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The brain and the stress axis: The neural correlates of cortisol regulation in response to stress

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ABSTRACT

The hypothalamic–pituitary–adrenal (HPA) axis is the major endocrine stress axis of the human organism. Cortisol, the final hormone of this axis, affects metabolic, cardiovascular and central nervous systems both acutely and chronically. Recent advances in neuroimaging techniques have led to the investigation of regulatory networks and mechanisms of cortisol regulation in the central nervous system in human populations. In the following review, results from human and animal studies are being presented that investigate the specific role of hippocampus (HC), amygdala (AG), prefrontal cortex (PFC), and brainstem nuclei in cortisol regulation in response to stress. In general, the types of stressors need to be distinguished when discussing the contributions of these structures in regulating the HPA axis. We propose a basic framework on how these structures communicate as a network to regulate cortisol secretion in response to psychological stress. Furthermore, we review critical studies that have substantially contributed to the literature. Possible future research avenues in the field of neuroimaging of cortisol regulation are discussed. In combination with investigations on genetic and environmental factors that influence the development of the HPA axis, this emerging new research will eventually allow the formulation of a more comprehensive framework of functional neuroanatomy of cortisol regulation.

Introduction

Cortisol, the major stress hormone in humans, targets an array of both peripheral systems and central processes (Lupien et al., 2007; McEwen, 1998); the fine-balanced regulation of stress-induced as well as basal cortisol secretion is thus essential for the maintenance of homeostasis (McEwen, 2000; Tsigos and Chrousos, 2002). When triggered outside of circadian or pulsatile dependencies, cortisol release is specific to stress (Herman et al., 2005). Animal studies have shown that a collection of networks spanning from brainstem nuclei to specific limbic system structures exercises their regulatory functions on HPA axis function and glucocorticoid (mainly cortisol in mammals, corticosterone in rodents) regulation (Herman et al., 2003). The key target of these various direct and indirect pathways is the paraventricular nucleus (PVN) of the hypothalamus (Herman et al., 2003). Stress refers to a situation in which demands are perceived to exceed one's personal resources (Lazarus, 2006). Upon perception of acute stress, cells within the PVN release corticotropin releasing hormone (CRH), which travels through the infundibulum to the pituitary gland, where it stimulates secretion of adrenocorticotropic hormone (ACTH) into the bloodstream (Brown, 2000). ACTH eventually reaches the adrenal cortex, where it binds to receptors that stimulate secretion of cortisol into the bloodstream (Brown, 2000). The majority of cells in the human body have receptors for cortisol, thus cortisol has a broad variety of effects throughout our system, including metabolic, cardiovascular, and immune responses (Buckingham, 2006; McEwen, 1998).

Cortisol regulates its own release via the negative feedback loop in the central nervous system (CNS), where it binds to specific receptors throughout the limbic system, including hippocampus (HC), amygdala (AG), and prefrontal cortex (PFC) (Feldman and Weidenfeld, 1995; Herman and Cullinan, 1997; Herman et al., 2005). The basal, non-stressful secretion of cortisol follows a circadian rhythm, beginning with a distinct sharp rise of cortisol at the time of awakening, followed by a steady decline over the course of the day, with the lowest levels in the early morning hours (Weitzman et al., 1971). In the following article, we will specifically focus on examining neural correlates of cortisol regulation in response to stress, while acknowledging a growing number of articles that investigate neural correlates of basal cortisol secretion and regulation (e.g., Bruehl et al., 2009; Buchanan et al., 2004; Cunningham-Bussel et al., 2009; Pruessner et al., 2007; Putnam et al., 2008; Tessner et al., 2007; Wolf et al., 2005).

The contribution of specific regulatory networks in the CNS to cortisol regulation in response to stress is influenced by a number of factors. First, different stressor types, such as reactive versus

