Psychological Medicine

cambridge.org/psm

Original Article

Cite this article: Hanson JL, Knodt AR, Brigidi BD, Hariri AR. Heightened connectivity between the ventral striatum and medial prefrontal cortex as a biomarker for stress-related psychopathology: understanding interactive effects of early and more recent stress. *Psychological Medicine* https://doi.org/10.1017/S0033291717003348

Received: 16 March 2017
Revised: 17 October 2017
Accepted: 20 October 2017

Key words:
child maltreatment; stress; early adversity; reward; ventral striatum; medial prefrontal cortex

Author for correspondence:
Jamie Hanson, E-mail: jamie.hanson@pitt.edu

Heightened connectivity between the ventral striatum and medial prefrontal cortex as a biomarker for stress-related psychopathology: understanding interactive effects of early and more recent stress

Jamie L. Hanson[1,2], Annchen R. Knodt[3], Bartholomew D. Brigidi[3] and Ahmad R. Hariri[3]

[1]Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA; [2]Learning Research & Development Center, University of Pittsburgh, Pittsburgh, PA, USA and [3]Laboratory of NeuroGenetics, Department of Psychology & Neuroscience, Duke University, Durham, NC, USA

Background. The experience of childhood maltreatment is a significant risk factor for the development of depression. This risk is particularly heightened after exposure to additional, more contemporaneous stress. While behavioral evidence exists for this relation, little is known about biological correlates of these stress interactions. Identifying such correlates may provide biomarkers of risk for later depression.
Methods. Here, we leverage behavioral, experiential, and neuroimaging data from the Duke Neurogenetics Study to identify potential biomarkers of stress exposure. Based on the past research, we were specifically interested in reward-related connectivity and the interaction of early and more recent stress. We examined psychophysiological interactions between the ventral striatum and other brain regions in relation to these stress variables, as well as measures of internalizing symptomatology ($n = 926$, participant age range = 18–22 years of age).
Results. We found relatively increased reward-related functional connectivity between the left ventral striatum and the medial prefrontal cortex in individuals exposed to greater levels of childhood maltreatment who also experienced greater levels of recent life stress ($\beta = 0.199$, $p < 0.005$). This pattern of functional connectivity was further associated with elevated symptoms of depression ($\beta = 0.089$, $p = 0.006$). Furthermore, using a moderated mediation framework, we demonstrate that this functional connectivity provides a biological link between cumulative stress exposure and internalizing symptomatology.
Conclusions. These findings suggest a novel biomarker linking cumulative stress exposure with the later experience of depressive symptoms. Our results are discussed in the context of past research examining stress exposure in relation to depression.

Introduction

Unfortunately, one in eight children in the United States will experience some form of maltreatment by 18 years of age (Wildeman *et al.* 2014). Such adversities can significantly impact mental health, as child maltreatment is associated with a 60–70% increase risk for lifetime mood and anxiety disorders (Chapman *et al.* 2004; Danese *et al.* 2009; Green *et al.* 2010). Though well studied and well replicated in psychological and epidemiological research, the biological mechanisms mediating the association between maltreatment and later psychopathology remain unclear.

Suggestive from investigations focused on multiple dimensions of stress exposure is that this risk may be particularly heightened if an individual is exposed to maltreatment and then later, more contemporaneous, stressful experiences. Maltreatment often alters the physiological and behavioral stress response including impairment in the ability to effectively regulate negative or positive emotion (Glaser *et al.* 2006; Kim & Cicchetti, 2010; Herts *et al.* 2012). Indeed, high levels of recent stress after child maltreatment have been found to predict subsequent increases in symptoms of anxiety and depression, as well as clinical diagnosis (Hammen *et al.* 2000; Harkness *et al.* 2006; Espejo *et al.* 2007; Shapero *et al.* 2013).

While past research has focused on psychosocial measures and stress interactions, less work has centered on neurobiological processes. Preliminary evidence suggests that child maltreatment increases reactivity to acute stress through physiological pathways, such as alterations in blood pressure (Leitzke *et al.* 2015; Gooding *et al.* 2016), cardiac output (McLaughlin *et al.* 2013), and cortisol release (Tarullo & Gunnar, 2006; Heim *et al.* 2008). Limited work, to date, has examined how different forms of stress (early; more recent) may interact and be related to alterations in the brain. Such gaps are important to fill-in as the brain is positioned to mediate the effects of external stressors, especially those psychosocial in nature, on such

CAMBRIDGE UNIVERSITY PRESS

physiological pathways. Thus, identifying the impact of child maltreatment on the brain directly could deepen basic knowledge of how such adversity can become embedded in our physiology and behavior (Hanson *et al.* 2015*b*). In addition, understanding how differences in the brain connect with different types of stress exposure could inform the search for strategies to mitigate the negative sequelae of child maltreatment leading to resiliency and greater wellbeing.

