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Effects of acute cortisol administration on response inhibition in patients with major depression and healthy controls

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ABSTRACT

Glucocorticoids (GCs) have repeatedly been shown to impair hippocampus-mediated, declarative memory retrieval and prefrontal cortex-based working memory in healthy subjects. However, recent experimental studies indicated that patients with major depressive disorder (MDD) lack these impairing effects. These missing effects have been suggested to result from dysfunctional brain GC receptors. The purpose of the present study was to investigate whether response inhibition, an executive function relying on the integrity of the prefrontal cortex, would be impaired after cortisol administration in patients with MDD. In a placebo-controlled, double blind crossover study, 50 inpatients with MDD and 54 healthy control participants conducted an emotional go/no-go task consisting of human face stimuli (fearful, happy, and neutral) after receiving a dose of 10 mg hydrocortisone and after placebo. GC administration had an enhancing effect on inhibitory performance in healthy control participants, indicated by faster responses, while no GC effect was revealed for the patients group. Moreover, patients showed an overall worse performance than healthy participants. In conclusion, this study further supports the hypothesis of impaired central glucocorticoid receptor function in MDD patients. Regarding the importance of inhibitory functioning for daily living, further studies are needed to examine the impact of glucocorticoids on response inhibition.

1. Introduction

In the last decades, neuroendocrine research has indicated that glucocorticoids (GCs) affect cognitive performance, particularly hippocampus-mediated declarative memory and prefrontal cortex-mediated working memory for emotional material (Belanoff et al., 2001; Het et al., 2005; de Quervain et al., 2008; Wolf, 2009). This evidence is of high relevance for major depressive disorder (MDD) which has been characterized by both cognitive dysfunctions and glucocorticoid alterations.

About 50–70% of patients with MDD are characterized by functional abnormalities of the hypothalamus–pituitary–adrenal (HPA) axis including cortisol hypersecretion (Parker et al., 2003; Barden, 2004; Pariante and Lightman, 2008) and a reduced peripheral sensitivity of glucocorticoid receptors (GR) (Holsboer, 2000; Calfa et al., 2003). GRs are widely distributed throughout the brain and are found in high densities in the hippocampus and the prefrontal cortex (PFC; Patel et al., 2000; de Kloet, 2003), two brain areas closely related to cognitive function.

One of the major cognitive impairments in MDD is PFC mediated executive dysfunction (Ottowitz et al., 2002; Rogers et al., 2004; Beblo et al., 2011). A key component of executive functions is referred to as 'inhibitory control' which allows inhibiting the processing of irrelevant information and thereby impacts working memory efficiency (Hasher et al., 1999). Understanding the underlying mechanisms of inhibition deficits in MDD

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is of special interest, as inhibitory deficits have been associated with rumination, poor treatment response and relapse (Joormann, 2010). Inhibition is usually examined by paradigms assessing response inhibition which refers to the ability to withhold a pre-potent cognitive or motor response (Lezak, 1995). Prominent tasks to investigate response inhibition are the Stroop Color and Word Test (SCWT, Stroop, 1935) and Go/No-Go tasks (e.g. Menon et al., 2001). Using these tasks with either neutral or emotional stimuli, several studies yielded impairments in response inhibition in patients with MDD indicated by slower response times and/or more errors of commission compared to healthy control subjects (Degl'Innocenti et al., 1998; Murphy et al., 1999; Schatzberg et al., 2000; Kaiser et al., 2003; Stordal et al., 2004; Langenecker et al., 2005; Markela-Lerenc et al., 2006; Gohier et al., 2009), even in a remitted state (Biringer et al., 2005; Paelecke-Habermann et al., 2005; Nakano et al., 2008). These impairments have been related to structural and functional brain abnormalities, particularly volume reduction and hypoactivation of the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) (Davidson et al., 2002; Ottowitz et al., 2002; Rogers et al., 2004).

