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Associations between brain activity and endogenous and exogenous cortisol – a systematic review

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Abstract

To arrive at a coherent understanding of the relation between glucocorticoids and the human brain, we systematically reviewed the literature for studies examining the associations between endogenous or exogenous cortisol and human brain function. Higher levels of endogenous cortisol during psychological stress were related to increased activity in the middle temporal gyrus and perigenual anterior cingulate cortex (ACC), decreased activity in the ventromedial prefrontal cortex, and altered function (i.e., mixed findings, increased or decreased) in the amygdala, hippocampus and inferior frontal gyrus. Moreover, endogenous cortisol response to psychological stress was related to increased activity in the inferior temporal gyrus and altered function in the amygdala during emotional tasks that followed psychological stress. Exogenous cortisol administration was related to increased activity in the postcentral gyrus, superior frontal gyrus and ACC, and altered function in the amygdala and hippocampus during conditioning, emotional and reward-processing tasks after cortisol administration. These findings were in line with those from animal studies on amygdala activity during and after stress.

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Keywords

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1. Introduction

While considerable research has examined the long-term adverse effects of glucocorticoids on the brain (Andela et al., 2015; Judd et al., 2014; Lupien et al., 2009), glucocorticoids also affect brain function acutely following endogenous release or exogenous administration (Dedovic et al., 2009a). Acute changes in glucocorticoids are thought to influence a range of processes including general memory, arousal and emotional processing (Joels, 2018; Ulrich-Lai and Herman, 2009). Yet, a coherent account of how such acute changes in endogenous and exogenous cortisol influence human brain function as measured using functional magnetic resonance imaging (fMRI) is still lacking. This is due partly to the challenge of co-evaluating data from studies that have employed a variety of experimental methodologies, imaging protocols and analytical approaches, as well as differences in dosing, timing and frequency of cortisol measurements. In this review, we aim to identify commonalties and differences across studies, search for replicated findings, and summarize how acute cortisol is associated with human brain function.

Glucocorticoids, specifically corticosterone in rodents and cortisol in humans, are the end-product of the hypothalamic-pituitary-adrenal (HPA) axis, which plays an important role in the stress response (de Kloet et al., 2005; Reul and De Kloet, 1986). Cortisol crosses the blood-brain barrier and binds to both glucocorticoid and mineralocorticoid receptors in the brain (de Kloet et al., 2005; Reul and De Kloet, 1986). Cortisol has both acute non-genomic and slow gene-mediated effects on the brain. The acute effects seem to be mostly related to activation of specific circuits, whereas slow effects seem to be mostly related to normalization of earlier enhanced activity (Joels, 2018). In the current review we focus on the acute effects of cortisol. Animal studies have the ability to directly manipulate the HPA axis to address predictable hypotheses and have shown acute effects of glucocorticoids on activity of the amygdala, hippocampus, paraventricular nucleus and prefrontal cortex (Joels et al., 2012; Ulrich-Lai and Herman, 2009). These effects might facilitate a quick and adaptive response to stressors (Joels, 2018; Ulrich-Lai and Herman, 2009). It is important to bridge animal and human research on the acute effects of glucocorticoids on brain function, as individual differences in these effects could be related to individual differences in coping with stress (de Kloet et al., 2005).

Recent human studies have investigated associations between acute increases in endogenous and exogenous cortisol levels and the brain under controlled conditions. Studies of endogenous cortisol usually induce elevations in cortisol by employing short, acute psychological stressors, such as tasks involving uncontrollability and/or social-evaluative threat (Dickerson and Kemeny, 2004). A meta-analysis has shown that cortisol peaks 0–20 minutes after such stressors (Dickerson and Kemeny, 2004). Studies of exogenous cortisol use oral or intravenous administration, usually in a placebo-controlled design. Each type of study has advantages and disadvantages (Table 1). In short, studies of endogenous cortisol

are most similar to stressful events in daily life and induce a natural physiological response. However, the endogenous cortisol response might be related to subjective experience of the stressor which is variable. For example, one of the more frequently employed stressors, the Trier Social Stress Test (Kirschbaum et al., 1993), elicits a two-to-three fold increase in cortisol in about 70–80% of participants 10–20 minutes after the stressor (Kudielka et al., 2007). Therefore, it is difficult to differentiate a failed stress induction from a dysregulated stress response system, especially if only one system is investigated (Andrews et al., 2013). On the other hand, exogenous administration of cortisol provides tight experimental control and induces higher levels of cortisol, which might improve signal-to-noise ratio in terms of cortisol elevation, and the opportunity to test for causal effects. However, administration of exogenous cortisol does not represent a natural physiological stress reaction, as the stress response is a combination of three interacting systems (sympathetic nervous system, HPA-axis and subjective emotional experience (Andrews et al., 2013). As endogenous and exogenous cortisol might reflect different processes, it is important to integrate the findings both within each domain (endogenous versus exogenous) as well as across the two domains. This will provide a coherent understanding of associations between glucocorticoids and human brain function, as well as to identify important areas for future research.

We systematically reviewed the literature examining the relation between endogenous and exogenous cortisol and human brain function. We reviewed fMRI studies that measured brain activity *during* a psychological stressor or cortisol administration, and during tasks performed shortly *after* a psychological stressor or cortisol administration. In this way, we focused on the acute effects of cortisol. The first research question is how cortisol relates to brain activity as measured with fMRI during (a) psychological stress, or (b) cortisol administration. The second research question is how cortisol relates to brain activity during fMRI tasks after (a) psychological stress, or (b) cortisol administration. Based on findings from animal research (Joels et al., 2012; Ulrich-Lai and Herman, 2009), we hypothesize that endogenous and exogenous cortisol are related to activity in the amygdala, hippocampus, paraventricular nucleus and prefrontal cortex.

Regarding the latter hypothesis, the literature has focused on brain activity during a variety of tasks: conditioning, emotional stimuli, reward processing, decision-making, and non-emotional tasks (mostly working memory, detection and memory retrieval tasks). Conditioning tasks usually present one stimulus paired with an aversive stimulus and one stimulus without an aversive stimulus, to measure how participants learn to distinguish between stimuli (Lonsdorf et al., 2017). Emotional tasks usually present participants with pictures of emotional faces (Vuilleumier and Pourtois, 2007) or pictures from the International Affective Picture System (IAPS) (Lang et al., 2001). Reward processing tasks are used to measure how participants respond to anticipating and receiving rewards (Wang et al., 2016). Decisionmaking tasks measure how participants make (risky) decisions (Schonberg et al., 2011). Non-emotional tasks measure working memory or memory retrieval of neutral stimuli such as neutral images or spatial locations (Roozendaal et al., 2009).

## 2.	Methods

### 2.1	Search strategy

Inclusion criteria and search terms were defined separately for studies on endogenous and exogenous cortisol. For studies on endogenous cortisol, the following inclusion criteria were used: (a) acute psychological laboratory stressors, defined as tasks that lasted less than one hour and did not serve a function outside the laboratory setting (Dickerson and Kemeny, 2004), including physical-psychological stressor combinations; (b) fMRI during or shortly after the psychological stressor or control condition (maximum of 30 minutes between stressor and fMRI[1]); (c) salivary or plasma cortisol assessed before and during/after the psychological stressor; (d) healthy adult humans; (e) in English. A literature search was performed on PubMed and Web of Knowledge using the following search terms: fMRI (or functional MRI or functional magnetic resonance or neuroimaging) and cortisol (or HPA or hypothalamic-pituitary-adrenal axis or neuroendocrine or hydrocortisone or psychoneuroimmunology or psychoimmunology or psychoneuroendocrinology), excluding rat.

