Journal of Affective Disorders 180 (2015) 104–111

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

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

Poornima Kumar [a,b,*], George M. Slavich [c,d], Lisa H. Berghorst [e], Michael T. Treadway [f], Nancy H. Brooks [a], Sunny J. Dutra [g], Douglas N. Greve [h], Aoife O'Donovan [i,j], Maria E. Bleil [k], Nicole Maninger [l], Diego A. Pizzagalli [a,b,*]

[a] Center for Depression, Anxiety and Stress Research, McLean Hospital, Belmont, MA, USA
[b] Department of Psychiatry, Harvard Medical School, MA, USA
[c] Cousins Center for Psychoneuroimmunology, University of California, Los Angeles, USA
[d] Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA
[e] Department of Psychology, Harvard University, Cambridge, MA, USA
[f] Department of Psychology, Emory University, Atlanta, GA, USA
[g] Department of Psychology, Yale University, New Haven, CT, USA
[h] Department of Radiology, Massachusetts General Hospital, Charlestown, MA, USA
[i] Department of Psychiatry, University of California, San Francisco, CA, USA
[j] San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA
[k] Department of Family and Child Nursing, University of Washington, WA, USA
[l] California National Primate Research Center, University of California, Davis, USA

ARTICLE INFO

Article history:
Received 18 March 2015
Accepted 19 March 2015
Available online 28 March 2015

Keywords:
Stress
Depression
Anhedonia
Life events
fMRI
Reward processing

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).

* Correspondence to: Center for Depression, Anxiety and Stress Research, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA. Tel.: +1 617 855 4244.
E-mail addresses: pkumar@mclean.harvard.edu (P. Kumar), dap@mclean.harvard.edu (D.A. Pizzagalli).

http://dx.doi.org/10.1016/j.jad.2015.03.035
0165-0327/

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

rated the degree to which they experienced 12 different emotions (e.g., *tense*, *anxious*, *relaxed*, *in-control*) during the prior run on scales from 1 to 5 (1=not at all/very slightly, 3=moderately, 5=extremely). Participants were compensated $55 for their time, and earned between $10 and $60 from the task. Detailed description of the task and stress manipulation can be found in Kumar et al. (2014).

2.3. Life stress assessment

All of the stressors that participants experienced in the 6 months prior to the MRI scan were assessed using the Life Events and Difficulties Schedule (LEDS; Brown and Harris, 1989). The LEDS involves a 2-hour semi-structured interview that systematically inquires about potential acute and chronic stressors occurring in 10 domains of functioning (e.g., health, work, education, relationships, etc.). In addition to the standard LEDS procedure, in the present study, the interviewer summarized the acute life events and chronic difficulties that were extracted from the interview and asked participants to rate their perceived severity of those stressors on a 1 (*None*) to 5 (*Severe*) scale. A total subjective perceived stressor severity score was calculated by summing each participant's severity scores for acute life events and chronic difficulties. As per LEDS definitions, acute life events unfold over a relatively short period of time (e.g., 2–15 days) and include stressors such as learning about an impending job loss or broken engagement. Chronic difficulties are present at least for 4 weeks and include difficulties such as ongoing marital, financial, work, or housing problems (Brown and Harris, 1989).

2.4. Functional MRI task (monetary incentive delay task)

Briefly, participants were presented with a visual cue (1.5s) indicating the reinforcer type (+$ or 0$), followed by a target (0.2 s). This signaled the participants to press a button as quickly as possible. During reward trials, successful trials were rewarded by a monetary feedback if reaction times were within the 66th percentile of those from the previous run (for Run 1, a practice run was used for these calculations). Gains for successful reward trials were between $0.95 and $1.15 (mean: $1.05). For no-incentive trials, a "No change" feedback was presented regardless of RT. The task included 4 runs of 33 trials (~9 min each), with 22 reward and 11 no-incentive trials pseudo-randomized in each run. Subjects completed a brief practice before the first run. The practice run was identical to the design described above except that no feedback was provided.

2.5. Acute stress manipulation

An acute stress manipulation involving a social-evaluative component (i.e., negative feedback about task performance) and sudden $5 penalty deductions were built into the monetary incentive delay task. Participants received negative feedback immediately after completing runs 1 and 2, which was expected to induce stress during the completion of runs 2 and 3 ("stress runs"). In contrast, participants received positive feedback about their performance following the practice, and the end of run 3, making runs 1 and 4 "no stress" runs. To sustain the stress manipulation, a multicolored bar [with three different colored zones: red ("$5 Penalty"), yellow ("neutral"), and green ("Penalty Not Possible")] was visible at the bottom of the screen throughout the task. During the stress blocks, the pointer moved close to the red "$5 penalty" zone throughout the stress runs, with penalties occurring twice during run 2 and once during run 3. During the no-stress runs, the multicolored bar was shades of yellow, green, and blue ("safe"), and participants were informed that they could disregard the bar for those runs.

