



Profiling coping strategies in male and female rats: Potential neurobehavioral markers of increased resilience to depressive symptoms[☆]



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ABSTRACT

Coping strategies have been associated with differential stress responsivity, perhaps providing a valuable neurobiological marker for susceptibility to the emergence of depressogenic symptoms or vulnerability to other anxiety-related disorders. Rats profiled with a flexible coping phenotype, for example, exhibit increased neurobiological markers of emotional regulation compared to active and passive copers (Bardi et al., 2012; Lambert et al., 2014). In the current study, responses of male and female rats to prediction errors in a spatial foraging task (dry land maze; DLM) were examined after animals were exposed to chronic unpredictable stress (CUS). Brains were processed following the DLM training/assessment for fos-activation patterns and several measures of neuroplasticity in relevant areas. Behavioral responses observed during both the CUS and DLM phases of testing suggested that males and females employ different means of gathering information such as increased ambulatory exploration in males and rear responses in females. Fecal samples collected during baseline and following CUS swim exposure revealed higher corticosterone (CORT) in active copers, whereas flexible copers had higher dehydroepiandrosterone (DHEA) and DHEA/CORT ratios, both indications of enhanced emotional regulation. Focusing on the neural analysis, flexible copers exhibited fewer fos-immunoreactive cells in the basolateral amygdala and a trend toward lower activation in the insula while encountering the prediction error associated with the DLM probe trial. Coping profiles also differentially influenced markers of neuroplasticity; specifically, flexible copers exhibited higher levels nestin-immunoreactivity (ir). Further, less hippocampal glucocorticoid receptor-ir was observed in the flexible copers than the active and passive copers. In sum, flexible coping rats exhibited evidence of emotional resilience as indicated by several neurobiological measures; however, despite increased rates of depression and related symptoms reported in human females, sex effects weren't as pervasive as coping strategy profiles in the analysis of neurobiological markers employed in the current study.

1. Introduction

It has been proposed that the lack of reliable biological predictive markers of psychiatric illness contributes to the dearth of effective therapies and rising prevalence rates (Kapur et al., 2012). In contrast, biomarkers for medical conditions such as cardiovascular disease have led to timely preventative measures and a corresponding reduction in associated deaths (Zethelius et al., 2008). Focusing on depression, it is noteworthy that hypersecretion of cortisol has been associated with up to 50% of patients diagnosed with major depression disorder (MDD), although individual differences abound (Kendler et al., 1999; Strickland et al., 2002). Consequently, various distortions of the hypothalamic-pituitary-adrenal (HPA) axis may provide valuable information about

emerging emotional disorders (Charney, 2003).

Because stress and anxiety are closely associated with emotional disorders, effective coping strategies provide an opportunity for animals to gain emotional control in unpredictable, stressful environments (McEwen et al., 2015). Although HPA activation is necessary for survival, especially in the context of acute stressors, hypersecretion of glucocorticoids for extended durations leads to disrupted cellular functioning and eventual physiological dysfunction (Mackin and Young, 2004). In the brain, excessive cortisol levels have been linked to atrophic effects in the hippocampus, a brain area compromised in MDD (Feder et al., 2009). Consequently, coping strategies that regulate excessive HPA activation may serve as an important buffer against the emergence of MDD and anxiety disorders (Compare et al., 2014; Gaffey

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Animals exhibiting active coping strategies in the presence of environmental stressors generally exhibit lower glucocorticoid responses than animals exhibiting more passive coping responses (Lu et al., 2009). Thus, specific coping strategies may lead to emotional resilience by enhancing survival with minimal allostatic load (Yehuda et al., 2006; Lambert et al., 2014). Adding to the complexity of the stress response is the secretion of dehydroepiandrosterone (DHEA) which has been described as having anticorticosteroid effects in the brain (Feder et al., 2009). High plasma DHEA sulphate/cortisol levels were found in individuals participating in challenging military survival training and exhibiting both optimal performance and emotional resilience (Morgan et al., 2004). Further, male veterans with PTSD exhibiting the most improvement in symptoms had higher plasma levels of DHEA (Yehuda et al., 2006). Focusing on rodents, in the Flinder-sensitive line of rats known for their susceptibility to depressive responses, lower DHEA levels were observed in brain areas associated with depression such as the amygdala, prefrontal cortex and nucleus accumbens (Genud et al., 2009). Thus, it is important to consider both corticosteroid and DHEA levels when determining potential vulnerability and resilience to MDD symptom emergence in various stressful situations (Bardi et al., 2010).