For studies on exogenous cortisol, the following inclusion criteria were used: (a) cortisol administration; (b) placebo-controlled; (c) fMRI during or after cortisol administration (on the same day); (d) healthy adult humans; (e) in English. A literature search was performed on PubMed and Web of Knowledge using the following search terms: fMRI (or functional MRI or functional magnetic resonance or neuroimaging) and cortisol and administration (or exogenous or oral or IM or IV or cortisone or corticosterone or corticosteroid or corticoid or glucocorticoid or prednisone or prednisolone or dexamethasone or hydrocortisone or glucocorticoid or methylprednisolone or steroid or cosyntropin or corticorelin), excluding rat. Both literature searches were performed before September 12th, 2019. No limit was set for year of publication or country/region of study. To ensure literature saturation, we scanned the reference lists of included studies and relevant reviews and meta-analyses identified through the search. After duplicates were removed at least two review authors independently screened the titles and abstracts yielded by the search. We obtained full text for all titles that appeared to meet the inclusion criteria or where there was any uncertainty. At least two review authors screened the full text reports independently and decided whether these meet the inclusion criteria, disagreements were resolved through discussion. We recorded the reasons for excluding studies after full-text screening (see flow diagram in Supplementary Figure 1). If correlations between cortisol and brain activity were not reported in the manuscript, we contacted the authors to gather that information.

## 3.	Results

### 3.1	Literature overview

The literature search for endogenous cortisol resulted in 1083 manuscripts, of which 65 studies met the inclusion criteria (see flow diagram in Supplementary Figure 1). The correlation between cortisol and brain activity during psychological stress was reported in 22

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[1]Cortisol peaks 0–20 minutes after a stressor (Dickerson and Kemeny, 2004), so cortisol would most likely peak during the fMRI task.

of these studies, but there was high variability in reported statistics: five studies reported Montreal Neurological Institute (MNI) coordinates (Akdeniz et al., 2014; Boehringer et al., 2015; Kukolja et al., 2008; Radke et al., 2018; Root et al., 2009), six studies reported correlation coefficients for different regions of interest (ROIs) (Admon et al., 2015; Dahm et al., 2017; Lederbogen et al., 2011; Mareckova et al., 2017; Ming et al., 2017; Pruessner et al., 2008), four studies reported no statistics but rather reported that no effects arose (Dedovic et al., 2014; Kogler et al., 2015; Kogler et al., 2017; Orem et al., 2019), five studies only compared cortisol responders and non-responders (Dedovic et al., 2009b; Khalili-Mahani et al., 2010; Streit et al., 2014; van Stegeren et al., 2007; Wheelock et al., 2016), and two studies focused on perfusion fMRI data (Wang et al., 2007; Wang et al., 2005). The correlation between cortisol and brain activity during tasks right after psychological stress was reported in 20 studies. Eighteen studies measured both cortisol and brain activity during or after psychological stress but did not report the correlation between the two, and we did not get the information after we contacted the authors. In addition, five studies focused on connectivity analyses, one study focused on changes in cortisol elicited by exercise treatment, and one study did not include the cortisol data in the manuscript.

The literature search for exogenous cortisol resulted in 328 manuscripts, of which 30 studies met the inclusion criteria (see flow diagram in Supplementary Figure 2). We included different cortisol compounds in the search, but almost all studies used hydrocortisone, except two studies using prednisolone (Buades-Rotger et al., 2016; Serfling et al., 2019). The correlation between cortisol and brain activity during cortisol administration was only examined and reported in one study (Lovallo et al., 2010). The correlation between cortisol and brain activity during tasks after cortisol administration was reported in 29 studies.

The inconsistency in statistical procedures, paradigms, and definitions of cortisol response precluded quantitative review of cross-study associations between endogenous or exogenous cortisol and human brain function. Therefore, we used a qualitative, systematic approach to answer the two research questions. Only effects that were replicated were interpreted and described in the text (Figure 1–2); however, all findings are reported in Tables 2, 3, and 4. We focused on the associations between acute cortisol and human brain function, as the direction of the effect is unclear as cortisol might not have had the time to impact the brain. In addition, the cortisol response was measured differently across studies (e.g. area under the curve, peak minus baseline).

3.2 Is cortisol related to brain activity *during* psychological stress or cortisol administration?

3.2.1 Endogenous cortisol—In these studies, the stressor occurred while the participants were in the MRI scanner, so cortisol probably peaks right after the MRI scan. It should be noted that the relation between cortisol and brain activity is correlational, and that these associations might also be influenced by other variables. At the whole-brain level, higher levels of endogenous cortisol during psychological stress in the MRI scanner were related to increased activity in the middle temporal gyrus and altered function (increased activity in some and decreased activity in other studies) in the inferior frontal gyrus (Table 2, Figure 1). Specifically, for the middle temporal gyrus, higher cortisol levels were related to

more activity in response to fear evoking images (Root et al., 2009) and during social exclusion in the Cyberball task (Radke et al., 2018). For the inferior frontal gyrus, higher cortisol levels were related to less activity in response to fear evoking images (Root et al., 2009) and during memory retrieval in older subjects (Kukolja et al., 2008). However, higher cortisol levels were related to more activity in this same region during social exclusion in the Cyberball task (Radke et al., 2018). Two studies did not find associations between cortisol and brain activity on a whole-brain level during the Montreal Imaging Stress Task (MIST) (Dedovic et al., 2014; Orem et al., 2019), although they did not find increased levels of cortisol in response to this task either.

ROI analyses of endogenous cortisol have focused on different ROIs based on the literature or on whole-brain findings. These studies revealed that higher levels of endogenous cortisol were related to increased activity in the perigenual anterior cingulate cortex (ACC), decreased activity in the ventromedial prefrontal cortex (vmPFC) and altered function in the amygdala and hippocampus (Figure 1). First, higher endogenous cortisol levels were related to increased activity in the perigenual ACC during the MIST (Boehringer et al., 2015) and during ScanSTRESS (an arithmetic task) (Akdeniz et al., 2014). Of note, other regions of the ACC were not related to endogenous cortisol during the MIST (Dedovic et al., 2014; Pruessner et al., 2008) nor during ScanSTRESS (Dahm et al., 2017). Second, higher endogenous cortisol levels were related to reduced activity in the vmPFC during the MIST (Ming et al., 2017; Wheelock et al., 2016) and while watching fear evoking images (Root et al., 2009). Third, an increased endogenous cortisol response was related to increased activity in the amygdala while watching fear evoking images (Root et al., 2009; van Stegeren et al., 2007), and to decreased activity in the amygdala during the MIST (Lederbogen et al., 2011). In contrast, three other studies found no relation between cortisol and amygdala activity during psychological stress (Dahm et al., 2017; Kogler et al., 2015; Orem et al., 2019). Fourth, higher levels of endogenous cortisol were related to decreased activity in the hippocampus during the MIST (Khalili-Mahani et al., 2010; Lederbogen et al., 2011; Pruessner et al., 2008), and to increased activity in the hippocampus while watching fear evoking images (Root et al., 2009). Three studies using the MIST showed no relation between endogenous cortisol and activity in the hippocampus (Dedovic et al., 2014; Kogler et al., 2015; Orem et al., 2019), but the MIST did not elicit a significant increase in cortisol in these studies.

Since psychological stressors elicit a cortisol response in only a fraction of participants (Dickerson and Kemeny, 2004; Kudielka et al., 2007), six studies focused on the comparison between those participants who demonstrated an increase in cortisol ('responders') and those who did not ('non-responders'). Two of these studies found that responders showed more activity in the amygdala than non-responders during ScanSTRESS (Streit et al., 2014) and while watching fear-evoking images (van Stegeren et al., 2007).

3.2.2 Exogenous cortisol—Only one study investigated the relation between exogenous cortisol and brain activity during hydrocortisone administration and found decreased activity in the hippocampus and amygdala (Lovallo et al., 2010).

3.3 Is cortisol related to brain activity during tasks performed *after* psychological stress or cortisol administration?

3.3.1 Endogenous cortisol—In these studies, the stressor occurred before the participants performed a task in the MRI scanner, so the peak in cortisol is around the same time as the task. It should be noted that the relation between cortisol and brain activity is correlational, and that these associations might also be influenced by other variables. Only two studies investigated associations between endogenous cortisol and brain function during a conditioning task and reported that higher levels of cortisol were related to less activity in the left nucleus accumbens (NAcc) in men but not women (Merz et al., 2013), and to more activity in the right ventral putamen (Lewis et al., 2014). Endogenous cortisol during psychological stress was related to increased activity in the inferior temporal gyrus and altered function in the amygdala during subsequent emotional tasks (Figure 2 and Table 3).

