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Glutamatergic stimulation of the left dentate gyrus abolishes depressive-like behaviors in a rat learned helplessness paradigm

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ABSTRACT

Background: Episodic experiences of stress have been identified as the leading cause of major depressive disorder (MDD). The occurrence of MDD is profoundly influenced by the individual's coping strategy, rather than the severity of the stress itself. Resting brain activity has been shown to alter in several mental disorders. However, the functional relationship between resting brain activity and coping strategies has not yet been studied. In the present study, we observed different patterns of resting brain activity in rats that had determined either positive (resilient to stress) or negative (vulnerable to stress) coping strategies, and examined whether modulation of the preset resting brain activity could influence the behavioral phenotype associated with negative coping strategy (i.e., depressive-like behaviors).

Methods: We used a learned helplessness paradigm—a well-established model of MDD—to detect coping strategies. Differences in resting state brain activity between animals with positive and negative coping strategies were assessed using ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). Glutamatergic stimulation was used to modulate resting brain activity.

Results: After exposure to repeated uncontrollable stress, seven of 23 rats exhibited positive coping strategies, while eight of 23 rats exhibited negative coping strategies. Increased resting brain activity was observed only in the left ventral dentate gyrus of the positive coping rats using FDG-PET. Furthermore, glutamatergic stimulation of the left dentate gyrus abolished depressive-like behaviors in rats with negative coping strategies.

Conclusion: Increased resting brain activity in the left ventral dentate gyrus helps animals to select positive coping strategies in response to future stress.

1. Introduction

Exposure to stress has been indicated as a major risk factor for depression in humans (Hammen, 2005; Fried et al., 2015). The pathogenic potential of exposure to a given stressor, however, is not solely dependent on the severity of the stress, as evidenced by individual variations in responses to the same stressor exposure (Southwick et al., 2005; Wood and Bhatnagar, 2015). Coping strategy is defined as an overall scheme adopted by an organism to manage internal or external stressful situations (Folkman and Lazarus, 1988). In general, coping strategies are simply classified as either active (positive) or passive (negative), based on the presence or absence of attempts to overcome the stress (Puglisi-Allegra and Andolina, 2015). From a psychological point of view, high self-esteem, social support, personal mastery, motivation, and optimism are considered to promote active coping in response to stress (Taylor and Stanton, 2007). Often coping strategies are associated with specific molecules in the brain. Several neuroregulators and brain receptors have been suggested to modulate coping responses. Serotonin neurotransmission and 5-HT1$_A$ gene expression are associated with divergent coping styles toward acute stress in mice (Veenema et al., 2004; Andolina et al., 2015). Arginine vasopressin (AVP) released within the amygdala following exposure to stress contributes to the generation of negative coping strategies (Ebner et al., 2002). Furthermore, mice overexpressing corticotropin-releasing hormone receptor exhibit positive

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coping responses in the forced swim test (FST) and tail-suspension test (Lu et al., 2008). Mice with Neuropeptide-Y receptor Y2 deficiencies exhibit positive coping behaviors in the FST (Tschenett et al., 2003). Induction of DeltaFosB in the nucleus accumbens after chronic exposure to stress has also been associated with positive coping strategies and the promotion of stress resilience (Vialou et al., 2010; Shin et al., 2015). However, the potential roles of coordinated activity of neurons in specific brain regions such as resting brain activity in the determination of coping strategies have received little attention. Moreover, no studies have investigated whether modulation of basal brain activity can control individual coping strategies.

Resting state (or simply resting) brain activity is defined as the brain activity that occurs while an individual does not focus on the outside world (Raichle et al., 2001). Resting brain activity is closely associated with executive functions such as decision making (Seeley et al., 2007), emotional processing (Sheline et al., 2010), and cognitive functions such as memory processing (Young et al., 2012). Among the brain regions showing resting brain activity, the default mode network (DMN) has been intensively studied in humans to reveal its close association with various psychiatric disorders including depression (Whitfield-Gabrieli and Ford, 2012; Mulders et al., 2015). For example, patients with MDD experiencing negative emotional process such as hopelessness exhibit decreased negative responses in the DMN (Grimm et al., 2008). Sheline et al. (2009) also reported that the decreased negative responses among DMN regions in MDD patients during passive viewing and reappraisal of negative pictures. Connectivity among the DMN regions is dissociated in the MDD patients (Zhu et al., 2012). Increased DMN functional connectivity in the anterior cingulated cortex, thalamus, precuneus is significantly correlated with duration of depressive episode (Greicius et al., 2007). Antidepressant treatment normalized an abnormal resting brain activity in a posterior subnetwork of the DMN (Li et al., 2013). In animal models, however, the studies of how resting brain activity affects psychiatric disease-relevant animal behaviors have been scarce. In particular, due to a lack of animal experiment, a causal relationship between resting brain activity and the determination of coping strategies has not yet been identified.