Potential clues in understanding neural correlates of different forms of stress exposure have emerged from research focused on the ventral striatum (VS), a subcortical brain structure supporting reward responsiveness and learning (Richard *et al.* 2013). Preclinical models have found exposure to stress leads to changes in VS functioning, as assessed by levels of transcription factors and gene expression (Haglund *et al.* 2007; Russo *et al.* 2012). Interestingly, in work with rodents, links between VS functioning and depressive behavior have been reported, with experimental upregulation of VS functioning often inducing effects similar to antidepressants (Nestler & Carlezon, 2006). Work in humans has provided additional suggestive evidence about different forms of stress exposure and reward neural circuitry. Early adversity, such as child trauma or neglect, has been shown to negatively influence functional responses of the VS to reward (Goff *et al.* 2013; Hanson *et al.* 2015*a*, 2016). Such VS dysfunction has been theorized to specifically underlie symptoms of depression, including anhedonia and apathy, and neuroimaging studies have reported decreased reward-related VS activity in depressed individuals (Forbes & Dahl, 2012; Admon & Pizzagalli, 2015*b*). Related to this work, Nikolova *et al.* (2012) reported that relatively lower reward-related VS activity interacted with relatively higher levels of recent life stress to predict core symptoms of depression, specifically higher anhedonia and lower levels of positive affect.

While this past work has logically been focused on the VS, this brain region is nested in a larger circuit of motor, cognitive, and limbic brain regions, including portions of the medial prefrontal cortex (mPFC), subregions of the anterior cingulate cortex, the thalamus, brain stem, and motor cortex (Haber & Knutson, 2009; Shepherd, 2013). Linking together research focused on depression, as well as stress exposure, suggests a potentially important role of the mPFC, specifically in mood dysregulation after different types of adversities. Subregions of the mPFC support reward responsivity, as well as the processing of self-referential and social information (Amodio & Frith, 2006; Haber & Knutson, 2009). Depressed individuals often show higher activity in this region (Forbes & Dahl, 2012), and greater reward-related activity in this area predicts poorer treatment response for internalizing symptomatology (Forbes *et al.* 2010). Interestingly, individuals with depression, who also report greater recent perceived stress, show higher reward-related mPFC activation while under acute stress (Kumar *et al.* 2015). Turning to research studies focused on stress exposure, mPFC activity during reward anticipation is related to proxies of stress exposure. For example, greater activity in mPFC was seen for individuals whose families had a longer childhood history of being on public assistance, or who were exposed to lower levels of maternal warmth during early childhood (Morgan *et al.* 2014; Romens *et al.* 2015). Similar data have been reported in work examining mPFC activity and child maltreatment during social reward tasks (Van Harmelen *et al.* 2014). Nonhuman animal data also support this idea, as helplessness and stress vulnerability in rodents was associated with enhanced activity in the mPFC (Kumar *et al.* 2014; Wang *et al.* 2014).

Examined collectively, past research suggests that alterations in the VS and mPFC as a function of stress exposure may mediate the expression of stress-related internalizing symptomatology. However, it is still not fully known how the functional dynamics between the VS and mPFC are impacted by stress exposure or contribute to the experience of depression or anxiety. One important exception is novel work focused on depression by Admon & Pizzagalli (2015*a*), using directed functional ('causal') connectivity analyses. These investigators found that initially, in both control and depressed individuals, activity in the mPFC was driving fluctuations in the VS. However, after a positive mood induction and over the course of a scanning session, controls exhibited a change in their connectivity to a more reciprocal pattern. In individuals suffering from depression, corticostriatal connectivity patterns did not change, with activity still being driven by the mPFC.

While Admon and Pizzagalli provided strong initial evidence that VS-mPFC connectivity may be aberrant in depression, it is important to note that past findings in depressed samples have not been perfectly uniform. Reports of lower mPFC activation during the processing of rewards or heightened mPFC activity only during the processing of losses or punishments have been noted in samples presenting with depression (Smoski *et al.* 2009; Mies *et al.* 2013; Admon *et al.* 2014; Quevedo *et al.* 2017). Some of these inconsistencies may be related to differences in stress exposure. Past neurobiologically focused work in depression often does not examine the effects of stress exposure, or at best examines a single form of stress (i.e. maltreatment or more contemporaneous stress). Assaying the connectivity in this broader corticostriatal circuit, while also probing multiple types of stress exposure, could provide insights into the pathophysiology of depression, as well as understanding the neural correlates of potential interactive effects of stress. Particularly useful may be the assessment of task-based connectivity; this functional magnetic resonance imaging (fMRI) analytic approach allows researchers to investigate brain networks, focusing on the interactions between brain areas and complementing task-based main effects (O'Reilly *et al.* 2012). Limited work to date focused on stress exposure and psychopathology has deployed such an approach.

To fill in these important gaps, here, we examined links between childhood maltreatment, recent life stress, reward-related VS-mPFC functional connectivity, and self-reported internalizing symptoms in a sample of 926 young adult volunteers. This would complement recent work from our group solely focused on VS reactivity after early, as well as more recent, stress exposure (Nikolova *et al.* 2012; Corral-Frías *et al.* 2015). Based on the literature reviewed above, we hypothesized the presence of relatively increased VS-mPFC functional connectivity in individuals with higher levels of childhood maltreatment, when they also reported higher levels of recent stress. Furthermore, building off recent work by Admon & Pizzagalli (2015*a*), we predicted that relatively increased VS-mPFC functional connectivity would map onto higher levels of internalizing symptoms.