At the whole-brain level, increased endogenous cortisol was related to increased activity in the inferior temporal gyrus while processing angry compared to neutral faces (Weldon et al., 2015) and emotional faces compared to neutral faces (Henckens et al., 2015). However, there were no whole-brain findings in a cognitive reappraisal task (Shermohammed et al., 2017). On the ROI level, two studies revealed that higher cortisol during psychological stress was related to more activity in the amygdala while processing emotional faces (Henckens et al., 2015; Oei et al., 2018), whereas one study found less activity in the amygdala during distracting IAPS pictures (Oei et al., 2012).

Two studies that focused on reward tasks did not report significant correlations with cortisol (Maier et al., 2015; Porcelli et al., 2012), and one reported a positive correlation between cortisol and activity in the NAcc (Oei et al., 2014). Only two studies focused on decision-making tasks and examined distinct ROIs: striatum (Lighthall et al., 2012) and middle frontal gyrus-dorsolateral prefrontal area (Gathmann et al., 2014) – hence no findings could be replicated. Similarly, six studies administered a non-emotional task in the MRI scanner after psychological stress (Khalili-Mahani et al., 2010; Luettgau et al., 2018; Muehlhan et al., 2011; Qin et al., 2009; Schwabe and Wolf, 2012; Vogel et al., 2016), but these studies examined different ROIs so there were no replicated findings.

3.3.2 Exogenous cortisol—In these studies, participants performed tasks in the MRI scanner after cortisol administration. Here, the associations between cortisol and brain activity are most likely to be related to cortisol, because of the tight experimental control with a placebo. Exogenous cortisol was related to increased activity in the ACC and hippocampus, and decreased activity in the amygdala during conditioning. First, during fear acquisition, exogenous cortisol was related to increased activity in the ACC to the unconditioned stimulus (Stark et al., 2006) and to the threat stimulus compared to the safe stimulus (Tabbert et al., 2010). Second, exogenous cortisol was related to decreased amygdala activity in response to the threat stimulus during fear acquisition (Merz et al., 2010, 2012b) and during fear extinction (Merz et al., 2018; Merz et al., 2014). Third, exogenous cortisol was related to increased activity in the hippocampus in response to a threat stimulus compared to the safe stimulus (Tabbert et al., 2010). However, this effect was at trend-level and only found in women (men showed the opposite effect) in Merz et al.

(2010). During fear extinction, exogenous cortisol was related to increased activity in the hippocampus in response to the safe stimulus compared to the threat stimulus (Tabbert et al., 2010), and decreased activity in the right hippocampus in response to the extinguished stimulus during early extinction (Merz et al., 2018). However, another study found no significant relation between cortisol and brain activity during acquisition and extinction (Merz et al., 2012a).

Exogenous cortisol was also related to increased activity in the postcentral gyrus, superior frontal gyrus and ACC, and altered function in the amygdala and hippocampus during emotional tasks after cortisol administration (see Figure 2 and Table 4). On the whole brain level, exogenous cortisol was related to increased activity in the postcentral gyrus while watching negative and neutral human features (Buades-Rotger et al., 2016) and during a Go/NoGo task with food stimuli, which was administered only in men (Serfling et al., 2019). Furthermore, exogenous cortisol was related to increased activity in the superior frontal gyrus while watching negative and neutral human features (Buades-Rotger et al., 2016) and during an emotional sentence processing task (Abercrombie et al., 2011). On the ROI level, higher cortisol levels were related to increased activity in the ACC during escapable threat in a Fear-and-Escape task (Montoya et al., 2015), during the viewing of happy faces in an emotional face processing task (in contrast to decreased ACC activity in response to sad faces) (Sudheimer et al., 2013), and only in women, not men, during a shifted-attention emotion appraisal task (Ma et al., 2017). No association between exogenous cortisol and ACC activity was found in one study that included only men using a Go/NoGo task with food (Serfling et al., 2019). Furthermore, higher cortisol levels were related to more activity in the amygdala during the viewing of aversive words (Henckens et al., 2012b) and happy faces (Sudheimer et al., 2013) in emotion interference tasks and during a Go/NoGo task with food in a study with only men (Serfling et al., 2019). Higher cortisol levels were also related to less activity in the amygdala in men when processing emotional pictures (Henckens et al., 2010). Finally, higher cortisol levels were related to more activity in the hippocampus during a cry task (Bos et al., 2014) and an emotional picture processing task (van Stegeren et al., 2010), and to less activity in the hippocampus during an episodic encoding task with emotional and neutral IAPS pictures (Henckens et al., 2012a; Kukolja et al., 2011). No relation between exogenous cortisol and hippocampus activity during a Go/NoGo task with food were found in a study that included only men (Serfling et al., 2019).

Only two studies measured brain activity during reward tasks after cortisol administration, both found that exogenous cortisol was related to reduced activity in the amygdala (Kinner et al., 2016b; Montoya et al., 2014). However, Kinner et al. (2016b) found this effect only in men, whereas women showed the opposite effect, though this interaction with sex was at trend-level. In non-emotional tasks, exogenous cortisol was related to reduced activity in the hippocampus in a word recognition task (Oei et al., 2007) and in a novelty detection task with indoor and outdoor scenes (Brown et al., 2013), but not in an autobiographical memory test (Fleischer et al., 2019).

4. Discussion

The goal of the current study was to systematically review the literature on the associations between endogenous and exogenous cortisol and human brain function. We reviewed results from fMRI studies that measured brain activity *during* a psychological stressor or cortisol administration, and during tasks *after* a psychological stressor or cortisol administration. These studies revealed many inconsistent findings, due to heterogeneity in methodology, paradigms, cortisol sampling, and analyses. However, there were three sets of replicated findings: First, higher levels of endogenous cortisol were related to increased activity in the middle temporal gyrus and perigenual ACC, decreased activity in the vmPFC, and altered function (increased activity in some studies and decreased in others) in the amygdala, hippocampus and inferior frontal gyrus during psychological stress. Second, endogenous cortisol during psychological stress was related to increased activity in the inferior temporal gyrus and altered function in the amygdala during emotional tasks that followed psychological stress. Third, exogenous cortisol (hydrocortisone in all except two studies) was also related to increased activity in the postcentral gyrus, superior frontal gyrus and ACC, and altered function in the amygdala and hippocampus during conditioning, emotional and reward-processing tasks after cortisol administration.

The inconsistent associations between endogenous and exogenous cortisol and brain activity did not seem to be related to type of stressor, method of assessing cortisol (e.g., area under the curve, peak minus baseline), or task after the stressor. Associations with activity in the amygdala were most consistently found across all studies; cortisol was related to amygdala activity during and after psychological stress. Similar findings emerged in the studies on exogenous cortisol. Studies of endogenous and exogenous cortisol both have their unique advantages, with studies of endogenous cortisol being more ecologically valid and studies of exogenous cortisol offering tighter experimental control. That both endogenous and exogenous cortisol were associated with activity in the amygdala might suggest a specific effect of cortisol independent of other effects of stress. These amygdala findings are in line with a previous review (Dedovic et al., 2009a). However, the effects were generally small, in different directions, had different peak coordinates, and were not statistically significant in all studies.

The relation between cortisol and amygdala activity is consistent with animal studies, demonstrating that the limbic system plays an important role in the stress response (Ulrich-Lai and Herman, 2009). Furthermore, in rhesus monkeys, the central nucleus of the amygdala is a core component of the neural circuit underlying anxious temperament, which is related to an increased cortisol response in a stressful situation (Kalin, 2017). The amygdala interacts with the hippocampus and medial prefrontal cortex in regulating effects of glucocorticoids on spatial memory retrieval (Roozendaal et al., 2003) and working memory (Roozendaal et al., 2004). Indeed, activity in the hippocampus and vmPFC was also related to cortisol in the human studies reviewed here. Furthermore, some studies showed that differential amygdala connectivity is related to endogenous (Mareckova et al., 2017; Vaisvaser et al., 2013; Vogel et al., 2016) or exogenous cortisol (Buades-Rotger et al., 2016; Henckens et al., 2012b). However, these effects were found in different brain regions (right dorsomedial prefrontal cortex, hippocampus, hypothalamus, middle frontal gyrus, precentral

and postcentral gyrus, striatum, and thalamus) and some studies did not find significant associations between cortisol and amygdala connectivity (de Voogd et al., 2017; Henckens et al., 2010). Future research should focus on the connectivity between the amygdala, hippocampus, and vmPFC, during or shortly after stress, to gain insight into the mechanisms through which the amygdala influences memory in response to stress.