We hypothesized that the changes in resting brain activity representing glutamatergic neural circuit activity aid in the determination of coping strategies in response to a previously encountered stressor. In the present study, we used the learned helplessness paradigm, which is a well-established animal model of depressive-like behavior (Seligman and Maier, 1967), because coping strategies of animals are easily assessed by evaluating the presence or absence of escape behavior in response to a given aversive stressor. We further assessed the resting glucose metabolism of rats using FDG-PET technology in order to observe changes in resting brain activity depending on different coping strategies. Moreover, we attempted to alter previously determined negative coping strategies by modulating brain activity via glutamatergic stimulation. Our analysis identified a previously undocumented, potential role of resting brain activity in the left ventral dentate gyrus in the determination of individual coping strategies in response to stress exposure.

2. Materials and methods

2.1. Experimental schedules

The present study was divided into two parts. In the first part, we evaluated regional differences in resting brain activity between animals with positive and negative coping strategies using FDG-PET. The experimental schedule for part one is presented in Fig. 1A. Briefly, all animals were allowed 1 week of habituation time in the home cage. Because 10% of rats exhibit congenital helplessness behaviors even before exposure to inescapable shock (Vollmayr and Henn, 2001), initial coping strategies were analyzed using the escape test, which consisted of 30 escape trials. After an average of 4 h following the escape test, 1st FDG-PET images were acquired according to the subsequently described PET scanning

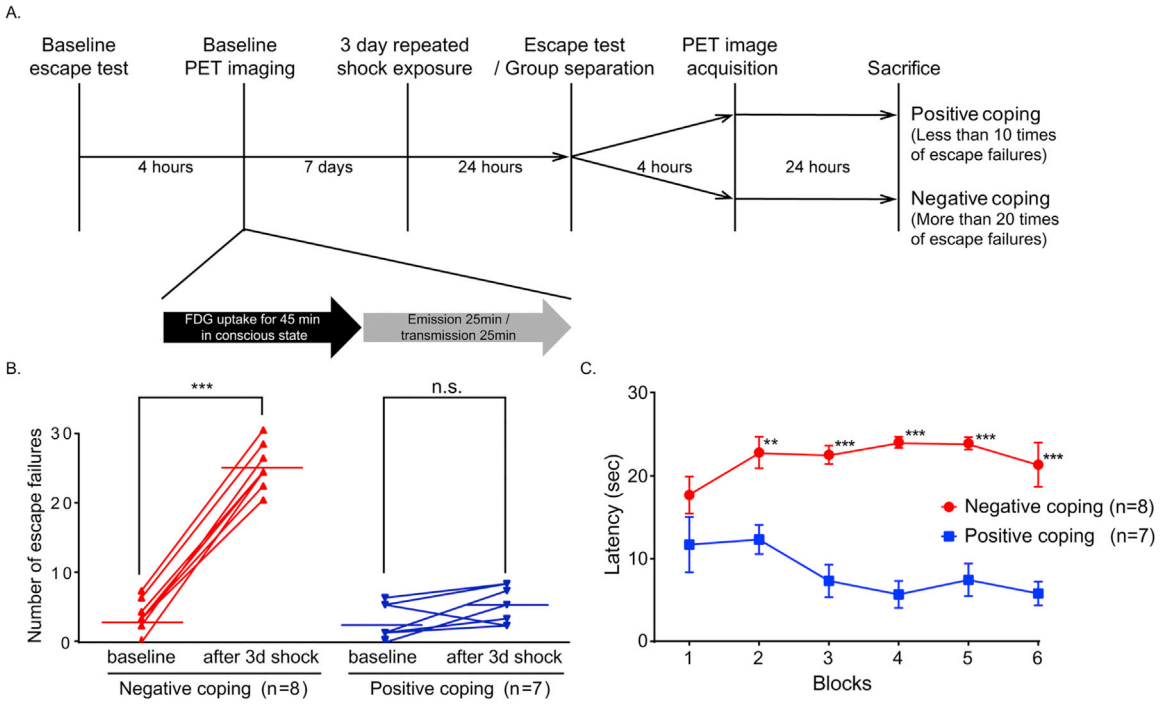

Fig. 1. PET imaging protocol and behavioral characteristics of negative versus positive coping rats. (A) Resting ^{18}F-FDG PET protocol. The experiment proceeded according to the following sequence: baseline assessment of escape performance, baseline PET image acquisition, shock exposure, escape test for group separation, post-shock image acquisition, and sacrifice. The PET protocol consisted of a 25 min emission image acquisition phase and a 25 min transmission image acquisition phase. (B) Following the determination of coping strategies, escape failures of the negative coping (NC) group increased, while escape failures of the positive coping (PC) group remained unchanged (NC group, n=8, baseline: 3.5±0.8, after 3d shock: 24.75±1.1, paired *t*-test: t=15.482, p<0.001; PC group, n=7, baseline: 4.1±2.0, after 3d shock: 5.0±1.0, no significance in paired *t*-test). (C) Following exposure to repeated uncontrollable stress, the mean escape latency of the NC group increased compared with that of the PC group for all blocks with the exception of first block (F_{group}=116.1, p<0.001 in RM ANOVA, **: p<0.01, ***: p<0.001).

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