Methods

Participants

Data were available from 926 participants (age range = 18–22 years old) who completed the Duke Neurogenetics Study (DNS) between January 2010 and July 2014. The DNS assessed a wide

range of behavioral and biological traits among non-patient, young adolescent, and adult university student volunteers, and was approved by the Duke University Medical Center Institutional Review Board. The authors assert that all procedures contributing to this work also complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

All participants provided informed consent before participation, and were excluded in the present sample if they met any of the following criteria: (a) medical diagnoses of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime history of psychotic symptoms; (b) use of psychotropic, glucocorticoid, or hypolipidemic medication; (c) conditions affecting cerebral blood flow and metabolism (e.g. hypertension); or (d) failed quality control criteria for fMRI data. Diagnosis of any past or current DSM-IV Axis I disorder or select Axis II disorders (antisocial personality disorder and borderline personality disorder) was assessed with structured clinical interviews (First *et al.* 1996; Sheehan *et al.* 1998). Such diagnoses were, however, not exclusion criteria, as the DNS sought to establish broad variability in multiple behavioral phenotypes related to psychopathology. One hundred and eighty-six subjects met criteria for having a current or past Axis I disorder, including alcohol dependence ($n = 52$), alcohol abuse ($n = 54$), any type of anxiety disorder ($n = 40$), or any type of major depressive disorder ($n = 37$). Three participants met criteria for at least one Axis II disorder ($n = 3$).

Self-report questionnaires

Participants completed a battery of self-report questionnaires to assess past and current experiences and behavior. The following were used for the present analyses: the Childhood Trauma Questionnaire (CTQ; Bernstein *et al.* 1997); Life Events Scale for Students (LESS; Clements & Turpin, 1996); the Mood and Anxiety Symptom Questionnaire-Short Form (MASQ; Clark & Watson, 1991). The CTQ is a 28-item, retrospective screening tool used to assess exposure to childhood maltreatment in five categories: emotional, physical and sexual abuse, and emotional and physical neglect. Each of the CTQ's five subscales has robust internal consistency and convergent validity with a clinician-rated interview of childhood abuse and therapists' ratings of abuse (Bernstein *et al.* 1995). Scores on each subscale (range = 5–25) were summed to provide a total score (range = 25–75). This instrument and approach has been employed in other recent research studies focused on child maltreatment (Dannlowski *et al.* 2012; Gorka *et al.* 2014). To assess the occurrence of common stressful life events within the past 12 months, we used a modified version of the LESS. In this checklist, participants indicated which stressful life events happened to them over the past year (e.g. broke up with romantic partner, family health problems; additional examples noted in our online Supplementary Materials). Recent symptoms of internalizing psychopathology were assessed using the MASQ. The MASQ is a well-validated measure, yielding four subscales assessing symptoms experienced within the last 7 days specific to anxious arousal and anhedonic depression, as well as general anxiety and general depression. In line with past research (Swartz *et al.* 2015), these four subscales were summed to create a measure of total internalizing symptoms.

Ventral striatum activity paradigm

To probe reward-related corticostriatal circuit function, participants completed a card-guessing paradigm consisting of three blocks each of predominantly positive feedback (80% correct guess), predominantly negative feedback (20% correct guess), and no feedback during BOLD fMRI. During each block, participants played a card-guessing game, resulting in positive or negative feedback for each trial. Participants were told that their performance on this game would determine a monetary reward to be received and were unaware of the fixed outcome probabilities associated with each block. Instead, all participants received $10. One incongruent trial was included within each task block (e.g. one of five trials during positive feedback blocks was incorrect, resulting in negative feedback) and all blocks were pseudo-randomly ordered to minimize expectancy effects and to increase participant engagement throughout the task. In addition to positive and negative feedback trials, participants also completed control trial blocks where valenced feedback was not presented. Additional information about the task is noted in our online Supplementary Materials.

A number of past studies have employed this block design task to elicit robust VS activity associated with positive feedback in contrast to negative feedback within the broader context of monetary rewards (Hanson *et al.* 2015*a*, 2016; Nikolova *et al.* 2016). This subtractive contrast was further motivated by work finding that corticostriatal activation occurs most robustly with nondeterministic feedback, and when subject's believe that their actions lead to specific outcomes (e.g. winning or losing money; Tricomi *et al.* 2004; Delgado *et al.* 2005).

fMRI data acquisition and analyses

Blood oxygen level-dependent functional neuroimaging data were acquired for each participant and then processed in SPM8 using our standard preprocessing parameters (see https://www.hariri-lab.com/methods/vs.html). Following preprocessing, linear contrasts employing canonical hemodynamic response functions were used to estimate the effects of different forms of feedback (e.g. positive and negative) for each individual.