2.6. Imaging data acquisition

A 1.5-T Symphony/Sonata scanner (Siemens Medical Systems, Iselin, N.J.) was used to acquire the MRI data. High-resolution structural data were acquired using a T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) imaging sequence with the following acquisition parameters: repetition time=2730 ms; echo time=3.39 ms; field of view=256 mm; voxel dimensions=$1 \times 1 \times 1.33$ mm^3; 128 slices. Functional MRI data were acquired using a gradient echo T2*-weighted echoplanar imaging sequence with titled slice acquisition and z-shimming to recover signal in regions affected by susceptibility artifacts (Deichmann et al., 2003) with the following acquisition parameters: repetition time=2500 ms; echo time=35 ms; field of view=200 mm; voxel dimensions=$3.125 \times 3.125 \times 3$ mm^3; 35 interleaved slices.

2.7. Behavioral analyses

2.7.1. Perceived stressor severity score

An independent *t*-test evaluated possible group differences in participants' perceived stressor severity scores.

2.7.2. Reaction time

Responses shorter than 150 ms or greater than 1000 ms, and those exceeding three standard deviations from the mean for each participant, were deemed as outliers and removed. Next, a $2 \times 2 \times 2$ repeated measures ANOVA with *Incentive* (Reward, No-Incentive) × *Stress* (Stress, No-stress) as within-subject factors and *Group* (HC, MDD) was run.

2.7.3. Affective ratings

Positive and negative affects were calculated by averaging the scores obtained on 5 positive (in control, alert, energetic, relaxed and happy) and 7 negative (tense, anxious, powerless, defeated, challenged, stressed and out of control) emotions, respectively, after every run. These ratings were then analyzed using a $2 \times 2 \times 2$ repeated measures ANOVA with *Valence* (Positive, Negative) × *Stress* (Stress, No-stress) as within-subject factors and *Group* (HC, MDD).

2.8. fMRI analyses

Functional MRI data were pre-processed and analyzed using FMRIB's FSL 4.1.5 (Smith et al., 2004) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). After removal of non-brain structures using BET (Smith, 2002), fMRI data were corrected for movement (using MCFLIRT; Jenkinson et al., 2002) and slice timing artifacts. Images were then spatial smoothed (Gaussian kernel with 6 mm full width at half-maximum), grand mean intensity normalized by a single multiplicative factor, and temporally highpass filtered (Gaussian-weighed least squares straight line fitting with σ=60 s). Finally, functional data were registered to the high-resolution structural image using FLIRT and co-registered structural images were normalized to 2 mm MNI standard space template using FNIRT (Jenkinson et al., 2002).

A general linear model (GLM) with regressors corresponding to reward cue, no-incentive cue, successful reward feedback, unsuccessful reward feedback, no-change feedback (for no-incentive trials) was implemented for each subject. For each event, the onset times of the events were convolved with a hemodynamic response function (modeled using a gamma function). Covariates of no

interest included the six rigid-body motion time courses from the motion correction, target onset, errors (e.g., trials in which the button was pressed before the target presentation) and penalties (only during stress runs, when $5 penalty was randomly presented). Contrast maps were constructed for reward anticipation (reward versus no-incentive cue) and consumption (gain versus no-change feedback).

As mentioned in Kumar et al. (2014), analyses were restricted to runs 1 and 2, as putative differences between these two runs may more strongly reflect the effects of "acute" stress and would eliminate possible carry-over effects of stress. To test the influence of recent perceived stress (as measured by the LEDS) on reward processing during the acute stressor, a whole brain correlation was performed with perceived stressor severity score as a dependent variable and the change in brain activation (Run2: stress–Run1: no-stress) during reward consumption as an independent variable across all participants. Due to a small sample size, the correlation was conducted across all subjects from both groups opting for a continuum approach. For follow-up analyses of clusters emerging from the whole brain correlation, parameter estimates were extracted from the consumption contrasts (from Run1: no stress and Run 2: stress) and correlation analyses were performed using SPSS.

2.9. Structural analyses

VBM analyses were implemented using the VBM8 toolbox in conjunction with SPM8 (http://dbm.neuro.uni-jena.de/author/admin/). To this end, T1 images were first normalized and segmented into gray matter, white matter and cerebrospinal fluid using the SPM8 DARTEL segmentation procedure (Ashburner, 2007). In order to restore individual subject volume estimates that may have been altered following normalization, all images were modulated by the non-linear components derived from the spatial normalization. By using the non-linear components only, the resulting images are both aligned to the template while retaining their original gray matter volume. As a result of this step, inclusion of intracranial volume as a covariate in random-effects analysis is not required. After normalization, images were smoothed using a 12-mm FWHM kernel. As chronic stressors and depressive episodes have been associated with structural deficits in the mPFC (Amat et al., 2008; Arnsten, 2009; Cerqueira et al., 2007; Dias-Ferreira et al., 2009; Radley et al., 2006; Wang et al., 2014; Treadway et al., 2015), we aimed to control for structural deficits that could influence functional activity in this region. Therefore, gray matter estimates were extracted from the ROIs and correlation analyses were performed in SPSS, after controlling for the gray matter variability. Age and gender were also controlled for, as both these factors are known to influence structural morphology in humans (Taki et al., 2011).

Data were inspected for possible outliers in all analyses. Values that exceeded three times the inter-quartile range (the difference between the third and first quartile) of mean parameter estimates were deemed to be outliers and were further investigated to identify if these were due to motion, registration error, or other sources of artifacts. If no problems could be identified and corrected, outlier data points were removed from the analyses.

