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Prednisolone increases neural reactivity to negative socio-emotional stimuli in healthy young men

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Abstract
Exogenous glucocorticoids are known to trigger affective changes, but these are highly variable across individuals. A better understanding of how synthetic glucocorticoids impact the processing of negative emotions in the human brain might help to predict such changes. In the present functional magnetic resonance imaging (fMRI) study, we sought to uncover the slow effects of a synthetic glucocorticoid infusion on the neural response to socio-emotional scenes using a within-participant, double-blind, placebo-controlled design. In two separate sessions, 20 young males were given either an intravenous prednisolone dose (250 mg) or placebo in a cross-over, randomized order. Four hours later, they were scanned while viewing drawings of persons in a neutral or negative emotional situation. On the next morning participants provided a blood sample for serum cortisol measurement, which served as a manipulation check. Prednisolone strongly suppressed morning cortisol, and heightened brain reactivity to emotional stimuli in left amygdala, left caudate head, right inferior frontal gyrus, bilateral supplementary motor area, and right somatosensory cortex. Amygdala reactivity was related to lower self-reported fatigue and higher irritability in the prednisolone condition. Moreover, prednisolone blunted inferior frontal and amygdala connectivity with other regions of the emotion-processing neural circuitry. Our results suggest specific brain pathways through which exogenous glucocorticoids may labilize affect.

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1. Introduction

Glucocorticoids are steroid hormones that act on multiple physiological systems. Natural glucocorticoids are a central component of the human stress response, diverting blood and glucose to compromised tissue and favoring functions that are crucial for immediate survival, such as attention, at the expense of those that are not, such as immune action (Sapolsky et al., 2000). Due to their immunosuppressive properties, synthetic glucocorticoids are commonly prescribed in clinical settings to treat diseases such as asthma or rheumatoid arthritis (Kadmiel and Cidlowski, 2013). However, psychological side-effects of glucocorticoid treatment are common (Brown, 2009). Exogenous glucocorticoids are known to cause highly heterogeneous emotional changes, ranging from favorable effects such as fear reduction (Soravia et al., 2006) to increases in negative affect (Plihal et al., 1996), and can even lead to severe psychiatric conditions such as mania and depression (Judd et al., 2014; Kenna et al., 2011). Unfortunately, the precise cerebral mechanisms linking glucocorticoid intake and affective dysregulation are still insufficiently understood. Expanding the existing knowledge on this issue can aid to anticipate the emotional response to glucocorticoids, and potentially inform treatment planning.

Within 20 min after reaching the brain, glucocorticoids bind mostly to membrane mineralocorticoid (MR) receptors and increase the excitability of limbic structures (de Kloet et al., 2005), particularly the ventral hippocampus and the basolateral amygdala (Joels et al., 2012). This effect is thought to be partially driven by reduced inhibitory gamma-aminobutyric acid (GABA) action along with heightened glutamatergic and noradrenergic transmission (Joels et al., 2012; Roozendaal et al., 2006; Yuen et al., 2011). At a slightly longer time scale (i.e. 20–60 min), glucocorticoids seem to lower limbic activity, especially in the dorsal hippocampus (Joels et al., 2012). This might account for some of the anxiolytic effects observed after glucocorticoid administration (e.g. Putman et al., 2010; Soravia et al., 2006). The slow (i.e. in the hour range) effects of glucocorticoids are triggered by their action on nuclear glucocorticoid receptors (GR) and subsequent alteration of gene expression patterns. Nuclear GR activation dampens synaptic transmission in some areas (e.g. CA1 region of the hippocampus), and potentiates it in others (e.g. medial prefrontal cortex and basolateral amygdala; Joels et al., 2012), presumably promoting cognitive control and memory consolidation while maintaining alertness (Henckens et al., 2010; Joels et al., 2012). Whereas this mechanism might underlie the glucocorticoid-induced facilitation of emotional memory (Buchanan and Lovallo, 2001; Roozendaal et al., 2006), excessive limbic stimulation might also influence the development of affective symptomatology in glucocorticoid-treated patients (Brown, 2009). Nevertheless, as most knowledge on central glucocorticoid effects comes from rodent studies, such extrapolations are only tentative. Furthermore, the effect of glucocorticoids on some brain structures appears to be highly dependent on the context and the subjects' state (Joels and Baram, 2009). It is thus necessary to explore both the basal and reactive human neurophysiology in vivo in order to better understand the impact of glucocorticoids on affective processing.

Functional magnetic resonance imaging (fMRI) studies in humans have shown that acutely administered glucocorticoids rapidly (i.e. after 15–20 min) deactivate the limbic circuitry, both at rest (Lovallo et al., 2010; Strelzyk et al., 2012) and in response to sad pictures (Sudheimer et al., 2013). On the other hand, the slow genomic effects of a glucocorticoid dose can bias amygdala reactivity toward fearful relative to happy faces, which might reflect heightened vigilance to negatively valenced stimuli (Henckens et al., 2010). However, Sudheimer et al. (2013) presented only sad, neutral, and happy stimuli, making it unclear whether their results apply to other negative emotions, and Henckens et al. (2010) presented only faces, which lack the ecological validity of more complex social situations. Moreover, in both studies glucocorticoids were administered orally, a route that is sensitive to individual variation in absorption rates (Hindmarsh and Charmandari, 2015), and employed a between-subjects design, in which preexisting differences between groups might preclude pharmacological effects. Also, in these studies participants were given hydrocortisone, which mimics endogenous cortisol but might not be fully comparable to other synthetic glucocorticoids due to differences in relative GR and MR affinity (Sapolsky et al., 2000).

To overcome these limitations, in the present fMRI study we sought to elucidate the slow effects of intravenous synthetic glucocorticoid administration on the neural reactivity to contextualized socio-emotional stimuli. In addition, we inspected whether glucocorticoid-induced changes in brain activity could predict subsequent mood changes, as persons with stronger glucocorticoid-induced reactivity to negative emotional situations might be at higher risk for affective imbalance. We followed a within-subject, placebo-controlled, double-blind procedure.

We used a paradigm composed of complexity-controlled and contextualized scenes with emotional vs neutral and two- vs one-person content that was devised to capture automatic, spontaneous empathic processes (Preston and de Waal, 2002). The task has been validated and employed in previous fMRI studies, and yields a consistent pattern of activation in the so-called mentalizing network (Beyer et al., 2014; Brunnlieb et al., 2013; Krämer et al., 2010). Hence, it constitutes an adequate paradigm to test our pharmacological manipulation, a high-dose infusion of the synthetic glucocorticoid prednisolone (Czock et al., 2005; Russell et al., 2010). Prednisolone crosses the blood-brain-barrier efficiently (Bannwarth et al., 1997), reaching peak concentrations in cerebrospinal fluid before two hours (Balis et al., 1987), and, like most other glucocorticoids, it is subject to hepatic metabolism and renal excretion (Czock et al., 2005). While comparable to hydrocortisone in many aspects, prednisolone has an approximately four-fold higher affinity to GR, and its effects are longer-lasting (12–36 h vs 8-12 h; Fietta et al., 2009; Liu et al., 2013). As prednisolone is widely used to treat inflammatory and autoimmune diseases (Liu et al., 2013), investigating its affective and neurophysiological effects can provide valuable clinical insights.

All in all, our main goal was to identify brain regions through which synthetic glucocorticoids might influence the processing of affective information. By using a tightly controlled design, an intravenously administered drug with high GR affinity, and an established fMRI paradigm, we aimed to