To understand potential circuit-level interactions during reward processing, we focused on task-based functional connectivity between the VS and other brain regions involved with reward processing using the generalized psychophysiological interaction (gPPI) toolbox in SPM8 (McLaren *et al.* 2012). For these analyses, deconvolved time courses were extracted from VS regions-of-interest for each subject. These regions-of-interest were 10-mm sphere centered around the left or right VS (approximate Montreal Neurological Institute, MNI, coordinates for left VS $x = -12$, $y = +12$, $z = -10$; for right VS $x = +12$, $y = +12$, $z = -10$; derived from the Talairach Daemon option of the WFU PickAtlas Tool, version 1.04). Extracted VS time-series data were entered into first-level statistical models that included a psychological regressor corresponding to positive feedback > negative feedback for the card tasks detailed above, as well as the psychophysiological interaction term. Individual beta images corresponding to this interaction were then used in a second-level random effects model accounting for scan-to-scan and participant-to-participant variability to determine brain circuitry that varied as a function of VS BOLD signal and experimental condition.

Whole-brain analyses were completed for the left and right VS separately, using multiple regression models with maltreatment,

more contemporaneous stress exposure, and the interaction of these two forms of adversity entered as independent variables. To correct for multiple comparisons, we deployed AFNI's 3dClustSim using cluster-size thresholding based on Monte Carlo simulation. This program creates multiple simulated null data sets from which a distribution of cluster sizes corresponding to a desired corrected p value can be determined. An initial statistical threshold of $p < 0.001$, uncorrected was chosen. Based on this threshold, the number of comparisons in our imaging volume, and the smoothness of our imaging data, as measured by 3dFWHMx, a minimum cluster size of 120 voxels was required to have a corrected $p \leq 0.05$.

Statistical analyses

For all regions above this threshold, mean functional connectivity estimates were then extracted using the MarsBaR toolbox by averaging across every voxel in clusters in each region. Next, bivariate correlations were calculated to assess the relation between reward-related connectivity and internalizing symptomatology, controlling for age and sex. Moderated mediation models were then constructed to investigate the potential explanatory role of regions emerging from our PPI analyses. These models examined (1) whether maltreatment (X) was associated with internalizing symptomatology (Y) in the context of more contemporaneous life stress (W) and (2) if the observed association between stress and internalizing symptomatology was mediated by differences in corticostriatal connectivity (M). Statistical testing of mediation was done by nonparametric bootstrapping, with 95% confidence intervals (CIs) for indirect mediation effects. Mediation modeling was completed in R (http://cran.r-project.org) and included age and sex as covariates.

Exploratory analyses related to feedback valance and internalizing symptomatology

To better understand the effects of stress exposure on reward-related brain function, we also completed exploratory gPPI analyses for each feedback valence (positive or negative) by extracting the contrasts of positive feedback > control blocks (or negative feedback > control blocks) for our VS regions of interest. These analyses employed analogous analytic procedures as those noted above, but focused on the contrast of positive feedback > control blocks or negative feedback > control blocks.

Results

Sample demographics

For the CTQ total scores, the full-sample mean was 33.48 (standard deviation, S.D. = 8.47) and the range was 25–75, with a score of 25 being the lowest possible sum. These values are similar to previous research in a community sample (Scher *et al.* 2001). Similar to previous research (Covault *et al.* 2007), our participants reported an average of 4.403 (S.D. = 3.17) recent stressful life events. For the MASQ, the means and standard deviations for the total score were again similar to previous reports (mean = 111.73, S.D. = 26.3; e.g. Bogdan *et al.* 2010). Correlations between demographic variables and fMRI behavioral metrics (e.g. response time) are detailed in our online Supplementary Materials.

Functional connectivity, stress-interactions, and internalizing symptomatology

Examining connectivity for the left VS, PPI analyses for positive > negative feedback revealed task-dependent functional connectivity related to the interaction of maltreatment and more contemporaneous life stress. Specifically, relatively increased functional connectivity between the left VS and mPFC ($x = -10$, $y = +50$, $z = +20$, $\beta = 0.199$, $k = 1450$ voxels, $p < 0.05$ corrected) was seen in individuals who had experienced maltreatment (assessed by the CTQ), as well as more recent life stress (assessed by the LESS). This effect is shown in Fig. 1, and remained significant when controlling for DMS-IV diagnosis ($\beta = 0.206$, $p < 0.005$). No other regions emerged as significant in our PPI analyses of the left VS when focused on the interaction of maltreatment