3. Results

3.1. Behavioral results

3.1.1. Clinical and demographics data

Compared to healthy controls (HC), depressed participants reported higher BDI-II ($t(20)=7.56$, $p<0.001$) and SHPS ($t(20)=3.78$, $p<0.001$) scores (Table 1). No differences in age, gender, job status and household income were observed ($p>0.1$). However, healthy controls had a significantly greater number of years of education ($t(20)=2.39$, $p<0.05$).

3.1.2. LEDS perceived stressor severity score

An independent t-test revealed that MDD participants had a higher perceived stressor severity score than healthy controls [$t(20)=-3.40$, $p<0.005$] – a difference that was driven by the severity of chronic difficulties [$t(1,20)=-4.76$, $p<0.001$] rather than acute life events [$t(1,20)=-0.99$, $p>0.3$; see Table 1].

3.1.3. MID task results

To ensure consistency with the fMRI analyses, behavioral analyses were restricted to Runs 1 and 2. Overall, across all participants and runs, approximately 66% of reward trials (~15 trials) were successful (i.e., participants were faster than the set threshold of 66%), and 34% (~7 trials) were not successful (i.e., participants were slower than the 66% threshold), indicating that the RT calibration elicited the intended effects. There was no difference in the number of reward feedback delivered during the stress and no-stress runs ($p>0.05$) across and within groups (Table 1).

3.1.4. Reaction time

The $2\times2\times2$ ANOVA revealed a significant main effect of *Valence* [$F(1, 20)=39.54$, $p<0.001$]. No effects involving *Group* or *Stress* emerged ($p>0.1$), and both groups were faster to respond during reward than neutral trials under both stress and no-stress conditions ($p<0.05$; Fig. 1A and B).

Table 1
Demographics and task performance scores for MDD and healthy controls.

Variables	MDD	Healthy controls	*P* value
Age	35.83 ± 14.90	29.70 ± 10.14	n.s
Gender	6f, 6m	8f, 2m	n.s
Education	15.33 ± 1.56	17 ± 1.69	< 0.05
BDI	25.25 ± 9.07	1.90 ± 3.87	< 0.001
SHPS	5.42 ± 4.07	0.40 ± 0.96	< 0.001
LEDS perceived stressor severity score	27.50 ± 13.57	11.50 ± 7.36	< 0.005
LEDS perceived chronic difficulty severity score	16.00 ± 7.39	3.70 ± 3.77	< 0.001
LEDS perceived acute event severity score	11.50 ± 10.52	7.80 ± 5.85	> 0.1
FRs received during no-stress	14.83 ± 4.02	16.40 ± 4.93	n.s
FRs received during stress	13.0 ± 3.72	14.60 ± 3.17	n.s

Mean ± Standard Deviations; f-Females, m-Males; BDI-II, Beck Depression Inventory (Beck et al., 1996); SHPS, Snaith Hamilton Pleasure Scale (Snaith et al., 1995); FRs, Reward Feedbacks.

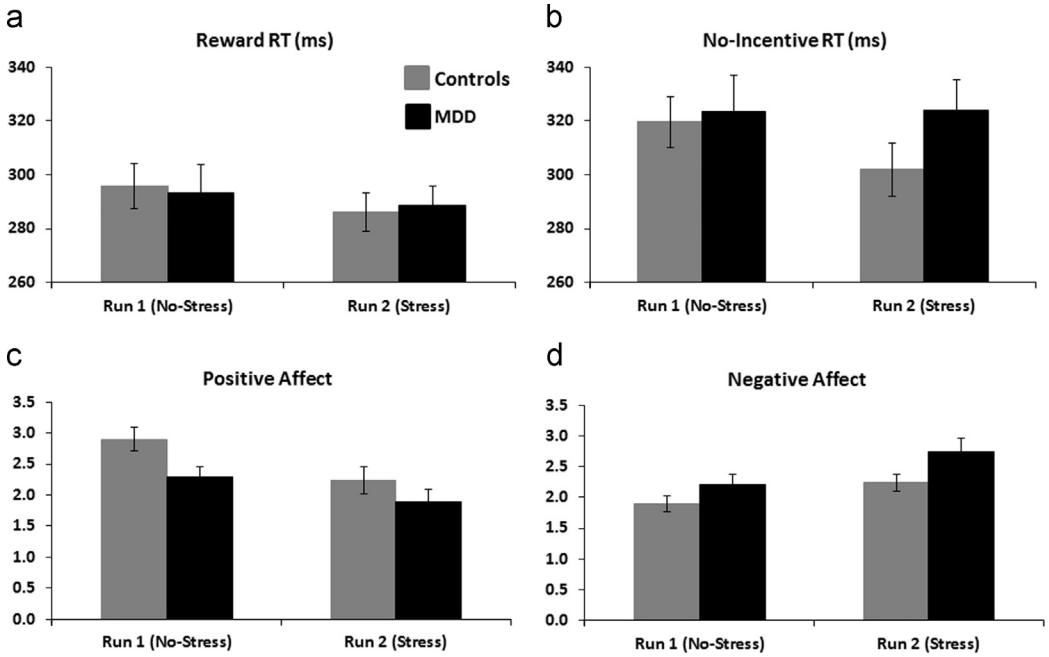

Fig. 1. Reaction times (A and B) and Affective ratings (C and D) across no-stress (Run 1) and stress (Run 2) runs. Error bars indicate standard errors.