Contrary to Selye's suggestion that the stress response is generalized and non-specific (Selye, 1936), evidence suggests that individual differences exist (Koolhaas et al., 1999; Ouwehand et al., 2008). These individual differences open the door for an exploration of biomarker-determined resilience subtypes that may be valuable in the prevention and treatment of psychiatric illness (Kapur et al., 2012). For example, effective coping strategies facilitate neurobiological adaptations to situations that threaten an animal's fitness (Wechsler, 1995). Extending from research conducted on piglets determining passive and active responses to being restrained on their backs for one minute (Koolhaas et al., 1999), this technique has been adapted for recently weaned rats. Accordingly, rats are gently restrained on their backs for one minute during which time the number of escape attempts are recorded. One week later, the assessment is repeated to determine consistently passive (few attempts) or active (greater number of attempts) coping styles; however, animals exhibiting variability by switching coping strategies (regardless of direction) are categorized as flexible (or variable) copers (Lambert, 2006). Using this technique to profile coping strategies in rats, flexible copers have been found to exhibit significantly more Neuropeptide Y (NPY)-immunoreactive cells, associated with emotional resilience, in the basolateral amygdala and bed nucleus of the stria terminalis than the other coping groups following exposure to chronic unpredictable stress (Hawley et al., 2010). In another study, following a cognitive training program with no chronic stress exposure, flexible rats exhibited higher levels of NPY-immunoreactive cells in the CA1 and CA3 hippocampal subfields than their passive and active counterparts (Bardi et al., 2012). When exposed to the activity-stress paradigm, in which animals are housed in running wheels and fed 1 h/day prompting excessive spontaneous levels of running, the flexible copers exhibited lower fecal corticosteroid metabolites than the other coping groups (Lambert et al., 2006).

The introduction of uncertainty in the form of prediction errors, in which a discrepancy between a predicted and observed outcome is experienced, provides an opportunity to observe an animals' response flexibility in a non- or moderately-threatening context (Bubic et al., 2010; Robinson et al., 2012; Steinberg et al., 2013). As the animal effectively updates relevant response-outcome contingency probabilities to determine the appropriate response in this novel situation, an enhanced sense of control over the uncertainty-induced stress is achieved (Moore et al., 2009). Referring back to the classic learned helplessness models assessing dogs' responses in threatening contexts, the presence of perceived controllability in uncertain situations has been associated with the development of emotional resilience against the emergence of depressive symptoms such as behavioral inhibition (Overmier and Seligman, 1967; Abramson et al., 1978; Gladstone and Parker, 2006).

When presented with a prediction error in a spatial task, for example, recent research suggests that contingency-trained animals exhibited more targeted search strategies than their noncontingent counterparts. Regardless of training, animals profiled as flexible copers exhibited enhanced evidence of neuroplasticity (i.e., doublecortin-immunoreactivity in the dentate gyrus), potentially associated with the cognitive training, when compared to their noncontingent-trained counterparts (Lambert et al., 2014). Disruptions of neuroplasticity, critical for neuronal adaptation in changing environmental landscapes, have been associated with the onset of mood disorders (Pittenger and Duman, 2008; Czeh and Simon, 2005).

In addition to neural plasticity, specific brain areas have been implicated in an individual's response to prediction errors and uncertainty. The anterior cingulate and medial prefrontal cortical areas have been implicated in the detection of environmental parameters associated with the prediction error (Ragozzino and Rozman, 2007; Rushworth and Behrens, 2008; Matsumoto and Tanaka, 2004; Alexander and Brown, 2011). Additionally, the insular cortex has been associated with processing the negative consequences associated with prediction errors — likely motivating the animal to avoid the prediction error in the future (Endepols et al., 2010) as well as promoting adaptive decisions in the uncertainty context (Rebola et al., 2012). Another cortical area, the retrosplenial cortex, is involved in the initiation of behavioral shifts necessary to complete tasks involving the balancing of emotional processing when completing demanding cognitive tasks (Vann et al., 2009). Finally, the lateral habenula has been implicated in behavioral suppression following exposure to uncertain situations (Li et al., 2011). Although behavioral suppression can be an adaptive response in the presence of a threatening stimulus, this response is considered to be a risk factor in children for subsequent development of depression and related anxiety disorders (Chao et al., 2010). Interestingly, heightened activity of the lateral habenula has been observed in patients diagnosed with depression (Savitz et al., 2011; Henn, 2012). Thus, when a prediction error is encountered, a network of various brain areas converges to facilitate the individual's accurate assessment of the changing contingencies so that an alternative adaptive response is generated. This contingency-correcting network of brain areas necessary for flexible coping, working in the context of stress-modulating neurobiological factors such as amygdala and HPA activation, is likely critical in the determination of adaptive versus maladaptive responses in various stressful and threatening contexts (Yang et al., 2010; Lambert et al., 2014).

In the current study, the influence of specific coping strategies was examined in the rats' responses to prediction errors in the dry land maze probe test; however, prior to training and testing in this task, all animals were exposed to chronic unpredictable stress to heighten HPA activation and susceptibility to depressive symptoms. Due to reported sex differences in susceptibility to depression with females experiencing the disorder at nearly twice the rates as males (Kessler, 2003; Nolen-Hoeksema, 2001; Ryba and Hopko, 2012), both males and females were assessed. Relevant behavioral responses were observed throughout the chronic unpredictable stress exposure, dry land spatial task and subsequent probe trial. Throughout the experimental manipulations, HPA activation was assessed via corticosteroid and DHEA levels. Following the behavioral assessments, activation of various brain areas was investigated as well as the presence of markers of neuroplasticity. Based on prior research in our laboratory, it was hypothesized that flexible copers would exhibit adaptive responses (e.g., higher DHEA/CORT ratios, increased hippocampal neuroplasticity and more strategic behavioral responses to prediction errors); further, due to sex-specific differences in emotional responsivity observed in past research, sex differences were expected to emerge in certain components of the dependent variables.

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