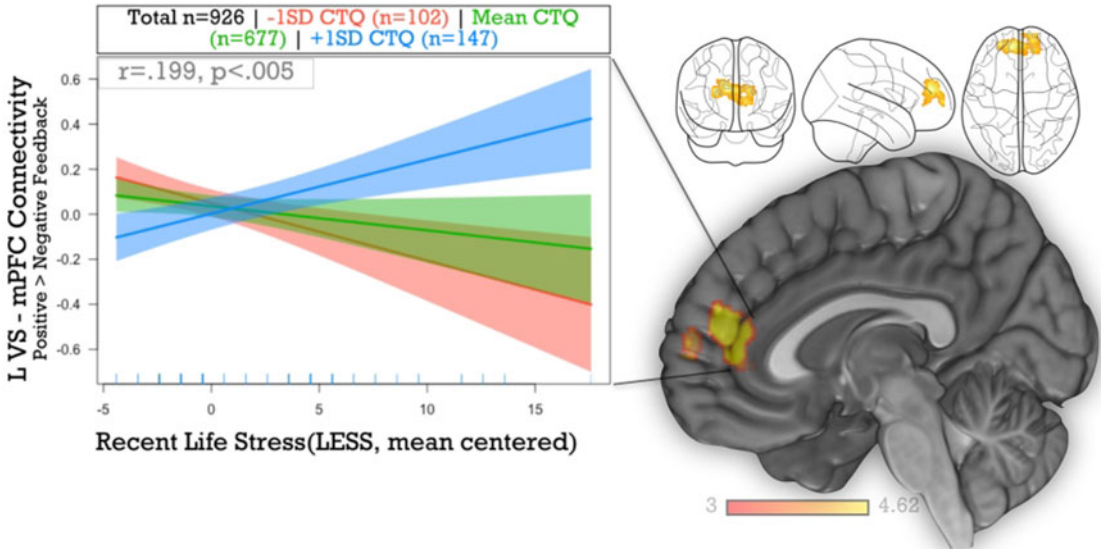

Fig. 1. Whole-brain regression analyses indicated that the interaction of maltreatment and recent life stress was related to heightened left VS-mPFC task-dependent coupling for positive > negative feedback. On the right side of the figure, this mPFC cluster is shown (bottom: surface rendering; top: 'glass-brain' representation). The left side of the figure depicts this interaction, with recent life stress graphed on the horizontal axis and left VS-mPFC coupling on the vertical axis. Levels of maltreatment are also shown, with lower (red), mean (green), and higher (blue) CTQ scores depicted in the figure.

and more recent life stress. Similarly, no other regions emerged in PPI analyses focused on maltreatment or more recent life stress in isolation. We also completed analyses focused on the interaction between categorical cutoffs for the CTQ and more recent life stress. These results were similar to models using continuous measures of the CTQ, and are noted in our online Supplementary Materials.

Given past work focused on corticostriatal circuitry and mood dysregulation, we assessed relations between VS-mPFC connectivity and internalizing symptoms as assessed by the MASQ. As predicted, we found a significant association between left VS-mPFC functional connectivity and total scores on the MASQ ($\beta = 0.089$, $p = 0.006$, Fig. 2). Greater coupling between these brain regions was related to higher self-reported depression and anxiety. This relation remained significant when controlling for DMS-IV diagnosis ($\beta = 0.093$, $p < 0.005$). Of note, PPI analyses using the right VS as a seed yielded similar results for both relations with stress and internalizing symptomatology. We also completed analyses with task-based activation levels for the VS and mPFC, these analyses are detailed in our online Supplementary Materials.

Statistical mediation

After finding the associations reported above, we next investigated whether individual differences in reward-related task-dependent VS-mPFC functional connectivity mediated the effects of stress exposure on internalizing symptomatology. Linear regression models indicated that the interaction of maltreatment and stress related to internalizing symptomatology ($\beta = 0.0827$, $p = 0.01$). When differences in VS-mPFC connectivity were entered into this model, the relation between stress exposure and internalizing symptomatology fell to $\beta = 0.0697$, $p = 0.03$ (covariates: age; sex). In support of our principal hypothesis, nonparametric bootstrapped mediation models indicated VS-mPFC functional connectivity explained 10.3% of the association between stress exposure and internalizing symptomatology (variance mediated = 10.3%, 95% CI = 0.6–36%, $p = 0.03$; Fig. 3).

Valence specificity and reward-related functional connectivity

While our primary analyses focused on functional connectivity related to positive > negative feedback, we also completed exploratory analyses focused on positive (or negative) feedback > control

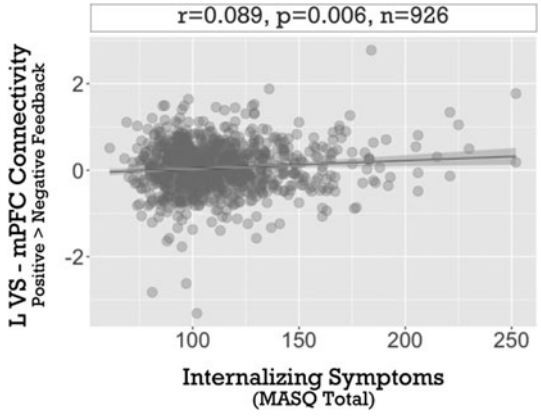

Fig. 2. This scatterplot depicts the relation between internalizing symptomatology and left VS-mPFC task-dependent coupling for positive > negative feedback. With greater levels of connectivity, higher levels of internalizing symptomatology were reported.

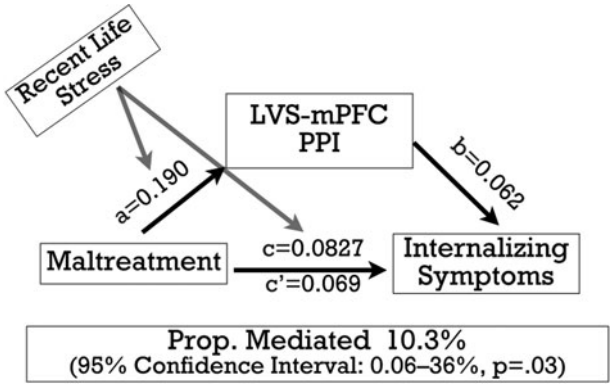

Fig. 3. Our moderated mediation statistical framework is shown in this figure. We examined whether maltreatment (as assessed by the CTQ) was associated with internalizing symptoms (as assessed by the MASQ) in the context of recent life stress (as measured by the LESS). When differences in VS-mPFC connectivity were entered into this model, the relation between stress exposure and internalizing symptoms was significantly reduced. Nonparametric bootstrapped models indicated that this VS-mPFC connectivity mediated 10.3% of this association.