3.1.5. *Affective ratings*

The $2 \times 2 \times 2$ ANOVA revealed significant *Valence* × *Group* [$F(1,20) = 10.98$, $p < 0.005$] and *Stress* × *Valence* [$F(1,20) = 34.40$, $p < 0.001$] interactions. As hypothesized, relative to controls, MDD individuals had lower positive affect during Run 1 [$t(20) = 2.43$, $p < 0.05$]. Post-hoc analyses revealed that similar to HC, MDD individuals had a significant increase in negative affect with stress (MDD: $t(11) = -3.52$, $p = 0.005$; HC: $t(9) = -3.67$, $p = 0.007$). However, whilst HC had a significant reduction of positive affect with stress, MDD individuals showed only a trend, possibly due to a floor effect (MDD: $t(11) = 1.81$, $p = 0.09$; HC: $t(9) = 3.46$, $p = 0.005$). Post-hoc tests for the significant *Stress* × *Valence* interaction indicated that both groups exhibited an increase in negative [$t(21) = -4.77$, $p < 0.001$] and decrease in positive affect [$t(21) = 3.52$, $p < 0.005$] in the no-stress versus stress condition, suggesting that the acute stress manipulation was successful (Fig. 1C and D). Finally, since we hypothesized that chronic stress would modulate neural responses to acute stress, correlations were performed between participants' LEDS perceived stressor severity scores and their affective responses to the fMRI-based stressor. For MDD individuals, LEDS perceived stressor severity score predicted the change in negative affect with acute stress. Specifically, depressed individuals with higher levels of perceived stressor severity showed greater increases in negative affect during the stress versus no-stress condition ($r = -0.61$, $p = 0.035$, Fig. 2). This effect was not observed in healthy controls ($r = 0.34$, $p > 0.1$). Although these two independent correlations were significantly different ($Z = 2.11$, $p < 0.05$), it is important to emphasize that the healthy controls had a truncated range in their change in negative affect and the correlation within the MDD group was influenced by an individual with the highest perceived stressor severity score.

3.2. *Imaging results*

Across all participants, a significant negative correlation was observed between neural activation change in a frontal cluster (including the mPFC) in response to reward feedback under stress compared to no-stress (Run 2 – Run 1), and the LEDS perceived stressor severity score ($x = 6$, $y = 56$, $z = 2$, $Z = 3.2$, cluster size = 772 voxels; Fig. 3). Thus, mPFC activation to reward feedback was

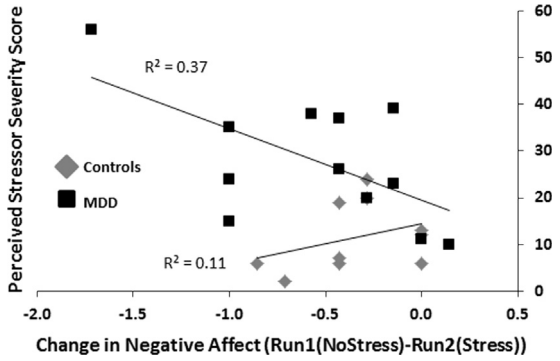

Fig. 2. Association between stress-induced change in negative affect and LEDS perceived stressor severity score across MDD and healthy individuals. Within the MDD group, the correlation was influenced by an individual with the highest perceived stressor severity score, who was, however, not identified as an outlier.

greater during acute stress than no-stress conditions in individuals with greater perceived stressor severity scores (see Fig. 3). The beta weights were extracted from the mPFC ROI and entered into SPSS and investigated for outliers. An extreme outlier as listed by SPSS was identified in the depressed group. Careful inspection of the data revealed that this outlier was not due to motion, registration error, or other sources of artifact, thus the values for this participant were removed from further functional analyses.

As previous studies have observed structural deficits in the MDD group in similar mPFC regions, gray matter estimates were extracted from this region and tested for group difference. Relative to healthy controls, depressed individuals had significantly lower gray matter in this region ($F(1,22) = 5.51$, $p = 0.031$; Cohen's $d = 0.95$), after controlling for gender and age. Critically, the correlation between LEDS subjective perceived stressor severity scores and reward-related mPFC response under stress versus no-stress conditions was confirmed after controlling for gray matter, age, and gender ($r = -0.58$, $p = 0.006$).

Follow-up analyses designed to further interrogate the data revealed several important findings. First, the correlation between LEDS subjective perceived stressor severity scores and mPFC response was mainly driven by the MDD group (MDD: $r = -0.80$, $p = 0.003$; HC: $r = -0.25$, $p = 0.49$). Second, the correlations linked to