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anticipatory stressors, lead to stimulation of the HPA axis through activation changes in distinct brain regions involved in glucocorticoid regulation (Herman et al., 2003). Reactive stressors are those that increase the demand on the system through a real sensory stimulus, such as pain, bodily injury, or an immune challenge, while anticipatory stressors tap into innate or memory programs, such as social challenges or unfamiliar situations (Herman et al., 2003). Another useful differentiation is that of physical versus psychological stressors (Dickerson and Kemeny, 2004; Pacak and Palkovits, 2001). An example for a physical stressor could be facing a wild animal, with the anticipation of bodily injury, while social evaluative threat would be considered a typical psychological stressor (Dickerson and Kemeny, 2004). Animal literature suggests that reactive stressors tend to implicate brainstem and specific hypothalamic nuclei, and the bed nucleus of the stria terminalis, which all have direct connections to the PVN (Herman et al., 2003). Anticipatory stressors, for their part, seem to engage limbic system regions, namely the HC, the amygdala AG and medial PFC areas (Herman et al., 2003). We have recently suggested that within the limbic system, physical stressors would engage more heavily the AG, while psychological stressors would emphasize the HC (Pruessner et al., 2008). While HC, AG and medial PFC areas have direct connections to some of the hypothalamic nuclei (Herman et al., 2003; Ongur and Price, 2000; Price, 2003), with respect to stress regulation, at the level of the PVN of the hypothalamus specifically, only indirect connections are found (Fernandes et al., 2007; Floyd et al., 2001; Herman et al., 1996; Hurley et al., 1991).

With recent developments in functional and structural neuroimaging methods, it has become possible to directly investigate these regulatory networks, non-invasively, in humans. There are a number of structural and functional studies that provide evidence for regulatory roles of the HC, AG and PFC areas in response to stressors in humans (Pruessner et al., 2008; Pruessner et al., 2007; Tessner et al., 2007; Wang et al., 2007; Wang et al., 2005). Further, some recent studies suggest a role for brainstem nuclei in cortisol regulation; however, it has to be noted that neuroimaging studies on brain activity changes in response to physical stressors are largely lacking from the literature.

Additional factors such as the sex of the subject might also play a role in cortisol regulation. For example, men and women differ in the cortisol secretion depending on the stressor type (Stroud et al., 2002), and this may be due to differences between the sexes in engagement of frontal and limbic structures in cortisol regulation (Wang et al., 2007). However, literature on this topic is just emerging and thus more studies are needed before sound conclusions can be drawn. Further, both animal and human studies on effects of early life experiences on cortisol regulation have shown that adverse events during critical development periods can change the stress sensitivity and responsivity of the HPA axis throughout life (Champagne et al., 2008; Fries et al., 2008; Lupien et al., 2000; McGowan et al., 2009). While a number of different mechanisms may mediate these effects, we will focus on the contribution of the dopaminergic neurotransmitter system and limbic system structures in HPA axis regulation, as this has been the focus of much of our research efforts of the past years.

Thus, in this review, we will first discuss methods to induce stress in neuroimaging, followed by a discussion of the contributions of limbic system structures such as the HC, the AG, and the PFC in regulating the HPA axis, and comparing it to brainstem and physiological regulation mechanisms of this system. Finally, we will review the impact of specific developmental factors on brain development and HPA axis regulation.

Methods to induce stress in neuroimaging paradigms

Recently, psychological stress paradigms suitable for neuroimaging environments have been developed in order to examine brain networks involved in regulation of cortisol in humans. To date, there are two psychological stress paradigms suitable for functional Magnetic Resonance Imaging environment that have been able to elicit a stress response: the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005), and a serial subtraction paradigm (Wang et al., 2005). The MIST requires performing computerized challenging mental arithmetic in the presence of negative social evaluation. The MIST reliably induces a significant HPA stress response, which is driven by about 50% of the participants, reflecting an inter-individual variability in reacting to a given stress stimulus. The serial subtraction paradigm consists of verbal serial subtraction from a four-digit number, while subjects are prompted for faster performance and have to restart the task upon making a mistake. The subjects show a significant cortisol stress response to this task as well. Furthermore, a recent study successfully adapted the Trier Social Stress Test (TSST; a standardized laboratory stressor consisting of public speaking and mental arithmetic in front of an audience) to a fluoro-18-deoxyglucose Positron Emission Tomography (PET) study design in order to elicit an increase in cortisol in a group of healthy males (Kern et al., 2008).

Studies from our lab using the MIST have shown that there is a decrease in activity in the limbic system, particularly in the HC, in response to stress (Pruessner et al., 2008). Moreover, we have found that the degree of deactivation of the HC was correlated with the overall cortisol stress response in the whole sample. These findings suggest that the HC may exercise a tonic inhibition of the HPA axis, which is removed upon stress perception allowing for the increase in cortisol secretion. Considering the findings of an inverse association between HC volume and cortisol stress response (Pruessner et al., 2007), one may ask the question about the exact nature of the association between structural integrity of a brain area and its function? While it has been suggested that HC volume might reflect differential neuronal and glial packing density, as well as differences in neuronal soma sizes (Stockmeier et al., 2004), how this exactly translates into differences in brain activity patterns is a question that needs to be addressed by future studies.