trials to better understand whether the differences observed were potentially driven by responses to one valence of feedback. Looking at positive feedback > control trials, we found that the interaction of maltreatment and more recent life stress was related to greater VS-mPFC connectivity for individuals exposed to maltreatment and stress later in development ($\beta = 0.1$, $p < 0.005$). In contrast, stress exposure was not related to VS-mPFC connectivity for negative feedback > control trials ($\beta = -0.008$, $p = 0.81$). Using a nonindependent correlation calculator, we found these two associations were significantly different from one another ($t = 6.13$; $p < 0.005$; Fig. 4). Such a pattern of results suggested that it is functional connectivity during positive feedback that might be particularly impacted by the interaction of maltreatment and more recent life stress. We also examined relations with specific internalizing symptomatology (e.g. somatic symptoms, positive affect, and interpersonal relations) and valence specific reward-related connectivity. Briefly, we found VS-mPFC connectivity for positive feedback > control blocks was related to the positive affect subscale of the CES-D ($\beta = 0.068$, $p = 0.03$) and the anhedonia subscale of the MASQ ($\beta = 0.076$, $p = 0.02$). No other significant relations emerged between positive feedback > control blocks and CES-D or MASQ subscales. In addition, no significant relations emerged between any CES-D or MASQ subscales and VS-mPFC connectivity for negative feedback > control blocks (see online Supplementary Materials for details).

Additional analyses ruling out potential third factors

To rule out that our findings were not driven by alternative factors, such as early socioeconomic status or general cognitive ability, we constructed additional regression models controlling for these variables. As noted in our online Supplementary Materials, our primary results were not impacted by these controls and yielded similar results to unadjusted models for VS-mPFC connectivity. Full details of these and related analyses are noted in our online Supplementary Materials.

Discussion

Our analyses demonstrate that higher levels of recent life stress, in the context of childhood maltreatment, are related to heightened

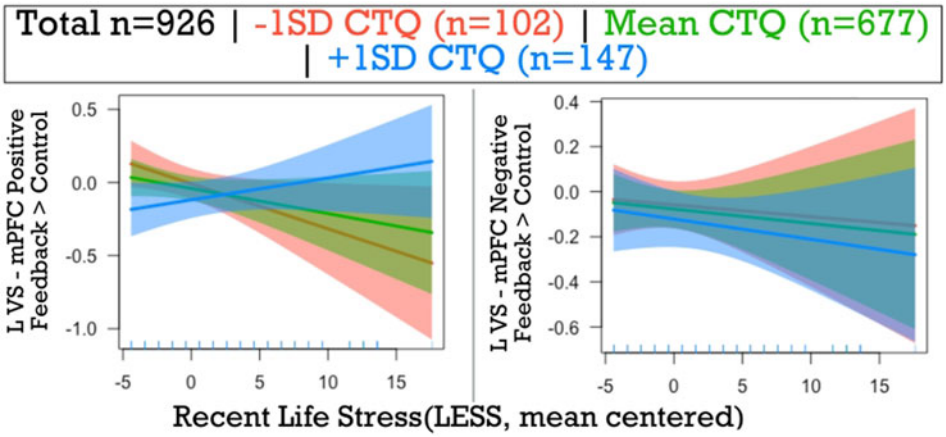

Fig. 4. We completed exploratory analyses focused on positive (or negative) feedback > control trials and the interaction of maltreatment and recent life stress. For both figures, recent life stress is graphed on the horizontal axis and left VS-mPFC coupling on the vertical axis. Levels of maltreatment are also shown, with lower (red), mean (green), and higher (blue) levels depicted in the figure. On the left side, the VS-mPFC coupling is during positive feedback > control trials, while the right side shows coupling for negative feedback > control trials. Interaction of maltreatment and more recent life stress was related to greater VS-mPFC connectivity for individuals exposed to maltreatment, and also stress later in development ($\beta = 0.1$, $p < 0.005$; left side). These stress exposures were not related to VS-mPFC connectivity for negative feedback > control trials ($\beta = -0.008$, $p = 0.81$).

VS-mPFC connectivity for positive > negative feedback. This elevated coupling was associated with greater reports of depression and anxiety. Furthermore, using a moderated mediation approach, we found that this corticostriatal circuit connectivity (for positive > negative feedback) partially explained links between stress and internalizing symptomatology. Collectively, our results suggest an important role for corticostriatal connectivity in understanding connections between stress exposure and mood dysregulation.

