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HPA axis response to social stress is attenuated in schizophrenia but normal in depression: Evidence from a meta-analysis of existing studies

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SUMMARY

We conducted a meta-analysis to investigate the HPA axis response to social stress in studies that used the Trier Social Stress Test (TSST), or comparable distressing paradigms, in individuals with either depression or schizophrenia. Sample size-adjusted effect sizes (Hedge's *g* statistic) were calculated to estimate the HPA axis stress response to social stress. We used a meta-regression model to take into account the moderating effect of the baseline cortisol level. Participants with depression show an activation pattern to social stress similar to that of healthy controls. Despite a normal cortisol production rate, individuals with schizophrenia have lower cortisol levels than controls both in anticipation and after exposure to social stress. Participants with depression and higher cortisol levels before the task have an increased cortisol production and reached higher cortisol levels during the task. This may be explained by the presence of an impaired negative feedback. The activation pattern present in schizophrenia may explain the reduced ability to appropriately contextualize past experiences shown by individuals with psychosis in social stressful situation.

Contents

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1. Introduction

Social stress plays a crucial role in the onset and relapses of both depression and psychosis. These disorders are both characterized by high basal levels of cortisol (Mondelli et al., 2010a; Zunszain et al., 2011), the main stress hormone produced by the hypothalamic–pituitary–adrenal (HPA) axis. However, whether the HPA axis response to social stressors differs between depression and psychosis is still unclear. Indeed, findings remain inconsistent, as only few studies have been conducted to date, and all have used relatively small samples. Social stressors in a laboratory setting (such as talking in public in a controlled environment) are good proxy for real life stressors (Allen et al., 2014; Green et al., 2012); therefore, clarifying the HPA axis response to these stressors may help understand its contribution to the onset of depression and psychosis in real life.

Individuals with severe psychiatric disorders are more likely to have experienced more frequent and more intense psychosocial difficulties than people without past or current mental health conditions (Mauritz et al., 2013). Indeed, exposure to social stress is one of the prime factors in precipitating depression (Kendler et al., 1999; Schwabe et al., 2012) and is also strongly associated with onset of psychosis, schizophrenia in particular (Holtzman et al., 2013). Psychosocial difficulties have been described to influence various aspects of the clinical presentation, such as symptoms severity and treatment response, in both depression and psychosis (Hammen et al., 1992; Schafer and Fisher, 2011). Interestingly, emotional reactivity to daily life events appears to be different in patients with affective and psychotic disorders, as individuals with depression have been described as less vulnerable to stressors and daily hassles than individuals with psychosis. Specifically, individuals with depression show a significant increase in negative affect in subjectively stressful situations, while individuals with non-affective psychosis show an increase in negative and a decrease in positive affect (Myin-Germeys et al., 2003). Indeed, when taking into account self-reported measures of sensitivity to stress, such as arousal and anxiety, individuals with schizophrenia show greater emotional reactivity to psychosocial stressors (Palmier-Claus et al., 2013).

It has been suggested that the exposure to social adverse experiences precipitates depression, at least in part, trough the hyper-activity of the HPA axis in vulnerable individuals (Pariante and Lightman, 2008). The HPA axis is finely regulated by negative feedback; cortisol binds to the glucocorticoid receptor outside (such as in the pituitary gland) and inside the brain (hippocampus and hypothalamus) and produces an inhibitory signal that leads to reduction of HPA axis activity. Elevated plasma cortisol levels at rest have been observed in approximately 50% of patients with major depression, particularly in the evening, when it is at the lowest point of the circadian rhythm (Rubin et al., 1987; Sachar et al., 1973). This increased cortisol production is known to be related to a reduced feedback inhibition by endogenous glucocorticoids (Pariante and Lightman, 2008).

Elevated cortisol levels during the day have also been reported in psychosis, particular at illness onset, as well as during acute relapses; moreover, in both psychosis and depression higher basal cortisol levels have been associated with smaller hippocampal volume (Lorenzetti et al., 2009; Mondelli et al., 2010b, 2011), a pivotal region in emotion regulation (Fan et al., 2013; Rive et al., 2013). However, recent findings have also highlighted different patterns of HPA axis activity between depression and psychosis: individuals with depression, as well as individuals at familiar risk of developing depression, have an increased cortisol awakening response (Bhagwagar et al., 2005; Mannie et al., 2007). In contrast, patients with psychosis, and schizophrenia in particular, have a reduced cortisol awakening response (Mondelli et al., 2010a; Pruessner et al., 2013). The cortisol awakening response is a recognized measure of acute reactivity of the HPA axis (Dickerson and Kemeny, 2004). A blunted awakening response in schizophrenia suggests reduced HPA axis reactivity, consistent with evidence of a reduced HPA axis reactivity to stress in schizophrenia (Breier et al., 1988). Interestingly, a reduced reactivity to stress and more reduced cortisol awakening response have been associated with more severe symptoms and worse cognitive function in schizophrenia (Aas et al., 2011; Belvederi Murri et al., 2012). Whether this different pattern of cortisol response to awakening in depression and schizophrenia is mirrored by a similar different pattern of cortisol reactivity to psychosocial stressors is still unclear.

Reflecting spontaneous variation in the circadian glucocorticoid oscillation, the morning cortisol response to awakening is useful to study the reactivity of the HPA activity. However, it has not always been interpreted equivalent to reactivity to psychological stressor (Schmidt-Reinwald et al., 1999). Furthermore, the awakening cortisol response tests individual's adrenal cortex capacity without appraising the function of any suprahypothalamic structure (e.g. the limbic system) (Schmidt-Reinwald et al., 1999). The limbic system is indeed a primary channel between exogenous stressors and endogenous physiological signals (Guerry and Hastings, 2011). In both depression and schizophrenia structural irregularities and abnormal connectivity of the limbic system have emerged in recent years (Kasai et al., 2003; Ottet et al., 2013; Peng et al., 2013; van Eijndhoven et al., 2013). Although some gray matter volume reductions are common to both disorders, there are diverging patterns of connectivity between the frontal cortex and the cerebellum (depression), and in intra-limbic connections with the fronto-temporal cortex (schizophrenia), which may lead to specific abnormalities in mood regulation, cognition and negative symptoms (Kasai et al., 2003; Oertel-Knochel et al., 2013; Peng et al., 2013; van Eijndhoven et al., 2013).

Given the importance that stress reactivity bears in facilitating relapses and worsening symptomatology in both depression and schizophrenia, understanding the HPA axis response to acute stressors in these disorders would help us better understand, and possibility differentiate, the biological mechanisms underlying their pathophysiology (Belvederi Murri et al., 2012; Holtzman et al., 2013; Kendler et al., 1999; Mannie et al., 2007).

Although a number of studies have used psychological stressors to investigate higher-order functioning of the HPA axis (e.g. cortisol secretion in consequence of concurrent internal and external stimuli), there is a lack of meta-analytic studies in this area (Guerry and Hastings, 2011). Indeed, there have been only two meta-analyses on the HPA axis response in depression and none in patients with schizophrenia. Lopez-Duran et al. (2009) explored both HPA axis basal activity and its response to pharmacological challenges in depressed children and adolescents to understand the changes associated with prolonged stress, and Burke et al. (2005) investigated the HPA axis reactivity to both cognitive and psychological stressors combining together different sources of stress and biological mechanisms (Schmidt-Reinwald et al., 1999). Thus, consolidated evidence on the HPA axis reactivity to acute stressors of psychological nature in either depression or psychosis has not been achieved yet.