Cortisol has both acute non-genomic and slow gene-mediated effects on brain function (Joels, 2018). Here we focused on the acute effects of cortisol, with neuroimaging during or shortly after psychological stress or cortisol administration. In studies of endogenous cortisol, cortisol would peak right after or during neuroimaging, and thus it is unknown if cortisol has had the time to impact neural activity. Therefore, the relation between endogenous cortisol and brain function is solely correlational. In studies of exogenous cortisol, the associations are more likely to be related to cortisol, due to tight experimental control with a placebo. However, the time between cortisol administration and subsequent neuroimaging varied, which makes it unclear if cortisol has had the time to impact neural activity. It is important to take the time between the stressor or cortisol administration and the subsequent fMRI task into account, as this could reflect different underlying processes. A few studies compared the relation between brain function and the acute versus slow effects of cortisol (Henckens et al., 2012a; Henckens et al., 2010, 2011, 2012b) and most of these showed differences between the acute and slow effects (Henckens et al., 2012a; Henckens et al., 2011, 2012b). Therefore, future research should compare the acute and slow effects of cortisol to enhance understanding of the modulatory effects of timing.

While the negative effects of cortisol on human brain functioning are usually emphasized, some studies have shown positive effects of cortisol. For example, patients with depression were better at retaining a relatively positive memory bias after cortisol administration (Abercrombie et al., 2011), and patients with social anxiety disorder showed a reduced early bias for implicit social threat after cortisol administration (van Peer et al., 2010). The positive effects of cortisol administration are putatively achieved by inhibiting automatic processing of goal-irrelevant threatening information and by increasing early approach-avoidance responses (Putman and Roelofs, 2011). Moreover, some studies have examined whether cortisol can be used as a treatment for internalizing disorders. For instance, dexamethasone was more effective than placebo in the treatment of depression (Arana et al., 1995), and glucocorticoids reduced symptoms in post-traumatic stress disorder and specific phobias (de Quervain and Margraf, 2008). These studies on the positive effects of cortisol highlight the complexity of the effects of glucocorticoids on the brain.

Several limitations should be taken into account. First, we were not able to do a meta-analysis due to considerable heterogeneity in methodology: different stress tasks, fMRI paradigms, cortisol dosage, frequency and time of the day, the time between stress and the following fMRI-task, cortisol response calculations (such as area under the curve, difference scores, etc.), and analytical approaches employed. Second, not all stress tasks elicited a significant increase in cortisol. One reason might be that essential components of stress tasks, such as uncontrollability and social evaluation (Dickerson and Kemeny, 2004), were not present in these tasks. Also, the increase in cortisol is highly variant within individuals and across populations (e.g. clinical versus non-clinical), reducing the possibility of

generalization. Third, null findings might not have been reported. Fourth, most studies were conducted by a few research groups, some studies possibly tested overlapping participants, underlining the need for independent replication. Fifth, we focused on the associations between acute increases in cortisol level and human brain function as measured with fMRI, but these associations can be studied at different levels using many techniques (e.g. cell level, EEG). Sixth, the pitfalls of studies of endogenous and exogenous cortisol should be taken into account. Even though studies of endogenous cortisol are more ecologically valid, the increase in cortisol level is small and the response to the stressor might be dependent on subjective experience of the stressor, which varies between people. Exogenous cortisol administration provides tight experimental control, but does not reflect a natural physiological stress reaction.

We have several recommendations for future studies on the associations between cortisol and human brain function. First, we recommend a more standardized approach to reporting results. For whole-brain analysis, results should be reported from all contrasts that were tested. For ROI analysis, anatomically defined ROIs should be used and findings from all ROIs should be reported. All results should be reported, even if associations were not statistically significant, as this would allow for future meta-analysis of the associations between brain function and cortisol. Second, we recommend within-subjects designs, to compare associations between cortisol and brain activity within individuals, whenever possible. Third, future research should investigate the role of cortisol on brain activity in psychopathology. For example, cortisol might suppress hippocampus activation, increase activity in the amygdala, and reshape dendrites in the hippocampus, amygdala and ventral PFC in patients with mood disorders (Erickson et al., 2003). These findings should be replicated and the effects of cortisol on the development and maintenance of psychopathology should be studied further. Fourth, previous research has shown that the long-term adverse effects of cortisol change over development (Lupien et al., 2009), and that adolescents are particularly sensitive to effects of stress (McCormick et al., 2010). Therefore, we recommend investigating the associations between acute increases in cortisol levels and the brain during adolescence, when most internalizing disorders develop (Kessler et al., 2005). Fifth, many studies have found interactions between cortisol and sex (Kinner et al., 2016a; Merz et al., 2010, 2012b; Stark et al., 2006), whereas other studies have only included men (Henckens et al., 2012a; Serfling et al., 2019). Thus, future research should recruit large samples with the same number of men and women to further investigate sex differences in the associations between cortisol and the brain. In addition, in women, sex hormone levels over the course of the menstrual cycle and the use of hormonal contraceptives might also influence the relation between cortisol and the brain (Herrera et al., 2019; Herrera et al., 2016). However, this has not been studied extensively. Sixth, the increase in cortisol level in studies of exogenous cortisol is larger than the increase in cortisol level in studies of endogenous cortisol. Future studies with a lower dose of exogenous cortisol should supplement the findings from studies of endogenous cortisol. Seventh, many different factors influence the cortisol response, such as time of day, diurnal cortisol slopes and dosage. For instance, animal research has shown that glucocorticoids act in an ultradian, pulsatile pattern (Lightman and Conway-Campbell, 2010). In healthy humans, the same dose of cortisol administered in different patterns influenced brain

function and behavioral responses in several emotional and cognitive tasks differently (Kalafatakis et al., 2018). We recommend studying whether individual differences in this pulsatile pattern are related to individual differences in the associations between cortisol and brain function. Eight, future studies should use a multimodal assessment of the stress response, by combining effects of cortisol, other physiological measures, subjective anxiety, and neural measures.

In summary, our systematic review on the associations between endogenous and exogenous cortisol and human brain function shows that cortisol is related to amygdala activity during and after psychological stress, a finding confirmed by cortisol administration studies. These findings support results from prior animal studies demonstrating amygdala activity during and after stress. Future studies should focus on connectivity between the amygdala and other brain regions during and after stress, therapeutic effects of cortisol, and the modulating effects of development, sex and psychopathology on the relation between cortisol and human brain function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- We reviewed relations between endogenous/exogenous cortisol and human brain function.

- Studies reported inconsistent findings, due to heterogeneity in methods and analyses.

