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Preliminary communication

Perceived life stress exposure modulates reward-related medial prefrontal cortex responses to acute stress in depression

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ABSTRACT

Introduction: Major depressive disorder (MDD) is often precipitated by life stress and growing evidence suggests that stress-induced alterations in reward processing may contribute to such risk. However, no human imaging studies have examined how recent life stress exposure modulates the neural systems that underlie reward processing in depressed and healthy individuals.

Methods: In this proof-of-concept study, 12 MDD and 10 psychiatrically healthy individuals were interviewed using the Life Events and Difficulties Schedule (LEDS) to assess their perceived levels of recent acute and chronic life stress exposure. Additionally, each participant performed a monetary incentive delay task under baseline (no-stress) and stress (social-evaluative) conditions during functional MRI.

Results: Across groups, medial prefrontal cortex (mPFC) activation to reward feedback was greater during acute stress versus no-stress conditions in individuals with greater perceived stressor severity. Under acute stress, depressed individuals showed a positive correlation between perceived stressor severity levels and reward-related mPFC activation ($r=0.79$, $p=0.004$), whereas no effect was found in healthy controls. Moreover, for depressed (but not healthy) individuals, the correlations between the stress ($r=0.79$) and no-stress ($r=-0.48$) conditions were significantly different. Finally, relative to controls, depressed participants showed significantly reduced mPFC gray matter, but functional findings remained robust while accounting for structural differences.

Limitation: Small sample size, which warrants replication.

Conclusion: Depressed individuals experiencing greater recent life stress recruited the mPFC more under stress when processing rewards. Our results represent an initial step toward elucidating mechanisms underlying stress sensitization and recurrence in depression.

1. Introduction

Major Depressive Disorder (MDD) is a complex and heterogeneous illness with a lifetime prevalence of 16.6% in the US and a high relapse rate (Kessler et al., 2005). Stress is one of the strongest proximal risk factors for MDD (Slavich and Irwin, 2014), with up to 80% of first lifetime major depressive episodes (MDEs) being preceded by a stressful life event (Brown and Harris, 1989; Hammen, 2006).

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According to the stress sensitization models, stress plays a stronger role in the first lifetime MDE, but as the illness progresses, neurobiological changes that occur in response to depression and stress may sensitize individuals, thereby increasing risk of future episodes following less severe life stressors (Kendler et al., 1999; Kessler, 1997; Monroe and Harkness, 2005). Therefore, it is critical to understand the mechanisms underlying the effects of stress on brain function and behavior in MDD.

Animal and human studies have shown that both acute and chronic stressors affect the dopaminergic system and reward mechanisms and can induce anhedonia (Cabib and Puglisi-Allegra, 2012; Pizzagalli, 2014), which is a cardinal symptom of MDD (American Psychiatric Association, 2013). Two critical regions implicated in stress regulation that receive dense projections from dopamine (DA) pathways are the basal ganglia [including the nucleus accumbens (NAc), caudate and putamen] and medial prefrontal cortex (mPFC; Cabib and Puglisi-Allegra, 2012). Stress has distinct effects on the DA system and reward-related behaviors depending on the phase of reward processing (anticipation/consumption; Kumar et al., 2014), nature of the stressor (acute/chronic or controllable/uncontrollable; Cabib and Puglisi-Allegra, 2012; Maier and Watkins, 2010; Maier et al., 2006), and susceptibility of the individual to stress (Wang et al., 2014). For example, pre-clinical studies have shown that acute stressors increase tonic DA release in the NAc, promoting escape/avoidance attempts, whereas uncontrollable stressors are associated with inhibition of NAc DA release, which has been linked to helplessness (Cabib and Puglisi-Allegra, 2012). Consistent with this preclinical evidence, we recently found that an acute laboratory stressor increased basal ganglia activation during reward anticipation among healthy controls (Kumar et al., 2014). Conversely, under acute stress, basal ganglia activation was reduced during reward consumption among healthy controls, mirroring patterns we previously observed in MDD samples under baseline (no-stress) conditions (Pizzagalli et al., 2009).

