. According to Lupien and McEwen (1997), the relationship between memory function and GCs is best explained by an apparent inverted U-shaped relationship, suggesting that both low and high levels of GCs impair the consolidation of memory, while moderate levels of

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GCs improve memory consolidation (Roozendaal, 2000). The relationship between working memory and GCs also appears to be dose-dependent (Lupien et al., 1999). The mechanisms underlying the non-linear relationship between GCs and cognitive functioning are thought to be related, in part, to the differential activation of receptors for GCs in the central nervous system, namely mineralocorticoid (Type I or MRs) and glucocorticoid receptors (Type II or GRs; de Kloet, 2003; Roozendaal, 2000). Clearly, more research is needed in this area, with an emphasis on dose–response studies.

GCs can also affect other parameters of information processing, including selective attention (Fehm-Wolfsdorf et al., 1993; Mölle et al., 1997; Skosnik et al., 2000). For instance, the administration of a high dose (40 mg) of exogenous cortisol abolished a threat-related attentional bias towards masked fearful faces relative to a placebo group, particularly among participants with high anxiety, suggesting that GCs reduce early fear processing (Putman et al., 2007). Similarly, the administration of a 50 mg dose of GCs, relative to placebo, attenuated a psychophysiological (i.e. P2 event-related potential) marker of early attentional bias to angry faces (van Peer et al., 2010). These results are consistent with other studies showing that doses of 10 to 40 mg of GCs decrease self-reported fear and negative affect during stressful circumstances (Het and Wolf, 2007; Soravia et al., 2006; Reuter, 2002), the fear-related startle reflex (Buchanan et al., 2001), and panic symptoms induced by a noradrenergic agonist (Vasa et al., 2009). In sum, high doses of exogenous cortisol may also have specific anxiolytic effects on tasks assessing emotional information processing.

Studies have also examined the effects of GCs on selective attention by inducing endogenous increases in cortisol using stress induction techniques prior to assessing cognitive function (Ellenbogen et al., 2006; Elzinga et al., 2005; Roelofs et al., 2007). As such, small elevations in cortisol during a laboratory stressor were associated with both facilitated shifts towards, and difficulties disengaging from, stimuli depicting threat (Ellenbogen et al., 2002, 2006). Specifically, the relationship between attentional shifting and cortisol levels occurred primarily for masked stimuli, where conscious recognition of the content of the pictures was impeded, indicating the automatic nature of this relationship (Ellenbogen et al., 2006, 2010). Hence, we have interpreted these results as demonstrating that early information processing of threat activates the HPA axis, but it is possible that the reverse is true: small elevations of cortisol levels may alter information processing and attention so that threatening information is preferentially attended to at an early stage of information processing. In sum, the findings from studies examining the relationship between GCs and affective processing suggest that cortisol can have both fear-reducing (i.e. attenuating early attentional biases to threat) and fear-enhancing (i.e. consolidation of emotional memories, associated with attentional biases for threat) properties. Although part of the discrepancy may be explained by methodological differences between studies, the functional consequences of high and low GC levels on emotional information processing may be quite different because of the differential occupations of MRs and GRs at different GC levels. Thus, mild elevations of cortisol may result in increased vigilance and sensitivity to threat, while larger elevations of cortisol may attenuate threat processing.

Despite the evidence that GCs alter early emotional information processing, the specific mechanisms by which these effects occur are not known. Of interest, changes in emotional information processing may occur, in part, because of changes in the efficiency at which attentional systems filter or inhibit incoming emotional information. Inhibition is an essential component of selective attention because it enables attention to be allocated to particular foci by suppressing the processing of task-irrelevant information (Posner, 1978). Individual differences in inhibition can be measured with a negative priming paradigm (Skosnik et al., 2000; Tipper, 1985). In negative priming tasks, semantically related distracting information (i.e. picture of a dog) ignored in the previous trial becomes the target (i.e. picture of a cat) on the subsequent trial. Inhibition occurs when reaction time for previously ignored semantically related information is slower than reaction time for information that was not ignored on the previous trial. The delay in reaction time associated with previously ignored information is purported to result from residual inhibition (Tipper, 1985; Tipper and Cranston, 1985). These procedures have recently been used with affective stimuli: inhibitory deficits for negative emotional words (Joormann, 2004; Joormann, 2006) and pictures displaying sad facial expressions (Goeleven et al., 2006) have been found in both dysphoric students (Joormann, 2004; Joormann, 2006), individuals with a history of depression (Joormann, 2004), and clinically depressed participants (Goeleven et al., 2006). These reports suggest that the inhibition of emotional information may be an important determinant of the regulation of emotion, and perhaps also of the stress response. Moreover, inhibition may represent one mechanism by which GCs exert their effects on information processing.

The causal relationship between GCs and inhibition has not been studied and warrants further investigation. To date, only one correlational study has examined the relationship between GCs and inhibition using negative priming. Stress-induced cortisol levels were associated with decreased inhibition of neutral information on a negative priming task (Skosnik et al., 2000), suggesting that moderate levels of GCs may impair the suppression of task-irrelevant information. More recently, the administration of 35 mg of hydrocortisone, in contrast to other research (Wolf et al., 2001a,b), was associated with improved performance on a working memory task with emotional distracters relative to the placebo administration (Oei et al., 2009). Hydrocortisone abolished the expected decrement in performance associated with the presence of emotional distracters, suggesting that the administration of a high dose of GCs improved inhibitory abilities associated with the functioning of the prefrontal cortex (Jonides et al., 1998). Taken together, these conflicting findings suggest that the effects of GCs on inhibition may be dose-dependent, with impaired and facilitated inhibition at low and high glucocorticoid levels, respectively. Because there are so few studies in this area, research on the effects of GCs on inhibition is clearly needed.

Consequently, the present study examined the effects of a low (10 mg) and high (40 mg) dose of the exogenous GC hydrocortisone on the inhibition of emotional information, assessed using a modified negative priming task (Goeleven et al., 2006). It was hypothesized that, relative to placebo, a low dose of hydrocortisone (analogous to endogenous GC levels induced by a moderate stressor) would impair the inhibition of pictures displaying threatening (angry) facial expressions relative to pictures displaying happy or sad facial expressions. This postulation was based on the negative relationship between cortisol levels and inhibition (Skosnik et al., 2000), and previous reports showing automatic processing biases for pictures depicting threat were predictive of elevated cortisol levels during stress (Ellenbogen et al., 2006, 2010). We speculated that impaired inhibition may underlie difficulties disengaging from threat. In contrast, it was posited that 40 mg of hydrocortisone would improve the ability to effectively inhibit threatening emotional information. This hypothesis was based on evidence that high levels of circulating GCs appear to abolish early attentional biases for fearful stimuli (Putman et al., 2007; van Peer et al., 2010), and on evidence of reduced interference by distracting pictures during a working memory task following the administration of a high dose of GCs (Oei et al., 2009). Finally, a secondary goal of this study was to investigate the influence of anxiety and depressive symptoms on inhibitory processes, as these symptoms are often associated with HPA axis dysregulation (Plotsky et al., 1998;