Another type of task deals with physical stressors, and can be designed to investigate the contribution of brainstem structures in cortisol secretion in response to stress. Here, the cold pressor test (CPT) is one such task that classically consists of emerging the non-dominant hand in ice-cold water (0 °C–4 °C) for a period of 5 min (Blandini et al., 1995). The CPT has been shown to elicit increases in ACTH (McRae et al., 2006) and salivary cortisol outside of the scanner (Bullinger et al., 1984; Pascualy et al., 2000; Porcelli et al., 2008), although some negative findings are reported as well (Duncko et al., 2007; Duncko et al., 2009; Kotlyar et al., 2008). Since pain is not reliably inducing HPA axis activation, it seems that the CPT must be considered pain — as well as stressful. It is of note that studies failing to show results assessed plasma cortisol levels (Kotlyar et al., 2008) or sampled salivary cortisol only at 30 min after the end of CPT (Duncko et al., 2007; Duncko et al., 2009), which may have been too late to observe the peak of cortisol secretion (van Stegeren et al., 2008).

Interestingly, the CPT is a common tool used in pain research and particularly within the context of brain imaging. To employ it in neuroimaging environments, the CPT is usually applied on the foot. In theory, this approach may allow for the investigation of the neural patterns involved in physical stress processing. However, pain research studies to date have not measured blood pressure, heart rate and, more importantly, cortisol secretion in response to the CPT. Therefore, any neural activity patterns observed in these studies cannot be explicitly linked to stress processing, since the confirmation of a CPT induced stress response within the scanner is lacking.

Some research groups use the CPT in combination with other cognitive tasks to examine the impact of stress/pain on specific cognitive processes. Porcelli et al. (2008) investigated the effects of physiological stress via the CPT on a PFC-loading working memory task with different levels of demand. This study had three stress

conditions: cold water, room temperature water and no water. A behavioral study was conducted prior to the imaging protocol where the CPT was administered to confirm its ability to induce a significant cortisol stress response. However, cortisol was not measured during the imaging part of the study. The neuroimaging results show that the greatest change from baseline was found in the PFC during cold water condition, with the largest percent signal change localized to the dorsal lateral PFC (Porcelli et al., 2008). The authors concluded that this amplified activity of the PFC could reflect the increased cognitive demand required to deal with stress (Porcelli et al., 2008). This study provides an insight into the neural activation related to reactive stress, although the study focused only on the function of the PFC, without accompanying physiological measures of stress. Here, more studies are needed that investigate the neural circuitry of stress in combination with physiological stress measures. It is not too surprising that the authors did not find brainstem activations given their region of interest analysis approach, as well as the fact that the brainstem activations are usually rather difficult to capture due to artifacts.

The Hippocampus and the HPA axis

A few studies have investigated the association between hippocampal structural integrity and the cortisol stress response. We recently observed a positive association between HC volume and the levels of self-esteem (Pruessner et al., 2005). Furthermore, we observed an inverse correlation between self-esteem and the cortisol stress response (Kirschbaum et al., 1995; Pruessner et al., 1999). Thus, it seems that self-esteem is both functionally and structurally associated with HC volume, which might explain the association of self-esteem with the cortisol stress response. In addition, we observed an inverse correlation between hippocampal volume and the cortisol response to a neuroimaging stress task (Pruessner et al., 2005). Furthermore, another study focusing on a pharmacological challenge of the HPA axis by hydrocortisone reported that total and right HC volumes were inversely associated with cortisol levels after hydrocortisone administration as well (Tessner et al., 2007). While these studies do point in the same direction, showing larger cortisol responses associated with smaller hippocampal volumes, the nature of the stressor needs to be taken into account and thus limits the direct comparability between these studies. Indeed, hydrocortisone administration exerts its effects on subsequent cortisol variation in the brain through occupation of glucocorticoid receptors and negative feedback, while psychological stress works though innervations of specific brain areas that are involved with the processing of these stimuli (McEwen, 1998).

Interestingly, we have recently found some evidence for a difference between men and women in involvement of limbic system structures (specifically, frontal poles and dorsolateral prefrontal cortex, and hippocampus) in cortisol secretion in response to a psychological stressor, with a stronger deactivation of the limbic system found in men when exposed to the MIST (Duchesne et al., in preparation). Furthermore, studies employing the serial subtraction paradigm to elicit stress have also put forth evidence to this effect in regard to the measured perceived stress, specifically in connection to the HC. It has been reported that in women, cerebral blood flow in the HC was positively correlated with perceived stress during the task, while it was negatively associated with perceived stress in men (Wang et al., 2007). Here, future studies will have to study these emerging sex differences in more detail to better understand the underlying processes.