Neuroendocrine research has provided accumulating evidence for an interrelationship between HPA axis dysregulation and deficits mainly in declarative memory, working memory and executive functions in patients with MDD, although the results are inconclusive and almost exclusively based on correlational data (for a recent review see Schlosser et al., 2011). Regarding response inhibition, cross-sectional studies indicated significant associations between measures of HPA axis function and inhibitory deficits on the SCWT in MDD patients (Egeland et al., 2005; Gomez et al., 2006), though not all studies agree (Gomez et al., 2009). To date, there is a paucity of studies investigating the acute effect of GCs on cognitive function in MDD. Bremner et al. (2004) were the first to investigate the impact of GCs on declarative memory in depressed patients and they found memory performance to be improved after chronic dexamethasone treatment in MDD patients, while being unchanged in healthy controls. In three recent experimental studies from our group, we consistently found that after a single administration of 10 mg hydrocortisone declarative and working memory were impaired in healthy participants, while memory performance in MDD patients was unaffected (Schlosser et al., 2010; Terfehr et al., 2011a, 2011b). Altogether, these results have been interpreted as first experimental evidence for a reduced central (brain) GR sensitivity in patients with MDD (Rohleder et al., 2010; Schlosser et al., 2011). To our knowledge, only four studies investigated the effect of acute cortisol elevation on inhibitiory control in healthy subjects (Wolf et al., 2001; Oei et al., 2009; Scholz et al., 2009; Zwissler et al., 2011). Scholz et al. (2009) demonstrated that a single psychosocial stress induction (Trier Social Stress Test, TSST) significantly impaired go/no-go performance in healthy men. In contrast, Zwissler et al. (2011) found inhibitory control of memory in a directed forgetting task not to be affected after a psychosocial stress induction (TSST) in healthy participants. Accordingly, Wolf et al. (2001) found no impairing effect of acute cortisol administration on SCWT performance in healthy men. Oei et al. (2009) even found an enhancing effect of hydrocortisone on inhibitory performance when examining distracter interference in a Sternberg working memory task in healthy men.

Effects of acute GC administration on executive functions in MDD other than working memory have not yet been studied. Thus, the purpose of the present study was to examine the effects of an acute GC administration on prefrontal cortex dependent executive functions, particularly response inhibition, in patients with MDD. First, due to a reduced central GR sensitivity, we proposed that hydrocortisone administration would not affect inhibitory performance in patients with MDD. Considering previous research on GC effects on declarative and working memory, we secondly predicted that inhibitory performance of healthy control participants would be impaired after hydrocortisone treatment compared to placebo treatment particularly when inhibiting emotional stimuli. Third, we hypothesized patients with MDD to perform generally worse in inhibitory control compared to non-depressed control participants.

In order to test these hypotheses, we utilized a placebo-controlled, double-blind, crossover design. After hydrocortisone and placebo treatment, respectively, 50 inpatients with MDD and 54 healthy control participants, matched for age, sex and years of education, conducted an emotional visual go/no-go task known to measure the ability to inhibit a pre-potent motor response.

2. Methods

2.1. Participants

Fifty-two inpatients (31 females, 21 males) and fifty-four healthy control participants (35 females, 19 males) were initially enrolled in this study. All patients and healthy control participants were reported on in previous studies from our group (Schlosser et al., 2010, MDD $n=16$, controls $n=16$; Terfehr et al., 2011a, MDD $n=44$, controls $n=51$; Terfehr et al., 2011b, MDD $n=57$, controls $n=56$). Patients were recruited at the Department of Psychiatry and Psychotherapy Bethel, Ev. Hospital Bielefeld, Germany, and at the Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf and Schoen Klinik Hamburg-Eilbek, Germany. Inclusion criteria for patients were a current MDD, single or recurrent according to DSM-IV criteria, and for both patients and control participants an age from 18 to 60 years. Criteria for exclusion for patients were current or lifetime schizophrenia, schizoaffective disorder, major depression with psychotic symptoms, bipolar disorder, current anorexia, substance abuse or dependence and attention-deficit/hyperactivity disorder. Exclusion criteria for both patients and control participants were (1) dementia, cognitive impairment; (2) CNS relevant somatic diseases, neurological diseases, metabolic diseases (e.g., thyroid disease, diabetes), organic shift in cortisol secretion (e.g., Morbus Cushing), immune-mediated diseases, severe cardiovascular diseases, current infections; (3) use of beta-blockers, benzodiazepines or steroids; (4) pregnancy or nursing. These criteria were assessed by exhaustive anamnesis and an additional examination by a psychiatrist. Additionally, control participants were excluded if they had any former or current DSM-IV Axis I disorder. Psychiatric diagnoses were made by trained psychologists using the Structured Clinical Interview for DSM-IV, SCID-I for Axis-I disorders (Wittchen et al., 1997). Severity of depressive symptoms was assessed by means of the Beck Depression Inventory (BDI, Beck and Steer, 1994).

Healthy control participants were recruited by local advertising. They received financial remuneration for their efforts (100 €).

Written informed consent was obtained from all participants. The study was approved by the University of Muenster Ethics Committee and the Ethics Committee of the Medical Council of Hamburg.

2.2. Material

In order to test response inhibition, we administered an emotional go/no-go paradigm. The paradigm was obtained from a study by Hare et al. (2005) and extended by three emotional conditions to complete condition variability. The emotional go/no-go task consisted of human face stimuli with three different