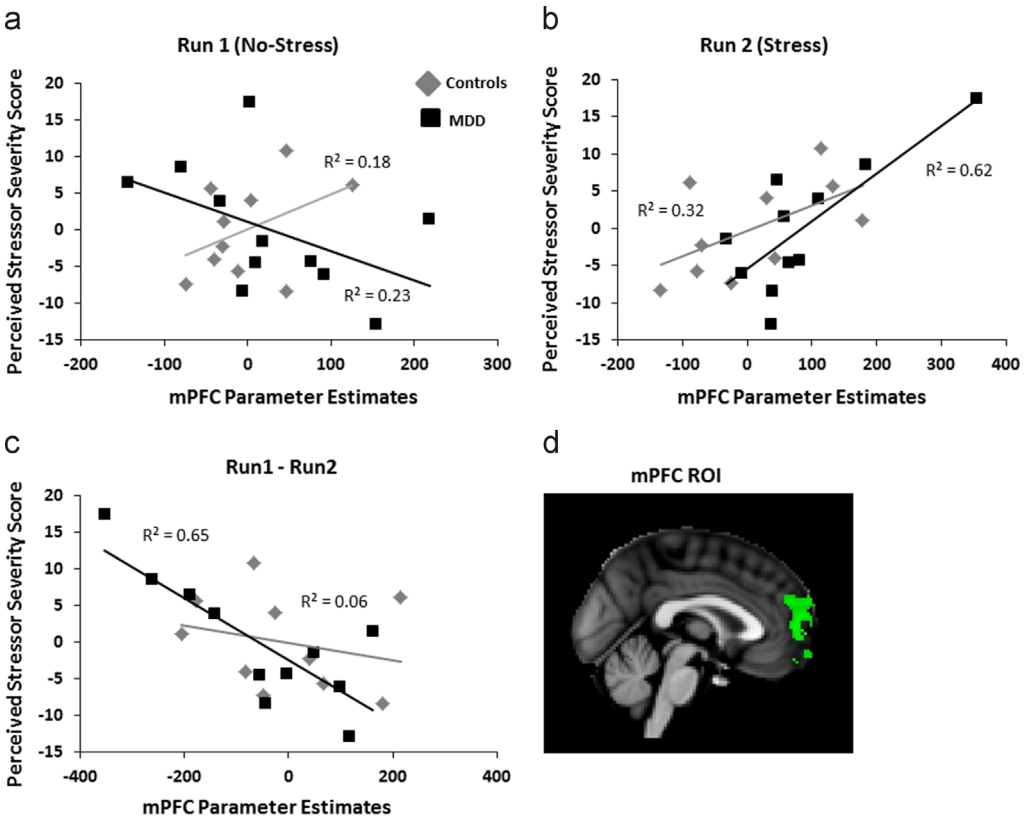

Fig. 3. Correlations between LEDS perceived stressor severity score and the mPFC activation during no-stress (Run 1) condition (3A), stress (Run 2) condition (3B), and change between Runs 1 and 2 (3C), (unstandardized residuals corrected for gray matter variability, age and gender). (D) mPFC ROI from the correlation analysis (peak voxel: $x=6$, $y=56$, $z=2$), $Z=3.2$, cluster size=772 voxels.

perceived life stress and mPFC activation under stress vs no-stress conditions were significantly different only in MDD individuals (stress: $r=0.79$, $p=0.004$ versus no-stress: $r=-0.48$, $p=0.14$; $Z=2.96$, $p=0.003$), but not in healthy controls (stress: $r=0.56$, $p=0.09$ versus no-stress: $r=0.43$, $p=0.22$; $Z=-0.27$, $p>0.5$; Meng et al., 1992). Third, whole brain correlational analysis did not reveal any other brain regions.

3.2.1. *Exploratory analyses*

As the NAc is often reported to be influenced by stress along with the mPFC, we conducted an exploratory Pearson correlation between participants' LEDS perceived stress severity scores and parameter estimates extracted from an NAc functional ROI during reward consumption. The NAc ROI was created by drawing a 10 mm sphere around the peak voxel ($x=-8$, $y=11$, $z=-15$) from Pizzagalli et al. (2009), as this region showed reduced activation in MDD during reward consumption relative to healthy participants. Across groups, a negative correlation emerged between LEDS perceived severity stress score and NAc activation in response to reward feedback under the stress relative to no-stress condition (Run 2–Run 1; $r=-0.46$, $p=0.03$). As in the mPFC, higher perceived stress severity scores were associated with potentiated reward-related NAc response in the stress condition. Further analysis revealed that this association was mainly driven by MDD participants' NAc responses in the stress condition (MDD: $r=0.74$, $p=0.01$; HC: $r=0.32$, $p=0.36$; Both groups: $r=0.64$, $p=0.002$).

4. Discussion

In the present study, we investigated the influence of recent stressors (both acute and chronic) on reward processing under lab-induced acute stress and no-stress conditions in MDD and healthy individuals. Whole-brain correlation analyses across groups revealed that individuals with higher levels of perceived stress showed the greatest change in the mPFC activation to reward feedback during acute stress. This effect was mainly driven by the MDD group. Specifically, while under acute stress, depressed individuals with greater recent perceived stressor severity scores showed potentiated reward-related mPFC activation, where as under no-stress, the association was reversed. In contrast, no evidence of stress-related mPFC modulation emerged among healthy individuals. Modulation of mPFC activation by both lab-induced acute stress and recent life stress experiences in depression is intriguing, especially in the context of animal studies highlighting the critical role of this region in stress adaptation, coping and resilience, particularly during reward processing (Horst and Laubach, 2013; Maier and Watkins, 2010; Ossewaarde et al., 2011). Finally, contrary to our hypotheses, whole-brain correlation analyses did not show a link between participants' perceived stressor severity scores and their NAc responses to reward, although ROI analyses indicated that, as for the mPFC, increased perceived stressor severity scores were associated with potentiated reward-related NAc response during acute stress. In light of the null findings from the whole-brain analyses, the NAc findings are not further interpreted.