The Amygdala and the HPA axis

The amygdala (AG), a critical part of the limbic system, is traditionally known for its role in processing threatening stimuli (Adolphs, 2008; Bishop, 2008; Roozendaal et al., 2008). Composed of several sub-nuclei, the AG has extensive reciprocal connections with several structures implicated in processing of sensory information: the olfactory cortex, the posterior thalamus, the ascending taste and visceral pathway, and the sensory association cortical areas (McDonald, 1998). Projections from the AG are sent to the periaqueductal gray, the basal nucleus of the stria terminalis, and the lateral hypothalamus (McDonald, 1998). The amygdala further displays important connectivity with the medial prefrontal cortex (Price, 2003).

These AG connections to various systems rapidly direct the appropriate action following threat detection (Armony and LeDoux, 1997). LeDoux and colleagues first demonstrated an increased activity in AG during a fearful experience by using a fear conditioning paradigm in rats (LeDoux et al., 1983). The emergence of neuroimaging techniques then quickly confirmed the importance of the AG in fear conditioning in humans (Buchel et al., 1999; Buchel et al., 1998; LaBar et al., 1998; Morris et al., 1998) but it also revealed an additional role: monitoring the environment and adjusting the level of vigilance of the organism depending on the valence of the stimuli, either positive or negative (Davis and Whalen, 2001; Murray et al., 2007).

In the animal literature, the AG is also known as an important regulator of the stress-related glucocorticoid secretion (Carrasco and Van de Kar, 2003; Jankord and Herman, 2008). It promotes the activation of the HPA axis when the organism is exposed to either a physical or psychological stressor (Herman et al., 2005). In humans, however, the evidence for this role of the AG is less well investigated. While the AG does express both glucocorticoid receptor types, as well as CRF receptors, no AG activity has been observed or related to an increase in cortisol levels during a psychological stress (Dedovic et al., 2009). Rather, previous studies have found associations between AG activity and changes in autonomic measures, such as arterial blood pressure, in response to a Stroop color–word stressor task, with greater change in mean arterial blood pressure positively correlating with greater AG activation (Gianaros et al., 2008). It is important to note that such changes in blood pressure measures reflect the involvement of the cardiovascular system, which is unspecific to stress (Dedovic et al., 2009).

On the other hand, there might well be another association between cortisol secretion and AG: it has been reported that AG stimulation leads to an increase of ACTH in humans (Gallagher et al., 1987), while a variation in endogenous levels of cortisol has been shown to modify AG activation in response to emotional pictures (van Stegeren et al., 2007). The critical point here is that the discrepancy between animal and human results, with regard to the role of the AG in cortisol regulation, might be explained by a potentially different role of the AG with respect to processing of fear and psychosocial threat in humans. Indeed, the stress tasks developed for use in neuroimaging studies on humans are mainly socially based, while the stress paradigms developed for animal research are fear related. We propose that when exposed to a psychosocial threat, it is the organism's social status or value that is threatened; on the contrary, a situation eliciting a fear reaction may rather represent a threat to one's physical integrity and wellbeing. Thus, it may be possible that neural mechanisms underlying those two sources of threat are different, with fear perception leading to the activation of the HPA axis by activating the AG, while a more social stress would involve an inhibition of the HC (Pruessner et al., 2008).

Interestingly, a recent study has contributed some evidence for an extension of the role of the AG in the context of threat and stress (Taylor et al., 2008). This study investigated the association between psychological resources (e.g. coping styles), cortisol reactivity to the TSST *outside* of the scanner, and AG activity during non-intentional threat regulation in response to fearful or angry faces *inside* the scanner. It should be noted that the approach taken in this study to investigate the neural correlates of the experimental task is not a common one. The subjects performed the behavioral stress task outside of the scanner, followed by another (threat) task inside the

scanner.). It was found that greater psychological resources were associated with lower cortisol stress response to TSST. In addition, greater psychological resources were associated with greater right ventrolateral PFC activity and less AG activity during a threat regulation task, but not threat sensitivity task. These results show that successful threat regulation in response to fearful or angry faces requires dampening of AG activity. Further, the relation of greater psychological resources to lower TSST cortisol reactivity was mediated by lower amygdala activity during threat regulation (Taylor et al., 2008). What these findings imply is that the role of AG is still that of fear monitoring, physical threat detection and regulation. However, the fact that greater AG activity in the scanner in response to a threat regulation is linked to greater TSST stress response outside of the scanner may imply that, for individuals with low psychological resources, a psychosocial behavioral stress task might not only translate into a threat to one's social value (HC based) but also into a real physical threat (AG based), which would be in accordance with their inability to self-regulate. Considering that HC function was not specifically examined in this study, this hypothesis still remains to be investigated.