The mPFC is thought to play a critical role in regulating DA release, and its activation is affected by the perceived controllability of the stressor (Maier and Watkins, 2010; Maier et al., 2006). Accordingly, uncontrollable stressors result in a greater increase of mPFC tonic DA levels when compared to exposure to a controllable stressor of identical intensity and duration (Cuadra et al., 1999; Valenti et al., 2012). In contrast, bilateral mPFC DA depletion increased stress-induced activity in the NAc (Cabib and Puglisi-Allegra, 2012; Pascucci et al., 2007; Scornaiencki et al., 2009). However, both mPFC morphology and function are influenced by prior experiences of chronic stress, which can impair this regulatory function. For example, changes in catecholamine levels, retraction of dendritic morphology, gene expression, and local circuit remodeling in the mPFC have been reported after exposure to chronic stress (Amat et al., 2008; Arnsten, 2009; Cerqueira et al., 2007; Dias-Ferreira et al., 2009; Radley et al., 2006; Wang et al., 2014). Similarly, prior experiences of stress have been shown to be associated with reduced mPFC activation during reward anticipation and consumption, reflecting poor encoding of rewards (Casement et al., 2014; Treadway et al., 2013). These studies suggest that stressors can influence both the structure and function of the mPFC, thereby modulating its critical role in stress adaptation, control, and resilience.

It is possible that depression, particularly recurrent depression with ongoing chronic stress, can affect mPFC structure and function in a way that causes the DAergic reward system to respond to an acute stressor as if it were uncontrollable. Consistent with this possibility, preclinical studies have shown that pre-exposure to a chronic stressor amplifies the response of mesocortical DA neurons in response to a subsequent acute stressor (Cabib and Puglisi-Allegra, 2012) and attenuates the ability of the stressor to activate NAc DA neurons (Valenti et al., 2012). These results highlight sensitization effects that are consistent with the kindling hypothesis and maintenance of depressive-like behavior. These dynamics may explain why as the illness progresses, individuals with MDD develop depressive episodes following increasingly lower levels of stress over time. To date, however, no study has investigated how experiences of recent life stress predict neural responses to reward under acute stress and no-stress conditions in depressed and healthy individuals.

To address this critical question, we conducted a proof-of-concept study in which we recruited unmedicated depressed and psychiatrically healthy individuals, and assessed acute and chronic life stressors that they experienced over the past 6 months using a state-of-the-art, interview-based measure of life stress. In addition, we characterized participants' neural responses to a monetary incentive delay task with fMRI under acute stress and no-stress conditions, which enabled us to examine how recent life stress exposure predicts reward processing in depressed and healthy individuals. Consistent with sensitization effects in the mPFC emerging from animal studies and its involvement in reward consumption, we hypothesized that the mPFC activation in response to rewards would be influenced by the perceived severity of recent stressors that depressed and healthy individuals experienced. Owing to findings highlighting mPFC volume reduction with repeated stressors or depressive episodes (e.g., Treadway et al., 2015), fMRI analyses controlled for gray matter variability among groups.

2. Methods

2.1. Participants

Twelve unmedicated individuals with current MDD (6 females, mean age: 35.8 ± 14.9) and 10 psychiatrically healthy (8 females, mean age: 29.7 ± 10.1) individuals participated in this study. All participants provided written informed consent to a protocol approved by the Committee on the Use of Human Subjects in Research at Harvard University and the Partners Human Research Committee. Participants were right-handed and reported no medical or neurological illnesses. Healthy controls had no current or past psychopathology, as assessed by the Structured Clinical Interview for the DSM-IV (SCID; First et al., 2002), and no current or past use of psychotropic medications. Findings related to the effects of acute stress (i.e., without consideration of life stressors) in healthy controls have been recently published in Kumar et al. (2014).

2.2. Procedure

During the initial screening visit, after the SCID session, participants completed the Beck Depression Inventory (BDI-II; Beck et al., 1996) and Snaith Hamilton Pleasure Scale (SHPS; Snaith et al., 1995) to assess their depressive and anhedonic symptoms, respectively. Within approximately 2 weeks of the MRI session, participants were administered the interview-based Life Events and Difficulty Schedule (LEDS; Brown and Harris, 1989) to assess all of the stressors they experienced over the past 6 months. Participants later underwent a single imaging session, during which time they performed a monetary incentive delay task (Knutson et al., 2000; see below). There were four separate runs of the MID task: two runs under no-stress conditions and two runs under stress conditions in the following order: (1) no-stress, (2) stress, (3) stress, and (4) no-stress. All reaction times associated with task performance were recorded. In addition, following each run, and prior to receiving performance evaluation, participants