- Associations between cortisol and amygdala activity were most consistently found.
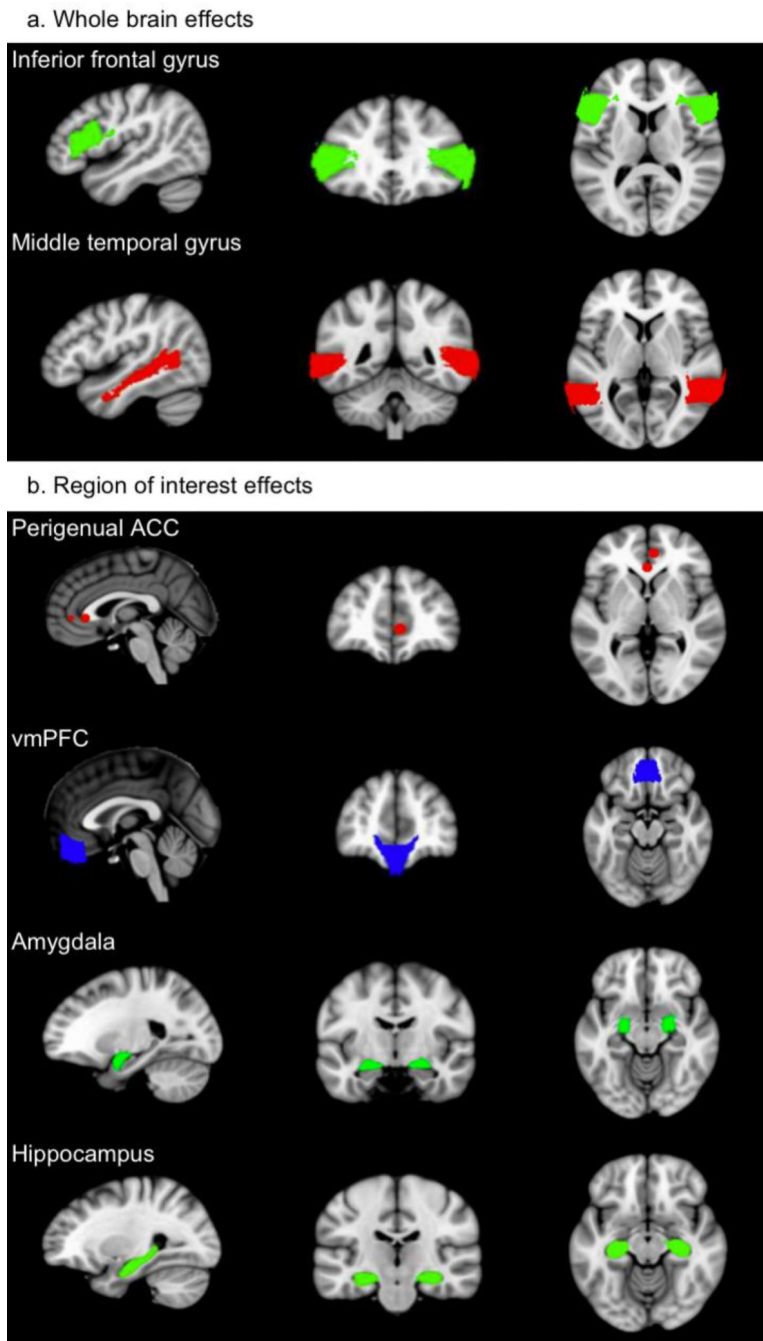
Figure 1.
Illustration of the brain regions that were related to endogenous cortisol levels in at least two studies at either whole-brain (a) or region of interest level (b) during psychological stress in the MRI scanner (regions from Harvard-Oxford atlas, perigenual ACC shown as 5 mm spheres around the peak coordinates from Boehringer et al. (2015) and Akdeniz et al. (2014)).
Note: red represents a positive correlation with cortisol, blue a negative correlation, and green altered function (positive in some studies, negative in others).
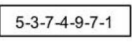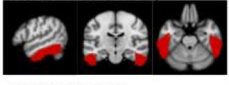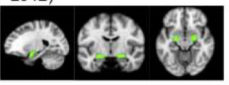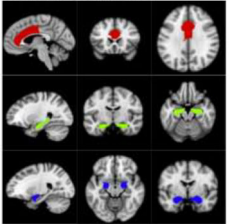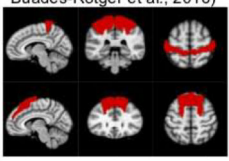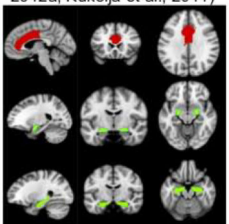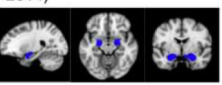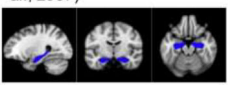
	Fear conditioning	Emotion	Reward	Decision-making	Neutral memory 5-3-7-4-9-7-1
Endogenous	WB: 1 study (Merz et al., 2013) ROI: Inconsistent (Lewis et al., 2014; Merz et al., 2013)	WB: Inf Temp Gyrus (↑ Henckens et al., 2015; Weldon et al., 2015) ROI: Amygdala (↑ Henckens et al., 2015; Oei et al., 2018; ↓ Oei et al., 2012)	WB: 1 study (Porcelli et al., 2012) ROI: Inconsistent (Oei et al., 2014; Maier et al., 2015)	WB: No studies ROI: Inconsistent (Gathmann et al., 2014; Lighthall et al., 2012)	WB: No studies ROI: Inconsistent (Khalili-Mahani et al., 2010; Luettgau et al., 2018; Muehlhan et al., 2011; Qin et al., 2009; Schwabe et al., 2012; Vogel et al., 2016)
Exogenous	WB: Inconsistent (Kinner et al., 2016a; Merz et al., 2010) ROI: ACC (↑ Stark et al., 2006; Tabbert et al., 2020) Hippocampus (↑ Merz et al., 2010; Tabbert et al., 2010; ↓ Merz et al., 2018) Amygdala (↓ Kinner et al., 2018; Merz et al., 2010, 2012b; 2014; 2018)	WB: Postcentral gyrus (↑ Buades-Rotger et al., 2016; Serfling et al., 2019) Superior frontal gyrus (↑ Abercrombie et al., 2011; Buades-Rotger et al., 2016) ROI: ACC (↑ Ma et al., 2017 Monotya et al., 2015; Sudheimer et al., 2013) Amygdala (↑ Henckens et al., 2012b; Serfling et al., 2019; Sudheimer et al., 2013; ↓ Henckens et al., 2010) Hippocampus (↑ Bos et al., 2014; Van Stegeren et al., 2010 ; ↓ Henckens et al., 2012a; Kukolja et al., 2011)	WB: 1 study (Kinner et al., 2016b) ROI: Amygdala (↓ Kinner et al., 2016b; Monotya et al., 2014)	No studies	WB: 1 study (Oei et al., 2007) ROI: Hippocampus (↓ Brown et al., 2013; Oei et al., 2007)

Figure 2.

Summary of replicated findings on the associations between brain activity and endogenous and exogenous cortisol after respectively psychological stress and cortisol administration (regions from Harvard-Oxford atlas).

Note: red represents a positive correlation with cortisol, blue a negative correlation, and green altered function (positive in some studies, negative in others). WB = whole-brain; ROI = region of interest; ACC = anterior cingulate cortex; Inf Temp Gyrus = inferior temporal gyrus; sup fr gyrus = superior frontal gyrus.

Table 1.

Overview of advantages and disadvantages of studies using endogenous and exogenous cortisol measures.

		Endogenous cortisol	**Exogenous cortisol**
Advantages		HPA-axis is centrally activated, with coordinated and controlled release of CRH, ACTH and finally cortisol.	Control over dosage
		Stress response is combination of three interacting systems: SNS, HPA-axis, subjective emotional experience (Andrews et al., 2013). These systems interact naturally, in a coordinated fashion and with the expected magnitude and speed.	Control over timing
		Immune system changes unfold naturally as a consequence of first ANS, and then HPA-axis changes.	Control with placebo is possible
			Blinding is possible
			Repeated exposure under exact dosage control is possible
			Increases cortisol levels in all participants Specificity - only cortisol is changed
Disadvantages		The stressor might not induce changes in cortisol.	Same dosage of cortisol may have different effects in different subjects, due to individual variation in number of glucocorticoid receptors, weight, or sex (Abercrombie et al., 2011).
		Response magnitude might be small and cannot be controlled	Cortisol increase independent of ACTH and CRH increase, resulting in an atypical CNS state (no CRH stimulation, but glucocorticoid feedback).
		Between-subject differences in stress reactivity	Cortisol increase independent of SNS and subjective emotional experience.
		Double-blind experimental designs are not possible	Low ecological validity
		Habituation complicates longitudinal or repeat-exposure experiments	
		Effect of stressor might change across development (Gunnar et al., 2009)	

Note: HPA = hypothalamic-pituitary-adrenal; CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone; SNS = sympathetic nervous system; ANS = autonomic nervous system; CNS = central nervous system

Table 2.

Overview of studies on the associations between endogenous cortisol and brain activity during psychological stress.