Prefrontal cortex and the HPA axis

Initial reports from animal studies on the involvement of the PFC in the regulation of the HPA axis and the subsequent stress response suggested a purely inhibitory role of the PFC (Herman et al., 2003). However, recent work indicates that specific components of the prefrontal cortex may play quite different roles in the regulation of cortisol secretion and that these may be stressor specific (Herman et al., 2003; Herman et al., 2005). Evidence from human studies on the role of PFC in cortisol regulation stems largely from functional neuroimaging studies investigating neural correlates of psychological stress processing (Dedovic et al., 2009; Kern et al., 2008; Wang et al., 2007; Wang et al., 2005).

Our own findings using the MIST suggest the involvement of orbitofrontal cortex and anterior cingulate cortex (ACC) in stress regulation (Pruessner et al., 2008). Specifically, in individuals who showed a significant stress response, a decreased activity was observed in these brain regions. Interestingly, a specific comparison between the responders and non-responders revealed that the brain areas that significantly differentiated between these two groups of subjects were right orbitofrontal/inferior frontal gyrus region and left ACC. Nevertheless, activity in these regions did not correlate specifically with cortisol. It has therefore been suggested that the role of these areas may be in the appraisal process and error monitoring, detecting social evaluative threat and inducing stress perception (Pruessner et al., 2008).

The involvement of ACC and orbitofrontal cortex is further supported by the study from Wang et al. (2005), although the direction of change in neural activity in the ACC differs. In this study, subjects were exposed to a serial subtraction paradigm inside the scanner. The authors found increased cerebral blood flow (CBF) in the dorsolateral PFC and the ACC, while decreases in CBF were found in the left ventrolateral PFC and the orbitofrontal cortex. In addition to measuring cortisol levels, the authors also assessed perceived stress levels. The output of cortisol within low and high stress tasks conditions, as measured by the area under the curve (AUC), correlated with activity in anteromedial PFC, while the subjective measure of perceived stress positively correlated with the different region right ventral PFC. The key finding of this study was that CBF in the right ventral PFC was correlated with both objective and subjective measures of psychological stress, and that this pattern of activation persisted even after the termination of the stress. This may suggest that the activation of the right ventral PFC could reflect a prolonged state of heightened vigilance and arousal elicited by the stressor (Wang et al., 2005).

Interestingly, the right PFC has also been identified as a factor that distinguishes brain activity patterns in response to psychological stress between men and women (Wang et al., 2007). This study has found an increase in cerebral blood flow in right PFC in men during the serial subtraction stress task, and post-stress baseline. While suppression of the orbitofrontal region was present in both men and women, for men it was observed during and post-stress, while for women only during the stress task. Limbic system activity was not observed in men, while in women, the stress task was associated with increases in basal ganglia and ventral striatum. In males, cortisol AUC was associated with a CBF increase in the right PFC and CBF reduction in the left orbitofrontal–inferior frontal gyrus. In women, cortisol related CBF increases were observed in the dorsal ACC and left thalamus.

This latter finding is of particular interest, especially when considering a recent study on neural correlates of the effect of social support on cortisol reactivity to social stressor. Here, it was observed that greater social support and diminished cortisol responses to a behavioral psychological stress task were associated with diminished activity in the dorsal ACC in response to an exclusion neuroimaging paradigm (Eisenberger et al., 2007). Here again, the approach taken in this study to investigate the neural correlates of stress was unusual as subjects performed the stress task *outside* of the scanner, and then underwent a social exclusion paradigm called Cyberball inside the scanner, where subjects got gradually excluded from ball tossing by other mock participants (Williams et al., 2000). Nevertheless, the findings are of interest as they point to the role of dorsal ACC in cortisol regulation through possible interaction with social support.