Our results connect to past work focused on 'stress sensitization'. There has been evidence that more recent life stress, following child maltreatment, precipitates greater subsequent increase in symptoms of anxiety and depression as well as full-blown clinical disorders (McLaughlin *et al.* 2010). The enhanced VS-mPFC connectivity that we reported here may be a biomarker of this vulnerability. Additional work is, however, needed to validate this idea, as our study design cannot truly speak to these effects and different forms of stress may be correlated. We do, however, find similar connections between neurobiology, stress exposure, and internalizing symptoms if we complete analyses where the interdependence of stress is minimized through regression residuals (see our online Supplementary Materials). Looking longitudinally or attempting to connect reward neurobiology to physiological reactions to acute stress (e.g. blood pressure) may provide greater clarity and increase evidence of biomarkers of 'stress sensitization'.

More generally, our findings contribute to the understanding of how functional connectivity of corticostriatal circuitry maps onto mood and anxiety. While our group has previously examined task-based reactivity in the corticostriatal circuitry, this is the first report from the DNS examining corticostriatal connectivity. We found that relatively increased VS-mPFC functional connectivity for positive > negative feedback is related to higher self-reported depression and anxiety. These results parallel recent work finding that individuals with anhedonia exhibit hyperconnectivity between the VS and mPFC (Wang *et al.* 2016). Similarly, our findings connect to work by Admon & Pizzagalli (2015*a*) noting mPFC activity was continually driving fluctuations in the VS for depressed individuals.

Our findings also connect with earlier work focused on neural circuitry, stress exposure, and internalizing symptomatology, and also raise new questions. A number of groups have reported lower VS activity during the processing of rewards in individuals exposed to early adversity (Goff *et al.* 2013; Hanson *et al.* 2015*a*, 2016), as well as more contemporaneous life stress (Nikolova *et al.* 2012). In past reports, this blunted VS activity to reward is associated with increased risk for depression and anhedonia in individuals exposed to stress (Nikolova *et al.* 2012; Corral-Frías *et al.* 2015). Interestingly, and in accordance with Nikolova *et al.* (2012), as well as Corral-Frías *et al.* (2015), we did not see a main effect of early adversity on VS activity (as noted in our online Supplementary Materials). The relations between neural activity, stress exposure, and psychopathology are likely more complex, suggesting subtypes of individuals exhibiting these neural patterns. For example, Corral-Frías *et al.* (2015) found that VS task-based reactivity moderated the relationship between early life stress and anhedonic symptoms of depression.

Of note, recent reports have found heightened mPFC activity when processing reward or experiencing social exclusion, in adolescents and young adults with higher levels of child adversity (Van Harmelen *et al.* 2014; Romens *et al.* 2015), as well as adolescents and adults with depression (Forbes & Dahl, 2012). Preclinical research supports these observations by linking heightened activity in the mPFC with learned helplessness and other depression-like behavioral deficits after exposure to stress (Kumar *et al.* 2014; Wang *et al.* 2014). Surprisingly, we found the interaction of early and more recent stress was related to lower levels of task-related activity in the mPFC (again, as noted in our online Supplementary Materials). The specific subdivision of the PFC may be different than past reports or these results could speak to the heterogeneity in individuals exposed to early adversity. It is likely that there may be unique neural profiles underlying distinctive deleterious effects of adversity. Individuals exposed to early adversity may show differences in task-based activity in the VS, task-based activity in the mPFC, task-based VS-mPFC connectivity, or combinations of these neural phenotypes. A great deal of work is needed to interrogate how individuals with each of these neural patterns may differ in forms of psychopathology, as well as psychosocial risk factors connected to psychopathology (e.g. detrimental emotion processing and regulation strategies). We hope to examine these patterns in the future work with the DNS and other large neuroimaging samples.

Thinking about the clinical relevance of our results, our effects are modest in magnitude, with neurobiology only explaining a small amount of variance in clinical measures. Given recent evidence of multiple neurophysiological subtypes of depression

(Drysdale *et al.* 2017), this fact is perhaps not surprising. Assessment of multiple neurobiological systems during different tasks (e.g. emotion reactivity, and reward reactivity) would likely improve the amount of variance explained, further expanding clinical relevance. One open, related question is what are the psychological processes underlying the neurobiology, central to our results? First to localize our findings, the strongest relations were seen between the VS and more anterior portions of the rostral mPFC, near Brodmann Areas 9 and 32. Work in basic cognitive neuroscience has found these regions relate to the processing of self-relevant feedback and the integration of this information into one's self-concept (Amodio & Frith, 2006). For example, assessment of one's own personality traits has been linked to activity in this portion of the mPFC (Northoff & Hayes, 2011). Many research groups have noted that this area is also important for attending to one's own emotions and mental states [*v.* those of other agents (Gilbert *et al.* 2006)]. Individuals who have been exposed to multiple forms of stress, as well as those with mood dysregulation, may have difficulty integrating feedback, particularly positive feedback, into their self-concept. As such, targeted assessment of self-related processing and integration of self-relevant positive feedback will be an important concept to richly measure stress exposure.