Reference	Participants (mean age, percentage females)	Stressor	Analysis	Results for HVs For ↑ cortisol - reported as either correlation with cortisol, or as a group difference
Whole brain				
Kukolja et al., 2008	20 HV young (M_{age}=23.8, 45%) 12 HV old (M_{age}=58.5, 33.33%)	Encoding and recognition task	WB	WB encoding: interaction cortisol and age in L middle frontal gyrus (pos relation in young subjects) WB retrieval: interaction cortisol and age in L middle frontal gyrus, R inferior frontal gyrus, R hippocampal formation (neg relation older subjects)
Radke et al., 2018	80 HV (M_{age}=24.54, 50%)	Cyberball task (social exclusion)	WB	↑inferior frontal gyrus, ↑ middle temporal gyrus
Dedovic et al., 2014	26 HV (M_{age}=21.9, 53.8%) 23 sub depr (M_{age}=21.9, 47.8%)	MIST	WB ROI	WB: No significant associations ROI: No significant associations with hippocampus, medial OFC, sgACC
Orem et al., 2019	239 HV (M_{age}=19.44, 47.3%)	MIST	WB ROI	WB: No significant associations ROI: No significant associations with amygdala, hippocampus
Root et al., 2009	20 HV (M_{age}=31, 45%)	Fear evoking images	WB ROI	WB: ↑L middle temporal gyrus and ↑ frontal regions (including R middle frontal gyrus and R middle orbital frontal gyrus), ↓ L&R insula, ↓ frontal regions (including R superior and inferior frontal gyri), ↓ L&R lateral orbital frontal gyrus ROI: ↑ amygdala, ↑ hippocampus, ↓ vmPFC
ROI				
Pruessner et al., 2008	40 HV (M_{age}=23.1, 50%)	MIST	ROI Resp vs non-resp	ROI: ↓ hippocampus, no association with ACC Resp < non-resp: L ACC, R orbitofrontal/inferior frontal gyrus, L dlPFC
Kogler et al., 2015	40 HV (M_{age}=24.5, 57.5%)	MIST	ROI	No significant associations with amygdala, hippocampus, putamen
Admon et al., 2015	29 HV (M_{age}=45.7, 45.7%) 31 rMDD (M_{age}=47.4, 51.5%)	International Affective Picture System (IAPS)	ROI	No significant associations with bilateral caudate, NAcc, putamen rMDD: ↑ caudate
Akdeniz et al., 2014	23 HV German (M_{age}=23.35, 60.9%) 23 HV Migrant (M_{age}=22.61, 52.2%)	ScanSTRESS (arithmetic task)	ROI	↑pACC
Boehringer et al., 2015	25 HV (M_{age}=41.88, 56%)	MIST	ROI	↑ pACC*
Lederbogen et al., 2011	32 HV (M_{age}=43.6, 50%)	MIST	ROI	↓ amygdala, ↓ hippocampus
Mareckova et al., 2017	41 HV (0.46%) 31 psychosis (0.48%) 27 MDD (0.52%) M_{age} males=45.02, M_{age} females=44.33	IAPS	ROI	↓ L OFC, ↓ L mPFC**
Kogler et al., 2017	77 HV (M_{age}=24.56, 51.9%)	MIST	ROI	No significant associations with R insula, R STG

Reference	Participants (mean age, percentage females)	Stressor	Analysis	Results for HVs For ↑ cortisol - reported as either correlation with cortisol, or as a group difference
Dahm et al., 2017	83 HV (M_age=27, 59%)	ScanSTRESS (mental spatial rotation and arithmetic subtraction)	ROI (mediation analysis)	No significant associations with amygdala, dACC, insula Mediation analysis: conscientiousness mediates the relationship between insula & amygdala activation and cortisol
Ming et al., 2017	36 HV (M_age=22.19, 50%) 36 MDE (M_age=22.81, 52.78%) 33 rem MDE (M_age = 21.67, 51.52%)	MIST	ROI	↓ vmPFC
van Stegeren et al., 2007	14 HV responders (50%) 14 HV non-responders (50%) M_age=20.93	emotional images	ROI Resp vs non-resp	ROI: ↑ amygdala Resp > non-resp: amygdala
Responders vs non-responders				
Dedovic et al., 2009	7 HV responders 13 HV non-responders	eventMIST	Resp v non-resp	Direct comparison not significant (resp > non-resp: dmPFC L&R, dlPFC R, temporal lobe L)
Khalili-Mahani et al., 2010	9 HV responders (0%) 10 HV non-responders (0%)	MIST	Resp vs non-resp	ROI: ↓ L hippocampus Resp > non-resp: middle temporal gyrus, R lateral PFC, R rostral ACC Resp < non-resp: hippocampus
Streit et al., 2014	42 HV (M_age=28, 47%)	ScanSTRESS (arithmetic task)	Resp vs non-resp	Resp > non-resp: amygdala
Wheelock et al., 2016	53 HV (M_age=18.68, 43.4%)	MIST	Resp vs non-resp	ROI: ↓ vmPFC Resp < non-resp: vmPFC, PCC, insula, superior temporal gyrus
Cerebral blood flow				
Wang et al., 2005	23 HV stress (M_age=24.1, 47%) 7 HV control (M_age=23, 60%)	arithmetic task	CBF	ROI: ↑ ventral R PFC, ↑ ACC, ↑ precuneus, ↑ L&R angular gyri/inferior parietal cortex, ↑ antromedial prefrontal cortex
Wang et al., 2007	32 HV (M_age=23.55, 50%)	arithmetic task	CBF	Males: ↑ R PFC, ↓ L OFC/ inferior FC Females: ↑ L thalamus, ↑ dACC, ↓ L IFC

Note: HV = healthy volunteer; WB = whole brain; L = left; R = right; pos = positive; neg = negative; MIST = Montreal Imaging Stress Task; ROI = region of interest; OFC = orbitofrontal cortex; sgACC = subgenual anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; Resp = responders; non-resp = non-responders; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; rMDD = major depressive disorder in remission; NAcc = nucleus accumbens; pACC = perigenual anterior cingulate cortex; mPFC = medial prefrontal cortex; STG = superior temporal gyrus; dACC = dorsal ACC; dmPFC = dorsomedial prefrontal cortex; IFC = inferior frontal cortex

*
Does not survive correction for multiple comparisons

**
only in females

Table 3.

Overview of studies on the associations between endogenous cortisol and brain activity on tasks after psychological stress.

Reference	Participants (mean age, percentage females)	Stressor	Task	Time between end of stressor and task	Results for HVs For ↑ cortisol - reported as either correlation with cortisol, or as a group difference (stress vs control)
Conditioning tasks					
Merz et al., 2013	48 HV stress (M_{age}=23.22, 50%) 48 HV control (M_{age}=23.22, 50%)	TSST outside scanner	Fear conditioning task	25 min	WB: no significant associations ROI: ↓ L NAcc* no associations with ACC, L amygdala
Lewis et al., 2014	7 HV stress responder (M_{age}=25.43, 57.1%) 9 HV stress non-responder (M_{age}=21.56, 55.6%) 13 HV control (M_{age}=23.41, 50%)	Cold pressor in scanner	Conditioning task	0 min	Resp > non-resp: R ventral putamen No significant associations with medial PFC, hippocampus, paracentral lobule
Emotional tasks					
Weldon et al., 2015	24 HV (M_{age}=37.2, 38%)	fMRI scan itself	Face processing task	0 min	WB: Fear-neutral: ↑ precuneus, ↑ lingual gyrus Anger-neutral: ↑ inferior temporal gyrus, ↑ superior parietal lobule, ↑ precuneus, ↑ rectal gyrus, ↓ cerebellar tonsil, ↓ inferior semi-lunal lobule Sad-neutral: ↑ bilateral motor cortex, ↑ posterior cingulate, ↑ R precuneus Happy-neutral: ↑ R putamen, ↑ rostral cingulate, ↑ L posterior middle temporal gyrus and precentral gyrus, ↑ bilateral precuneus, ↑ posterior cingulate, ↑ middle cingulate, ↑ cerebellum, ↑ inferior parietal lobule Faces-animals: ↑ L superior frontal gyrus
Henckens et al., 2015	118 HV (0%)	Movie clip in scanner	Face processing task	0 min	WB: Emotional faces: ↑ bilateral amygdala, ↑ hippocampus, ↑ parahippocampal gyrus, ↑ inferior temporal gyrus, Fearful vs happy: ↓ cluster in midbrain, covering the locus coeruleus, hypothalamus and amygdala↑ ROI: ↑ amygdala
Shermohammed et al., 2017	29 HV stress (M_{age}=21.13, 51.72%) 25 HV control (M_{age}=20.89, 48%)	speech stress induction task (adapted from TSST) outside scanner math stress induction task (adapted from MIST) in scanner	Cognitive Reapprasal task	Time of going into scanner for speech stressor 0 min for math stressor	WB: no significant associations
Li et al., 2019	27 HV (M_{age}=24.25, 0%) [25 included in cortisol analysis]	TSST outside scanner	Emotional face recognition	Time of going into scanner	ROI: ↑ L hippocampus in ll 5-HTTLPR carriers but not in ss/sl 5-HTTLPR carriers