The mPFC has been reported to be functionally and structurally vulnerable to chronic stress. The current voxel-based morphometry analyses revealed that, relative to healthy controls, the MDD group had reduced gray matter within the mPFC region showing stress-related functional modulation. Importantly, animal studies have shown that chronic stress cause changes in dendritic morphology, an increase in glucocorticoid receptors, spine loss, and altered synaptic transmission in the mPFC (Amat et al., 2008; Arnsten, 2009; Cerqueira et al., 2007; Dias-Ferreira et al., 2009; Radley et al., 2006; Wang et al.,

2014). Of note, non-human primate studies have shown that interventions designed to decrease stress responsiveness (by learning of successful coping strategies) increase the volume of mPFC (Katz et al., 2009; Lyons et al., 2002). Critically, the functional findings in the present study were robust while controlling for individual differences in mPFC gray matter density.

Functionally, the most intriguing finding was that depressed participants showed significantly different correlations between the LEDS perceived stressor severity scores and reward-related mPFC activation during acute stress versus no-stress condition. In particular, a significant correlation in the stress condition indicated that, during acute stress, depressed individuals with greater perceived stress exposure recruited the mPFC more strongly during reward consumption. This result can be explained by two pieces of evidence from the animal literature: learned helplessness and uncontrollability.

With respect to learned helplessness, Wang and colleagues recently proposed that cellular changes within the mPFC underlie resilience or susceptibility to stress-induced maladaptive behavioral response (Wang et al., 2014). Specifically, they showed that helplessness was associated with enhanced, whereas resilience was associated with reduced, excitatory synaptic transmission onto mPFC neurons that are actively recruited during behavioral response. In addition, increasing the synaptic transmission in the mPFC made resilient rats become susceptible to the stressor. The critical component is that prior exposure to stress was shown to be a catalyst for the induction of these changes (Wang et al., 2014). Our results of increased mPFC activity in depressed individuals who experienced recent stress to be more severe are consistent with Wang et al. (2014), although the cross-sectional nature of the current study cannot directly support a causal interpretation.

In terms of stress controllability, abundant evidence indicates that the mPFC controls stress responses via its regulation of striatal DA transmission, especially when the behavior needs to be adapted to the controllability or uncontrollability of the experience (Amat et al., 2005; Cabib and Puglisi-Allegra, 2012; Maier and Watkins, 2010; Maier et al., 2006; Wang et al., 2014). For example, both animal and human studies have shown that acute and chronic stressors increase DA levels substantially in the mPFC (Lataster et al., 2011; Nagano-Saito et al., 2013; Pruessner et al., 2008; Wang et al., 2005), with greater increases caused by uncontrollable stress (Bland et al., 2003). Furthermore, prior exposure to chronic stress amplifies this process, highlighting possible sensitization effects consistent with the kindling hypothesis (Post, 1992). Because DA exerts inhibitory effects on mPFC function, DA release in the mPFC in the face of uncontrollable stressors exerts a regulatory (inhibitory) control over DA activity in the NAc (e.g., Del Arco and Mora, 2008), and thereby expected to blunt DA release in mesolimbic pathways and maintain depressive-like behavior.

4.1. Limitations

Three main study limitations deserve mention. First, although the affective responses to the stress manipulation showed the expected patterns, no other (e.g., physiological) measures were used to evaluate stress responses. Second, although findings were consistent with *a priori* hypotheses concerning the effects of acute stress on neural processing, no findings emerged considering all four runs (data not shown), possibly due to habituation effects, limited statistical power, and/or the use of a mild stress manipulation. With respect to the latter point, monetary penalties like the ones employed here might not be particularly aversive, and more potent manipulations (e.g., threat-of-shock) might have triggered more reliable stress responses (Bogdan and Pizzagalli, 2006). A final limitation is that the sample size was small; hence, all results need to be considered with caution until replicated.

5. Conclusion

Although in need of replication, the present results provide initial evidence that experiences of recent life stress modulate neural correlates of reward processing under acute stress in depressed individuals. In particular, we found that perceived stressor severity scores modulated the reward-related activation in the mPFC, a region critically implicated in stress adaptation and controllability. More specifically, depressed individuals with greater perceived stressor severity recruited this region more under stress when processing rewards—a finding that is consistent with sensitization effects reported in the preclinical literature. This may explain why as depression progresses over time, risk of developing subsequent MDEs increases, even in response to more mild forms of stress. The findings may thus provide initial clues as to why depression is a highly recurrent, chronic, and impairing disorder for some individuals.

Role of funding source

This work was supported by NIMH R01 MH068376 and a NARSAD Independent Investigator award to DAP. PK was supported by the John and Charlene Madison Cassidy Fellowship in Translational Neuroscience through McLean Hospital, a Livingston and a NARSAD Young Investigator award. LB was supported in part by the Sackler Fellowship in Psychobiology and an NRSA Predoctoral Training Grant in Advanced Multimodal Neuroimaging. GS was partially supported by NIMH K08 MH103443. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest

Over the past three years, Dr. Pizzagalli has received honoraria/consulting fees from Otsuka Pharmaceutical, Pfizer, Servier, and Shire for activities unrelated to this project. MT has consulted for Boston Consulting Group unrelated to this project. All other authors report no conflict of interest.

