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### Research report

# Behavioral coping strategies in response to social stress are associated with distinct neuroendocrine, monoaminergic and immune response profiles in mice

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### ABSTRACT

Individual variation in behavioral coping strategies to stress implies that animals may have a distinct physiological adaptation to stress; these differences may underlie differences in vulnerability to stress-related diseases. This study was designed to test the hypothesis that different behavioral coping strategies (active vs. passive) are stable over time and that they would be associated with differences in hypothalamic–pituitary–adrenal (HPA) and sympathetic–adreno–medular (SAM) axes, and monoaminergic and immune activity. Male mice were subjected to social stress. Twelve days after the first social interaction, mice were subjected to a second identical social stress interaction. Behavior was videotaped and assessed during both sessions. One hour after the final social interaction, serum was collected for corticosterone and adrenaline concentrations and brains were collected for hypothalamic corticotrophin-releasing hormone (CRH) mRNA expression. Monoaminergic system activity was determined by mRNA expression of serotonin, dopamine and noradrenaline synthetic enzymes in the brain stem. Immune system activity was determined by mRNA expression of hypothalamic interleukin-1 $\beta$  (IL-1 $\beta$ ) and splenic IL-1 $\beta$  and interleukin-2 (IL-2). Mice engaging in a passive strategy had higher serum corticosterone and lower serum adrenaline concentrations than the active group. The passive group showed lower hypothalamic mRNA expression of IL-1 $\beta$  and CRH and lower splenic mRNA expression of IL-2 and IL-1 $\beta$  relative to mice in the active group. An active strategy was associated with higher expression of the dopaminergic synthetic enzyme, while a passive strategy was associated with decreased expression of the serotonergic synthetic enzyme. These findings indicate that individual coping strategies are stable over time and are related to differences in the physiological stress response and immune activity.

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### 1. Introduction

A wide variety of research has shown that social stress induces a profound influence on the humoral and cellular immune response, both in animals and in humans [1,2]. An understanding of how stress may alter the immune system through alterations in the hypothalamic–pituitary–adrenal (HPA) and sympathetic–adrenal medullary (SAM) axes will likely lead to a clarification of the role of stress in disease [3–5]. The HPA and SAM axes are the two major pathways through which the central nervous system can modulate the immune system. Immune system cells express receptors for glucocorticoids and catecholamines [6–8], which are secreted during the response to stress by the activation of the HPA and SAM axes. These hormones can regulate a wide variety of immune-

cell functions including cellular activation, cytokine production and cell trafficking [9–12]. Exposure to stressors can increase levels of plasma and brain proinflammatory cytokines such as IL-1 $\beta$  [13–15], especially in the hypothalamus [16]. It has been shown that IL-1 acts on this area to enhance release of corticotrophin-releasing hormone (CRH) [17,18] which in turn can induce the activation of the HPA axis activity.

In the periphery, stress has been shown to affect splenic IL-1 and IL-2 levels [19]. Moreover it has been shown that after acute social stress, splenic lymphocytes showed differences in in vitro proliferation rates [20]. The later effects were related indeed to differences in the development of an immunogenic tumor model (B-16) and individual behavioral coping strategies, raising the idea that immune consequences of social stress may depend on the subject's behavioral response to stress.

Supporting this idea, previous studies [21–23] have reported that the neuroendocrine and immune changes produced by social stress in defeated subjects depend on the behavioral characteristics shown during social interactions. Subjects that show different coping strategies (active or passive coping strategy) show different HPA and SAM activation patterns [24,25]. Additionally these

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