Reference	Participants (mean age, percentage females)	Stressor	Task	Time between end of stressor and task	Results for HVs For ↑ cortisol - reported as either correlation with cortisol, or as a group difference (stress vs control)
Oei et al., 2012	17 HV control (M_{age}=24, 0%) 17 HV stress (M_{age}=24.5, 0%)	TSST outside scanner	Working memory task	Time of going into scanner	ROI: ↓ ventral system, ↓ amygdala, ↓ IFG No significant associations with dorsal system (dlPFC and LPC)
Oei et al., 2018	61 offspring (M_{age}=66.23, 50.8%) 43 partners (M_{age}=65.86, 51.2%)	TSST outside scanner	Emotional Sternberg task	15 min	ROI: ↑ L amygdala No significant associations with right amygdala, R IFG, cingulate
Van Leeuwen et al., 2018	39 HV (M_{age}=33.73, 0%) 29 siblings of patients with SZ (M_{age}=33.17, 0%)	TSST outside scanner	IAPS pictures	33 min after start stressor (stressor around 13 min)	ROI: no significant associations in HV with precuneus, mPFC, L precentral gyrus, L STG, L&R vlPFC, superior frontal gyrus, middle cingulate, anterior insula, cerebellum
Reward tasks					
Porcelli et al., 2012	16 HV control (M_{age}=23.4, 50%) 16 HV stress (M_{age}=23.4, 50%)	Cold pressor in scanner	Card guessing task	0 min	WB: No significant associations
Oei et al., 2014	20 HV control (M_{age}=21.5, 0%) 17 HV stress (M_{age}=22.4, 0%)	TSST outside scanner	Backwards masked task	10 min	ROI: L&R NAcc
Maier et al., 2015	22 HV control (M_{age}=21, 0%) 29 HV stress (M_{age}=21, 0%)	SPECT outside scanner	Food choice task	12–17 min	ROI: No significant associations with amygdala, ventral striatum
Decision-making tasks					
Gathmann et al., 2014	16 HV stress (M_{age}=23.69, 43.75%) 17 HV control (M_{age}=24.06, 52.9%)	TSST outside scanner	N back tast, game of dice task	around 30 min	ROI: ↓ L middle frontal gyrus-dorsolateral prefrontal area (BA 9)
Lighthall et al., 2012	23 HV stress (M_{age}=22.4, 48%) 24 HV control (M_{age}=22.4, 50%)	Cold pressor outside scanner	Balloon Analogue Risk Task	24 min after start stressor (stressor around 3 min)	ROI: ↑ dorsal striatum * No significant associations with insula
Non-emotional tasks					
Qin et al., 2009	13 HV control (M_{age}=20, 100%) 14 HV stress (M_{age}=21, 100%)	Movie clip in scanner	N-back task	0 min	ROI: ↑ MPFC extending to ACC
Schwabe & Wolf, 2012	29 HV control (M_{age}=23.8, 50%) 30 HV stress (M_{age}=23.8, 50%)	SPECT outside scanner	Probabilistic classification learning task	25 min	ROI: ↑ caudate (cortisol baseline, not cortisol increase)
Vogel et al., 2016	98 HV (M_{age}=21.9, 0%) ** Stress/placebo Control placebo Stress/MR-blocker Control/MR-blocker	SPECT outside scanner	Spatial memory task	17 (+/- 4) min	ROI: ↑ amygdala (in placebo condition)
Khalili-Mahani et al., 2010	9 HV responders (0%) 10 HV non-responders (0%)	MIST in scanner	Image recognition task	0 min	Resp > non-resp: hippocampus during encoding; R rostral ACC, L lateral PFC during recognition

Reference	Participants (mean age, percentage females)	Stressor	Task	Time between end of stressor and task	Results for HVs For ↑ cortisol - reported as either correlation with cortisol, or as a group difference (stress vs control)
Luettgau et al., 2018	29 HV (M_{age}=23.48, 0%)	TSST outside scanner	n-back task	around 20 min	ROI: No significant associations with dlPFC
Muehlhan et al., 2011	29 HV (M_{age}=23.8, 12.8%)	fMRI scan itself	Visual detection task	0 min	ROI: No significant associations with thalamus

Note: HV = healthy volunteer; TSST = Trier Social Stress Task; SPECT = cold pressor with social element; WB = whole brain; ROI = region of interest; L = left; R = right; NAcc = nucleus accumbens; ACC = anterior cingulate cortex; Resp = responder; non-resp = non-responder; PFC = prefrontal cortex; MIST = Montreal Imaging Stress Task; IFG = inferior frontal gyrus; dlPFC = dorsolateral prefrontal cortex; LPC = lateral parietal cortex; BA = Brodman area; MPFC = medial prefrontal cortex

*
Only in males

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Only total participants was reported, not the numbers per group.

Table 4.

Overview of studies on the associations between exogenous cortisol and brain activity on tasks after cortisol administration.

Reference	Participants (mean age, percentage females)	Drug (dosage)	Task	Time between administration and task	Results for HVs For cortisol versus placebo
Conditioning tasks					
Merz et al., 2012b	62 cort (72.5%) 60 placebo (75%)	Hydrocortisone (30 mg)	Acquisition (implicit)	45 min	ROI: ↓ L amygdala, ↓ L anterior parahippocampal gyrus (treatment*sex hormone status)
Merz et al., 2010	20 cort (50%) 19 placebo (47.4%)	Hydrocortisone (30 mg)	Acquisition	45 min	WB: no significant difference ROI: ↓ amygdala; treatment*sex: insula, hippocampus*, thalamus*
Stark et al., 2006	17 cort (47.1%) 17 placebo (52.9%) M_{age}= 24.2	Hydrocortisone (30 mg)	Acquisition	15 min	ROI UCS: ↑ R ACC and PCC Treatment*time: dlPFC Treatment*sex: anterior cingulate, lateral OFC, mPFC
Tabbert et al., 2010	10 cort (100%) 10 placebo (100%) M_{age}=23.2	Hydrocortisone (30 mg)	Acquisition Extinction	45 min before start scan	Acquisition: ACC, hippocampus (CS+>CS−) Extinction: hippocampus, thalamus (CS→CS+) No significant difference in insula, amygdala
Merz et al., 2012a	49 cort (61%) 49 placebo (59%)	Hydrocortisone (30 mg)	Acquisition Extinction	45 min	Acquisition: no significant differences Extinction: no significant differences
Merz et al., 2018	20 cort (M_{age}=24.1, 0%) 20 placebo (M_{age}=24.8, 0%)	Hydrocortisone (30 mg)	Extinction	50 min	ROI: ↓ amygdala, ↓ R anterior parahippocampal gyrus, ↓ R hippocampus during early extinction
Merz et al., 2014	16 cort (M_{age}=24.3, 0%) 16 placebo (M_{age}=24.9, 0%)	Hydrocortisone (30 mg)	Extinction	45 min	ROI: ↓ amygdala, ↓ medial frontal gyrus, ↓ NAcc
Kinner et al., 2016a	30 cort (50%) 30 placebo (50%)	Hydrocortisone (30 mg)	Extinction recall	40 min	WB: no significant differences ROI: vmPFC (treatment*sex interaction: ↓ men ↑ women in cortisol group)
Kinner et al., 2018	32 cort (50%) 32 placebo (50%) M_{age}=23.6	Hydrocortisone (30 mg)	Renewal and reinstatement test	40 min	ROI: ↑ R amgydala (men), ↓ R amgydala (women) No significant differences in vmPFC, OFC, dACC, insula, NAcc, hippocampus
Emotional tasks					
Buades-Rotger et al., 2016	20 HV (M_{age}=24.35, 0%)	Prednisolone (250 mg)	Negative and neutral human figures	240 min	WB: ↑ primary somatosensory cortex/postcentral gyrus, ↑ middle frontal gyrus, ↑ superior frontal gyrus, ↑ inferior frontal gyrus, ↓ anterior cerebellum ROI: ↑ R inferior frontal gyrus, ↑ supplementary motor area/medial frontal gyrus, ↑ L caudate, ↑ L amygdala
Monotya et al., 2015	19 HV (M_{age}=22.6, 0%)	Hydrocortisone (40 mg) and primogel (320 mg)	Fear-and-Escape Task	80 min	WB: ↓ midbrain (main effect drug) ROI: AIC (inescapable threat anticipation), ↑ AIC & dACC (escapable threat)