A new study investigating glucose metabolic rate in healthy young men during psychological stress compared to a control task, reported a negative association between metabolic rate in rostral medial PFC and the cortisol stress response (Kern et al., 2008). Further, increase in metabolic rate in medial PFC was associated with a decrease in the AG/HC regions. Finally, a positive association was found between lateral PFC and stress-related cortisol secretion reflecting the fact that specific parts of PFC region (medial vs lateral) may be differentially involved in cortisol regulation. It is worth noting that the authors suggested that the effects observed may "reflect some form of glucocorticoid based regulatory mechanism rather than glucocorticoid independent short-term information processing of stress-relevant information" (Kern et al., 2008 p. 526), pointing to long-term rather than short-term regulatory mechanisms.

Physiological/physical stressors and the HPA axis

Up until now we have addressed the roles of HC, AG and PFC in cortisol regulation in response to mainly psychological stressors. A second group of stressors, termed physical, have been investigated mainly within the animal research field. These studies, employing an array of protocols such as ether exposure, hemorrhage or hypoxia (Herman and Cullinan, 1997), have shown that the major structure involved in the regulation of the HPA axis to physical stressors is the brainstem via the nucleus of the solitary tract (NTS) and ventrolateral medulla (VLM) (Buller et al., 2003).

Here, anatomical connections have been observed between the catecholaminergic axons of the brainstem, specifically the noradrenergic cells of the VLM and NTS, and the parvocellular zone of the PVN, allowing for an excitatory input to the HPA axis (Cunningham and Sawchenko, 1988; Pacak et al., 1995). Another line of evidence suggests that there is an impact of these structures in the regulation of the HPA axis. Foremost, Palkovits et al. have shown that during a pain task, there is a stress-induced norepinephrine release (Palkovits et al., 1999). Moreover, studies report a diminished stress response in animals when there is a disruption of the brainstem catecholaminergic inputs during ether, immobilization, histamine, insulin and footshock stress protocols (Gaillet et al., 1993; Gaillet et al., 1991; Li et al., 1996).

In regard to human studies, the literature on neural correlates of physical stress is sparse, particularly at the level of the brainstem. This is in part due to the nature of neuroimaging data acquisition and analysis, which requires repeated exposure to the task to be able to average out neural activity changes associated with the task. Furthermore, certain methods from animal research are simply not applicable in human studies. For example, most physical stressor tasks available from the rodent literature, such as hypoxia and hemorrhage, are not translatable to human research and/or are not compatible with an imaging protocol. Moreover, imaging the activity within the brainstem is additionally challenging due to degradation of the image quality that can result from the effect of pulsation of the basilar artery (Griffiths et al., 2001). In order to minimize this degradation, the researchers would need to acquire a given image slice at the same time in the cardiac cycle, a method called cardiac triggering (Griffiths et al., 2001; Guimaraes et al., 1998). Alternatively, one could apply a retrospective image-based correction technique that allows for removal of cardiac and respiratory related noises from the MR signal (Harvey et al., 2008).

Summarizing the functional findings on the contribution of hippocampus, amygdala, prefrontal cortex and brainstem in cortisol regulation

Functional neuroimaging studies have allowed us to investigate the contribution of HC, AG and PFC in cortisol regulation in response to psychological stress, non-invasively, in humans. On an individual basis, each study provides explanation of a specific set of processes that are involved in stress response and regulation. However, overall interpretation of the findings is hindered by the fact that these studies differ with respect to their methodological approaches. Nevertheless, we will attempt to formulate a basic framework on how HC, AG and PFC regions together may contribute to stress processing (Fig. 1).

The most consistent finding is that of decreased activity in orbitofrontal PFC being associated with increased cortisol secretion in response to a psychological stress task (Pruessner et al., 2008; Wang et al., 2005). Similarly, increased activity in medial PFC regions correlates with decreased cortisol secretion (Kern et al., 2008). Given that these regions play a role in gathering and integrating sensory information from the body and the surrounding environment (orbitofrontal PFC; (Gusnard and Raichle, 2001), participate in monitoring and control of one's emotional state (medial PFC and orbitofrontal PFC respectively; (Amodio and Frith, 2006; Fredrikson et al., 1995), monitor the perception and judgments of other people (medial PFC; (Amodio and Frith, 2006), these areas emerge as candidates for the processing of the stress response, by integrating perception, passive coping and possibly perseverance. Importantly, orbitofrontal PFC and ventromedial PFC possess a complex set of interconnections (Gusnard and Raichle, 2001), and have far reaching projection to the limbic system including hippocampus (Carmichael and Price, 1995), amygdala, hypothalamus, periaqueductal grey region and brainstem nuclei (Gusnard and Raichle, 2001).