Acknowledgments

The authors would like to thank Drs. Daniel Dillon, Ryan Bogdan and Avram Holmes for early contributions to the study design.

References

Amat, J., Baratta, M. V, Paul, E., Bland, S.T., Watkins, L.R., Maier, S.F., 2005. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nat. Neurosci. 8, 365–371.

Amat, J., Paul, E., Watkins, L.R., Maier, S.F., 2008. Activation of the ventral medial prefrontal cortex during an uncontrollable stressor reproduces both the immediate and long-term protective effects of behavioral control. J. Neurosci. 154, 1178–1186.

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, 5th ed. (DSM-5), TR.

Arnsten, A.F.T., 2009. Stress signalling pathways that impair prefrontal cortex structure and function. Nat. Rev. Neurosci. 10, 410–422.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. Neuroimage 38, 95–113.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck depression inventory-II. Psychological Corporation, San Antonio, TX, pp. 1–82.

Bland, S.T., Hargrave, D., Pepin, J.L., Amat, J., Watkins, L.R., Maier, S.F., 2003. Stressor controllability modulates stress-induced dopamine and serotonin efflux and morphine-induced serotonin efflux in the medial prefrontal cortex. Neuropsychopharmacology 28, 1589–1596.

Bogdan, R., Pizzagalli, D.A., 2006. Acute stress reduces reward responsiveness: implications for depression. Biol. Psychiatry 60, 1147–1154.

Brown, G., Harris, T., 1989. Life events and measurement. In: Brown, G., Harris, T. (Eds.), Life Events and Illness. The Guildford Press, London, pp. 3–45.

Cabib, S., Puglisi-Allegra, S., 2012. The mesoaccumbens dopamine in coping with stress. Neurosci. Biobehav. Rev. 36, 79–89.

Casement, M.D., Shaw, D.S., Sitnick, S.L., Musselman, S.C., Forbes, E.E., 2014. Life stress in adolescence predicts early adult reward-related brain function and alcohol dependence. Soc. Cogn. Affect. Neurosci. 10, 416–423.