Reference	Participants (mean age, percentage females)	Drug (dosage)	Task	Time between administration and task	Results for HVs For cortisol versus placebo
Ma et al., 2017	40 HV (M$_{age}$=22.8, 50%)	Hydrocortisone (100 mg)	Shifted-Attention Emotion Appraisal Task (SEAT)	120 min before start scan	WB: dmPFC (for treatment × sex: ↓ females ↑ males); ROI: vmPFC, sgACC (for treatment × sex: ↑ females)
Abercrombie et al., 2018	46 minimal EA (M$_{age}$=26.1, 100%), 14 moderate EA (M$_{age}$=31.4, 100%), 15 severe EA (M$_{age}$=28.6, 100%)	Hydrocortisone (20 mg)	Memory encoding with IAPS pictures	90 min	WB: L BA6-whole cluster, bilateral thalamus, R BA6/BA40; Moderating effects of childhood EA severity
Abercrombie et al., 2011	41 HV (26.7, 56.1%), 19 depressed (27.1, 52.6%)	Hydrocortisone (15 mg)	Emotional sentence processing task	60 min	WB: ↑ L superior frontal gyrus (only men)
Henckens et al., 2012a	18 HVs (median age=23, 0%)	Hydrocortisone (20 mg)	Picture encoding task	30 min (fast), 180 min (slow)	*Fast effects of cortisol*; WB: no significant differences; ROI: no significant difference in hippocampus; *Slow effects of cortisol*; WB: ↓ middle frontal gyrus; ROI: ↓ hippocampus
Bos et al., 2014	21 HV (M$_{age}$=22.8, 0%)	Hydrocortisone (40 mg) and primogel (320 mg)	Cry task	60 min	WB: no significant differences; ROI: ↑ hippocampus, ↑ thalamus
Henckens et al., 2012b	22 fast cort (0%), 22 slow cort (0%), 21 placebo (0%)	Hydrocortisone (10 mg)	Emotional interference task	60 min (fast), 270 min (slow)	*Fast effects of cortisol*; WB: no significant differences; ROI: ↑ amygdala[*]; *Slow effects of cortisol*; WB: ↓ cuneus; ROI: no significant difference in amygdala
Serfling et al., 2019	20 HV (M$_{age}$=24.6, 0%)	Prednisolone (250 mg)	Go/Nogo with food stimuli	240 min	WB: ↑ postcentral gyrus (NoGo relative to Go trials); ROI: ↑ L amygdala, ↓ R putamen (main effects), ↑ insula, ↑ amygdala (food-go>object-go); No significant differences in ACC, hippocampus
Kukolja et al., 2011	13 cort (M$_{age}$=24.1, 46.2%), 16 placebo (M$_{age}$=25.2, 50%), 13 RBX (M$_{age}$=24.1, 53.8%), 16 RBX-cort (M$_{age}$=24.9, 50%)	Hydrocortisone (30 mg)	Episodic encoding task with IAPS pictures	145 min	ROI: ↓ L hippocampus [for cort only]
Sudheimer et al., 2013	21 cort (M$_{age}$=21.5, 55%), 20 extended dose cort (M$_{age}$=21.7, 50%), 20 placebo (M$_{age}$=21.8, 50%)	Hydrocortisone (100 mg)	Emotional face processing task	120 min	ROI: ↓ sgACC (sadness), ↑ sgACC & amygdala (happy faces); No differences in vmPFC, amygdala
Van Stegeren et al., 2010	12 placebo/cort (0%), 12 placebo/placebo (0%), 12 placebo/YOH (0%), 12 YOH/cort(0%)	Hydrocortisone (20 mg) and yohimbine (20 mg)	Emotional picture processing task	45 min before start scan (yohimbine 60 min before start scan)	ROI: ↑ R hippocampus, ↑ L frontal gyrus [for placebo/cort]

Reference	Participants (mean age, percentage females)	Drug (dosage)	Task	Time between administration and task	Results for HVs For cortisol versus placebo
Henckens et al., 2010	22 fast cort (M_age=21, 0%) 23 slow cort (M_age=21, 0%) 23 placebo (M_age=21, 0%)	Hydrocortisone (10 mg)	Emotional picture processing task	75 min 285 min	*Fast effects of cortisol* ROI: ↓ amygdala *Slow effects of cortisol* ROI: ↓ amygdala
Kukolja et al., 2008	15 cort (M_age=23.9, 46.7%) 16 placebo (M_age=25.2, 50%) 15 RBX (M_age=24.1, 46.78%) 15 RBX-cort (M_age=25.1, 46.7%)	Hydrocortisone (30 mg)	Emotional faces	105 min	Do not report cortisol only vs placebo
Reward tasks					
Kinner et al., 2016b	30 cort (50%) 30 placebo (50%)	Hydrocortisone (30 mg)	MID	60 min	WB: no significant differences ROI: ↓ L pallidum, ↓ R anterior parahippocampal gyrus Treatment*sex interaction: L precuneus, anterior cingulate, L anterior parahippocampal gyrus (verbal reward), R amygdala (monetary reward)*, L hippocampus (verbal vs monetary reward) (↓ men, ↑ women)
Monotya et al., 2014	20 HV (M_age=23, 0%)	Hydrocortisone (40 mg) and primogel (320 mg)	MID	50 min	ROI: ↓ NAcc, ↓ BLA
Non-emotional tasks					
Oei et al., 2007	20 HV (M_age=22.8, 0%)	Hydrocortisone (20 mg)	Word recognition task	60 min	WB: ↓ R superior frontal gyrus, ↓ L putamen, ↓ R precuneus (only neutral words) ROI: ↓ R hippocampus (pooled words), ↓ hippocampus (only neutral words)
Brown et al., 2013	15 HV (M_age=25.3, 60%)	Hydrocortisone (80 mg, 5 times before scan, last dose morning of scan)	Novelty detection task (indoor & outdoor scenes)	240 min	ROI: ↓ hippocampus
Fleischer et al., 2019	33 HV (M_age=28.3, 100%)	Hydrocortisone (10 mg)	Autobiographical memory test	45 min	ROI: ↓ R amPFC
Henckens et al., 2011	22 fast cort (M_age=21, 0%) 23 slow cort (M_age=21, 0%) 23 placebo (M_age=21, 0%)	Hydrocortisone (10 mg)	n-back task	30 min (fast) 240 min (slow)	*Fast effects of cortisol* ROI: No significant difference in dlPFC *Slow effects of cortisol* ROI: ↑ dlPFC

Note: WB = whole brain; ROI = region of interest; L = left; R = right; cort = cortisol; H&B = Hormones and Behavior; UCS = unconditioned stimulus; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; mPFC = medial prefrontal cortex; SCAN = Social Cognitive Affective Neuroscience; NAcc = nucleus accumbens; vmPFC = ventromedial prefrontal cortex; dACC = dorsal ACC; HV = healthy volunteer; AIC = anterior insula; dmPFC = dorsomedial prefrontal cortex; sgACC = subgenual cingulate; EA = emotional abuse; BA = Brodman area; RBX = reboxetine; IAPS = International Affective Picture System; YOH = yohimbine; MID = monetary incentive delay task; BLA = basolateral amygdala; amPFC = anterior medial PFC

*
p-value between 0.05 and 0.1