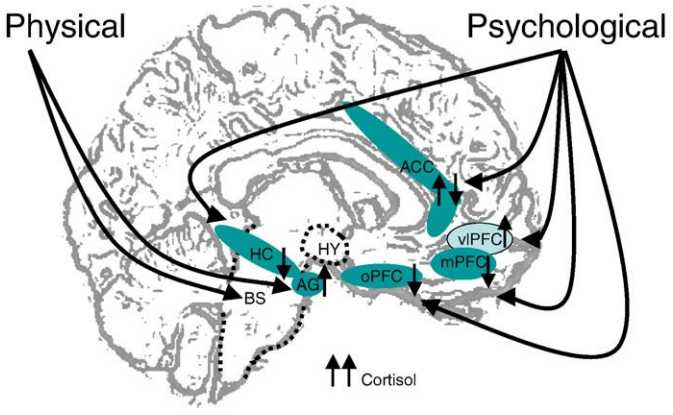

Fig. 1. Basic framework of brain areas involved in processing physical and psychological stressors. The model summarizes data from functional studies in human populations. It is based on a hierarchical integration of physical versus psychological stress processing in central nervous system (Herman et al., 2003). Animal studies indicate that physical or reactive stressors tend to implicate brainstem, while psychological or anticipatory stressors tend to engage limbic system regions. Given that amygdala has direct connection to key brainstem nuclei, it might play a more crucial role in processing of physical stressors. The influence of the PFC regions on the downstream regulators varies with region and nature of the stimulus. BS: brainstem; HY: hypothalamus; HC: hippocampus; AG: amygdala; PFC: prefrontal cortex; oPFC: orbital PFC; mPFC: medial PFC; vlPFC: ventrolateral PFC, different color indicates that this region is found on the lateral surface of the brain; ACC: anterior cingulate cortex.

Following a perception of a stressful psychological stimulus, an increase in cortisol response is observed. One way to achieve this is by curtailing the indirect tonic inhibition of PVN by HC, through HC deactivation (Pruessner et al., 2008). This process, from stress perception to stress response, could be modulated by activity in areas such as the ventrolateral PFC, and the ACC. For example, the ventrolateral PFC is involved in first-order executive processes such as active selection, comparison and judgment of stimuli, as well as processing information under conscious effort (Petrides, 2005). Findings of inverse associations between activity in this area and cortisol release (Taylor et al., 2008; Wang et al., 2005), may suggest a role for the ventrolateral PFC in active control of the cortisol release. Interestingly, while the ventrolateral PFC has scarce projections to the HC (Mohedano-Moriano et al., 2007), it has extensive positive connections to the ventromedial PFC (Marsh et al., 2009). This may be a mechanism that could allow ventrolateral PFC to counteract decrease in activity in orbital and medial PFC areas related to stress processing. Here, inadequate level of control may be associated with prolonged increased cortisol secretion. This would be supported by findings of increased ventrolateral PFC activity linked to lasting effect of stress and with increased cortisol secretion (Kern et al., 2008; Wang et al., 2005).

With respect to the ACC, its pattern of activity varies considerably across studies. Since the ACC plays a role in error monitoring and regulating adaptive behaviors in response to environmental cues (Bush et al., 2000; Luu and Posner, 2003), the variability in the findings might reflect differential error processing for different types of tasks.

Finally, the AG has extensive connection with the HC, hypothalamus, as well as brainstem (Jankord and Herman, 2008). As mentioned previously, with respect to the processing of psychological stress, AG might play a role in individuals for whom a psychological stressor might represent both a social and physical threat. Another likely scenario, given the AG's direct connections to the NTS of the brainstem (Jankord and Herman, 2008), is that AG may have a crucial role in processing of physical stressors.

It should be noted that data from animals and humans suggest a hierarchical integration of stress, where the influence of the PFC regions on the downstream regulators varies with region and nature of the stimulus (Herman et al., 2003), and possibly, nature of the regulatory and coping approach of an individual (Fig. 1). The current model presented above reflects but one possibility of this dynamic integration given the functional findings of present day in regard to processing of psychological stress.