Cerqueira, J.J., Mailliet, F., Almeida, O.F.X., Jay, T.M., Sousa, N., 2007. The prefrontal cortex as a key target of the maladaptive response to stress. J. Neurosci. 27, 2781–2787.
Cuadra, G., Zurita, A., Lacerra, C., Molina, V., 1999. Chronic stress sensitizes frontal cortex dopamine release in response to a subsequent novel stressor: Reversal by naloxone. Brain Res. Bull. 48, 303–308.
Deichmann, R., Gottfried, J.A., Hutton, C., Turner, R., 2003. Optimized EPI for fMRI studies of the orbitofrontal cortex. Neuroimage 19, 430–441.
Del Arco, A., Mora, F., 2008. Prefrontal cortex-nucleus accumbens interaction: in vivo modulation by dopamine and glutamate in the prefrontal cortex. Pharmacol. Biochem. Behav. 90, 226–235.
Dias-Ferreira, E., Sousa, J.C., Melo, I., Morgado, P., Mesquita, A.R., Cerqueira, J.J., Costa, R.M., Sousa, N., 2009. Chronic stress causes frontostriatal reorganization and affects decision-making. Science 325, 621–625.
First, M.B., Spitzer, R.L., Miriam, G., Williams, J.B., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition. (SCID-I/NP), Non-patien. ed. Biometrics Research. New York State Psychiatric Institute, New York.
Hammen, C., 2006. Stress generation in depression: reflections on origins, research, and future directions. J. Clin. Psychol. 62, 1065–1082.
Horst, N.K., Laubach, M., 2013. Reward-related activity in the medial prefrontal cortex is driven by consumption. Front. Neurosci. 7, 1–15.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825–841.
Katz, M., Liu, C., Schaer, M., Parker, K.J., Ottet, M.C., Epps, A., Buckmaster, C.L., Bammer, R., Moseley, M.E., Schatzberg, A.F., Eliez, S., Lyons, D.M., 2009. Prefrontal plasticity and stress inoculation-induced resilience. Dev. Neurosci. 31, 293–299.
Kendler, K.S., Karkowski, L.M., Prescott, C.A., 1999. Causal relationship between stressful life events and the onset of major depression. Am. J. Psychiatry 156, 837–841.
Kessler, R.C., 1997. The effects of stressful life events on depression. Annu. Rev. Psychol. 48, 191–214.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch. Gen. Psychiatry 62, 593–602.
Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., 2000. FMRI visualization of brain activity during a monetary incentive delay task. Neuroimage 12, 20–27.
Kumar, P., Berghorst, L.H., Nickerson, L.D., Dutra, S.J., Goer, F.K., Greve, D.N., Pizzagalli, D.A., 2014. Differential effects of acute stress on anticipatory and consummatory phases of reward processing. Neuroscience 266, 1–12.
Lataster, J., Collip, D., Ceccarini, J., Haas, D., Booij, L., van Os, J., Pruessner, J., Van Laere, K., Myin-Germeys, I., 2011. Psychosocial stress is associated with in vivo dopamine release in human ventromedial prefrontal cortex: a positron emission tomography study using [^{18}F]fallypride. Neuroimage 58, 1081–1089.
Lyons, M., Afarian, H., Schatzberg, A.F., Sawyer-glo, A., Moseley, M.E., 2002. Experience-dependent asymmetric variation in primate prefrontal morphology. Behav. Brain Res. 136, 51–59.
Maier, S.F., Amat, J., Baratta, M. V, Paul, E., Watkins, L.R., 2006. Behavioral control, the medial prefrontal cortex, and resilience. Dialogues Clin. Neurosci. 8, 397–406.
Maier, S.F., Watkins, L.R., 2010. Role of the medial prefrontal cortex in coping and resilience. Brain Res. 1355, 52–60.
Meng, X., Rosenthal, R., Rubin, D.B., 1992. Comparing correlated correlation coefficients. Psychol. Bull. 111 (1), 172–175.
Monroe, S.M., Harkness, K.L., 2005. Life stress, the “kindling” hypothesis, and the recurrence of depression: considerations from a life stress perspective. Psychol. Rev. 112, 417–445.
Nagano-Saito, A., Dagher, A., Booij, L., Gravel, P., Welfeld, K., Casey, K.F., Leyton, M., Benkelfat, C., 2013. Stress-induced dopamine release in human medial prefrontal cortex-18F-fallypride/PET study in healthy volunteers. Synapse 67, 821–830.
Ossewaarde, L., Qin, S., Van Marle, H.J.F., van Wingen, G.A., Fernández, G., Hermans, E.J., 2011. Stress-induced reduction in reward-related prefrontal cortex function. Neuroimage 55, 345–352.
Pascucci, T., Ventura, R., Latagliata, E.C., Cabib, S., Puglisi-Allegra, S., 2007. The medial prefrontal cortex determines the accumbens dopamine response to stress through the opposing influences of norepinephrine and dopamine. Cereb. Cortex 17, 2796–2804.
Pizzagalli, D.A, 2014. Depression, stress, and anhedonia: toward a synthesis and integrated model. Annu. Rev. Clin. Psychol. 10, 393–423.
Pizzagalli, D.A., Holmes, A.J., Dillon, D.G., Goetz, E.L., Birk, J.L., Bogdan, R., Dougherty, D.D., Iosifescu, D. V, Rauch, S.L., Fava, M., 2009. Reduced caudate and nucleus accumbens response to rewards in unmedicated subjects with major depressive disorder. Am. J. Psychiatry 166, 702–710.
Post, R.M., 1992. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am. J. Psychiatry 149, 999–1010.
Pruessner, J.C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., Renwick, R., Dagher, A., Meaney, M.J., Lupien, S., 2008. Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. Biol. Psychiatry 63, 234–240.
Radley, J.J., Rocher, A.B., Miller, M., Janssen, W.G.M., Liston, C., Hof, P.R., McEwen, B.S., Morrison, J.H., 2006. Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex. Cereb. Cortex 16, 313–320.
Scornaiencki, R., Cantrup, R., Rushlow, W.J., Rajakumar, N., 2009. Prefrontal cortical D1 dopamine receptors modulate subcortical D2 dopamine receptor-mediated stress responsiveness. Int. J. Neuropsychopharmacol. 12 (9), 1195–1208.
Slavich, G.M., Irwin, M.R., 2014. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. Psychol. Bull. 140, 774–815.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17, 143–155.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23 (Suppl 1), S208–S219.
Snaith, R.P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., Trigwell, P., 1995. A scale for the assessment of hedonic tone. The Snaith–Hamilton pleasure scale. Br. J. Psychiatry 167, 99–103.
Taki, Y., Thyreau, B., Kinomura, S., Sato, K., Goto, R., Kawashima, R., Fukuda, H., 2011. Correlations among brain gray matter volumes, age, gender, and hemisphere in healthy individuals. PLoS One 6, e22734.
Treadway, M.T., Buckholtz, J.W., Zald, D.H., 2013. Perceived stress predicts altered reward and loss feedback processing in medial prefrontal cortex. Front. Hum. Neurosci. 7, 1–10.
Treadway, M.T., Waskom, M.L., Dillon, D.G., Holmes, A.J., Park, M.T.M., Chakravarty, M.M., Dutra, S.J., Polli, F.E., Iosifescu, D. V, Fava, M., Gabrieli, J.D.E., Pizzagalli, D.A., 2015. Illness progression, recent stress, and morphometry of hippocampal subfields and medial prefrontal cortex in major depression. Biol. Psychiatry 77, 285–294.
Valenti, O., Gill, K.M., Grace, A.A., 2012. Different stressors produce excitation or inhibition of mesolimbic dopamine neuron activity: response alteration by stress pre-exposure. Eur. J. Neurosci. 35, 1312–1321.
Wang, J., Rao, H., Wetmore, G.S., Furlan, P.M., Korczykowski, M., Dinges, D.F., Detre, J.A., 2005. Perfusion functional MRI reveals cerebral blood flow pattern under psychological stress. Proc. Natl. Acad. Sci. USA 102, 17804–17809.
Wang, M., Perova, Z., Arenkiel, B.R., Li, B., 2014. Synaptic modifications in the medial prefrontal cortex in susceptibility and resilience to stress. J. Neurosci. 34, 7485–7492.