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Altered neural processing of emotional faces in remitted Cushing's disease

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Summary Patients with long-term remission of Cushing's disease (CD) demonstrate residual psychological complaints. At present, it is not known how previous exposure to hypercortisolism affects psychological functioning in the long-term. Earlier magnetic resonance imaging (MRI) studies demonstrated abnormalities of brain structure and resting-state connectivity in patients with long-term remission of CD, but no data are available on functional alterations in the brain during the performance of emotional or cognitive tasks in these patients.

We performed a cross-sectional functional MRI study, investigating brain activation during emotion processing in patients with long-term remission of CD. Processing of emotional faces versus a non-emotional control condition was examined in 21 patients and 21 matched healthy controls. Analyses focused on activation and connectivity of two a priori determined regions of interest: the amygdala and the medial prefrontal—orbitofrontal cortex (mPFC—OFC). We also assessed psychological functioning, cognitive failure, and clinical disease severity.

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Patients showed less mPFC activation during processing of emotional faces compared to controls, whereas no differences were found in amygdala activation. An exploratory psychophysiological interaction analysis demonstrated decreased functional coupling between the ventromedial PFC and posterior cingulate cortex (a region structurally connected to the PFC) in CD-patients.
The present study is the first to show alterations in brain function and task-related functional coupling in patients with long-term remission of CD relative to matched healthy controls. These alterations may, together with abnormalities in brain structure, be related to the persisting psychological morbidity in patients with CD after long-term remission.

1. Introduction

Cushing's disease (CD) is characterized by elevated endogenous cortisol levels and is related to physical and psychological morbidity in more than 70% of the patients (Newell-Price et al., 2006). After correction of hypercortisolism, physical and psychological symptoms improve substantially. However, patients with long-term remission of CD still demonstrate residual physical and psychopathological morbidity (Resmini, 2014; Tiemensma et al., 2010a), impairments in cognitive functioning (Hook et al., 2007; Ragnarsson et al., 2012; Resmini et al., 2012; Tiemensma et al., 2010b) and reduced quality of life (Van Aken et al., 2005). A recent study provided evidence for a role of specific genetic polymorphisms in the etiology of cognitive impairments in these patients (Ragnarsson et al., 2014), but the persistent symptoms in patients with long-term remission of CD are still ill-understood. Cortisol acts in the central nervous system by stimulation of mineralocorticoid receptors and glucocorticoid receptors. An appropriate balance in activation of these two receptor systems is required for adequate stress responses. Hyperactivation of the hypothalamic—pituitary—adrenal (HPA)-axis during active CD not only induces overactivation of the receptors, but also an imbalance in mineralocorticoid- and glucocorticoid receptor activation, both of which might result in inadequate stress responses and enhanced vulnerability to psychopathology (De Kloet et al., 2005). The residual psychological and cognitive morbidity after long-term remission of CD suggests that exposure to hypercortisolism not only has acute effects, but might also be related to persistent changes in the brain.

Several neuroimaging studies have observed changes in morphology and function of the brain during the active phase of CD (Andela et al., 2015). Using functional magnetic resonance imaging (fMRI), less activation in the left anterior superior temporal gyrus and higher activation in frontal, medial, and subcortical regions during the identification of emotional faces was measured, indicating altered activity of brain structures relevant to the perception, processing and regulation of emotion (Langenecker et al., 2012). In addition, adolescents with active CD demonstrated increased activation in the left amygdala and right anterior hippocampus during a memory task involving emotional faces (Maheu et al., 2008). Moreover, patients with active CD showed structural brain abnormalities, including hippocampal volume reduction and cerebral atrophy (Bourdeau et al., 2002; Starkman et al., 1992). Mainly short term follow-up studies (duration of follow-up: 6—40 months) demonstrated at least partly reversibility of these structural brain abnormalities (Bourdeau et al., 2002; Starkman et al., 1999), although no firm conclusions can be drawn about the completeness of reversibility since long-term follow-up studies are lacking. Recently, we and others have shown that patients with long-term remission of CD (mean duration of remission: 11.2 years) still have abnormalities in brain structure, as evidenced by smaller gray matter volumes in the anterior cingulate cortex, larger gray matter volumes in the left lobe of the cerebellum (Andela et al., 2013) and widespread reductions in white matter integrity (Van der Werff et al., 2014). In addition, these patients showed increased resting-state functional connectivity of the anterior cingulate cortex (Van der Werff et al., 2015). Furthermore, a spectroscopy study by Resmini and colleagues demonstrated persistent biochemical alterations in both the left and right hippocampus in cured CD patients (Resmini et al., 2013). Taken together, these findings indicate that patients with long-term remission of CD have persisting structural and biochemical brain abnormalities, as well as changes in functional connectivity at rest, after cure of previous hypercortisolism (Andela et al., 2015). However, it is presently unknown whether these alterations appear in conjunction with altered brain activity patterns during the performance of cognitive or emotional tasks.

Given the link between hypercortisolism and disturbances in the stress response (De Kloet et al., 2005), and the irritability, anxiety, and depressive symptoms reported by patients with long-term remission of CD (Tiemensma et al., 2010a), we decided to examine brain activity during the processing of emotional faces in these patients. Patients were part of the sample described previously (Andela et al., 2013; Van der Werff et al., 2015, 2014). Focus was on two regions of interest (ROIs): the amygdala and the medial prefrontal—orbitofrontal cortex (mPFC—OFC) (Shin and Liberzon, 2010). The amygdala and the mPFC, including the orbitofrontal cortex, are both part of the limbic system and involved in the regulation of the HPA-axis (Kim et al., 2011). Previous neuroimaging studies in patients with stress-related psychiatric disorders demonstrated hyperactivation of the amygdala and hypoactivation of the mPFC in response to emotional stimuli (Etkin and Wager, 2007; Shin and Wright, 2005), and it has been suggested that disturbances in the amygdala—mPFC circuitry lead to symptoms of anxiety (Kim et al., 2011). Considering the similarity in psychopathology between patients with CD and patients suffering from stress-related psychiatric disorders, we hypothesized that patients with long-term remission of CD would also show hypoactivaton of the mPFC