Development and other neurotransmitter systems interaction with cortisol

Apart from the nature of the stressor, factors such as early life experiences also play a role in cortisol regulation, most likely mediated through differential development of the stress processing areas in the brain. Studies investigating early life experience suggest that adverse events during critical development periods can change the

responsivity of the HPA axis as well as HC integrity throughout lifetime. Pioneering rodent studies have shown subtle variations in maternal care to have positive and long-lasting effects on stress responsivity. In particular, offspring of high maternal care (licking and grooming and arched-back nursing) mothers exhibited increased hippocampal glucocorticoid receptor mRNA expression, increased glucocorticoid negative feedback, decreased CRH mRNA expression in the hypothalamus, and decreased ACTH and corticosterone stress response (Liu et al., 1997). Maternal deprivation, on the other hand, was shown to be associated with decreased glucocorticoid receptor expression in the HC and the frontal cortex, decreased glucocorticoid negative feedback (Ladd et al., 2000), and increased CRH mRNA expression in the PVN, the central nucleus of the AG, the BNST and the locus coeruleus (Plotsky et al., 2005). Corticosterone and ACTH stress response were increased after maternal separation (Plotsky and Meaney, 1993). Thus, whereas a positive early life experience may trigger stress resistance and protect from later negative influence, an adverse early life environment may provoke stress vulnerability throughout lifetime.

There are likely several mechanisms at play that mediate these effects, including changes in the dopamine neurotransmitter system and limbic system structures. The dopamine system interacts with the HPA axis via diverse sites of reciprocal influence [e.g. glucocorticoid receptors located on dopamine neurons (Harfstrand et al., 1986)], and limbic system structures like the HC regulate the HPA axis via glucocorticoid negative feedback. In humans, we have recently started to replicate and extend the delineated animal data, thereby focusing specifically on associations between the HPA axis and the dopaminergic system, as well as HC integrity. In an initial Positron Emission Tomography (PET) study with the radioligand [11C]raclopride (Pruessner et al., 2004), we investigated dopamine and cortisol responses to a social evaluative and mentally challenging stressor performed in the scanner, the MIST (Dedovic et al., 2005). Results showed that only participants with low retrospective ratings of early life maternal care, which were assessed using the Parental Bonding Instrument (PBI; (Parker et al., 1979), exhibited a significantly increased cortisol stress response. Interestingly, these low maternal care participants also exhibited increased nucleus accumbens dopamine release in response to stress, whereby cortisol and dopamine levels were highly correlated. In a subsequent MRI study, we examined the associations between birth weight (believed to reflect a disadvantageous prenatal environment), PBI-assessed early life maternal care, and HC integrity (Buss et al., 2007). Right HC volume was reduced solely in women with adverse prenatal environment and low maternal care experience. Accordingly, high maternal care was hypothesized to offset the neurodevelopmental consequences of prenatal adversity. We could replicate correlations between PBI-assessed early life parental care and both cortisol stress responsivity to the MIST and HC integrity in a sample of healthy elderly volunteers between 60 and 75 years of age. Moreover, it was possible to statistically confirm a mediation model suggesting early life parental care to be a primary modulating variable in the association between HC volume and the cortisol stress response (Engert et al., submitted).

Stress sensitivity and responsivity of the HPA axis are most certainly influenced by a multitude of factors, including genetic predisposition, personality traits, coping mechanisms, life events in general, and early life experience in particular (Heim et al., 2001; Heim et al., 2004; Kudielka et al., 2009). We consider it especially noteworthy, however, that already subtle variations in early experience – such as the perception of parental care during the first 16 years of life – have a significant and long-lasting influence on the cortisol stress response and brain structures implicated in its regulation.

Conclusion

A complex network of structures contributes to cortisol regulation both during basal conditions, and in particular, in times of stress. The involvement of each of the regulatory agents from the brainstem structures to the limbic system and prefrontal cortex depends upon specific factors such as the nature of the stressors, sex of the subject and early life experience. While great strides have been made in furthering the understanding of the neurocircuitry of cortisol regulation in response to psychological stressors in human populations, additional research is needed. For example, the paradigms used in the domain of psychological stressors are largely achievement-based stress tasks. It would be of interest to develop a particular stress task where the challenge component is reduced, but where social evaluative threat still remains. Furthermore, studies are particularly needed within the domain of cortisol regulation in response to physical stressors and the specific involvement of brainstem nuclei. New developments in fMRI techniques should facilitate these undertakings. Finally, studies investigating genetic and environmental factors that influence the development of the HPA axis and the neighboring systems are also essential. Together, these multidisciplinary approaches will help the researchers gain an even greater understanding of the complex web that represents the functional neuroanatomy of cortisol regulation.

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