While we believe our results are important, our work is not without limitations. First, our study sample of generally high functioning and relatively resilient university students is not representative of the general population. Yet, we observed significant associations between stress exposure, brain function, and behavior. Our work therefore likely underrepresents the interactive effects of stress. Second, our measure of maltreatment, the CTQ, does not richly assess all the factors of this adversity likely to influence outcomes. Information about the subtype of maltreatment suffered, severity, frequency/chronicity, and other factors is important to consider moving forward. Future work responsive to these limitations could further clarify individual differences in neurobiological and psychological development. Third and related, there may be biases in the CTQ and other retrospective measures of maltreatment (Reuben *et al.* 2016). It will be important to also investigate the effects of contemporaneous stress exposure in samples with documented maltreatment. Finally, the experimental paradigm employed here assayed only one facet of reward processing. Work has noted that such processing is a complex, nonunitary phenomenon (Berridge & Robinson, 2003). Future work focused on reward anticipation, modulation, and other components of reward processing may aid in understanding different forms of stress exposure and/or connections with psychopathology.

These limitations notwithstanding, our results provide initial evidence that multiple forms of stress exposure interact to impact neural circuitry supporting reward processing. While previous investigations have had modest sample sizes and have only focused on stress during one developmental epoch (early maltreatment; more recent life stress), we were able to leverage our large sample size to understand interactions between different forms of stress. More broadly, our findings should encourage future research to consider the complex relationships between cumulative stress exposure and reward-related brain function in establishing novel strategies to predict, prevent, and treat stress-related psychopathology.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717003348

Acknowledgements. We would like to thank Spenser Radtke for help with data collection.

This work was supported by National Institute on Drug Abuse Grants R01DA033369 and R01DA031579 (to A.R.H.), Postdoctoral Fellowship Grant P30DA023026 provided by the National Institute on Drug Abuse through the Center for the Study of Adolescent Risk and Resilience (to J.L.H.), and Postdoctoral Fellowship Grant T32HD0737625 provided by the National Institute of Child Health and Human Development through the Center for Developmental Science, University of North Carolina at Chapel Hill (to J.L.H.).

Declaration of Interest. None.

References

Admon R and Pizzagalli DA (2015*a*). Corticostriatal pathways contribute to the natural time course of positive mood. *Nature Communications* **6**, 10065.

Admon R and Pizzagalli DA (2015*b*). Dysfunctional reward processing in depression. *Current Opinion in Psychology* **4**, 114–118.

Admon R, Nickerson LD, Dillon DG, Holmes AJ, Bogdan R, Kumar P, Dougherty DD, Iosifescu DV, Mischoulon D, Fava M and Pizzagalli DA (2014). Dissociable cortico-striatal connectivity abnormalities in major depression in response to monetary gains and penalties. *Psychological Medicine* **45**, 121–131.

Amodio DM and Frith CD (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience* **7**, 268–277.

Bernstein D, Handelsman L, Foote J and Lovejoy M (1995). Initial reliability and validity of the childhood trauma interview: a new multidimensional measure of childhood interpersonal trauma. *American Journal of Psychiatry* **152**, 1329–1335.

Bernstein DP, Ahluvalia T, Pogge D and Handelsman L (1997). Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. *Journal of the American Academy of Child and Adolescent Psychiatry* **36**, 340–348.

Berridge KC and Robinson TE (2003). Parsing reward. *Trends in Neurosciences* **26**, 507–513.

Bogdan R, Perlis RH, Fagerness J and Pizzagalli DA (2010). The impact of mineralocorticoid receptor ISO/VAL genotype (rs5522) and stress on reward learning. *Genes, Brain and Behavior* **9**, 658–667.

Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ and Anda RF (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. *Journal of Affective Disorders* **82**, 217–225.

Clark LA and Watson D (1991). Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology* **100**, 316–336.

Clements K and Turpin G (1996). The life events scale for students: validation for use with British samples. *Personality and Individual Differences* **20**, 747–751.

Corral-Frías NS, Nikolova YS, Michalski LJ, Baranger DAA, Hariri AR and Bogdan R (2015). Stress-related anhedonia is associated with ventral striatum reactivity to reward and transdiagnostic psychiatric symptomatology. *Psychological Medicine* **45**, 2605–2617.

Covault J, Tennen H, Armeli S, Conner TS, Herman AI, Cillessen AHN and Kranzler HR (2007). Interactive effects of the serotonin transporter 5-HTTLPR polymorphism and stressful life events on college student drinking and drug use. *Biological Psychiatry* **61**, 609–616.

Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, Poulton R and Caspi A (2009). Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Archives of Pediatrics and Adolescent Medicine* **163**, 1135–1143.

Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, Domschke K, Hohoff C, Ohrmann P, Bauer J, Lindner C, Postert C, Konrad C, Arolt V, Heindel W, Suslow T and Kugel H (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological Psychiatry* **71**, 286–293.

Delgado MR, Miller MM, Inati S and Phelps EA (2005). An fMRI study of reward-related probability learning. *NeuroImage* **24**, 862–873.

Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, Fetcho RN, Zebley B, Oathes DJ, Etkin A, Schatzberg AF, Sudheimer K, Keller J, Mayberg HS, Gunning FM, Alexopoulos GS, Fox MD, Pascual-Leone A, Voss HU, Casey BJ, Dubin MJ and Liston C (2017). Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine* **23**, 28–38.

Espejo EP, Hammen CL, Connolly NP, Brennan PA, Najman JM and Bor W (2007). Stress sensitization and adolescent depressive severity as a function of childhood adversity: a link to anxiety disorders. *Journal of Abnormal Child Psychology* **35**, 287–299.

First MB, Spitzer RL, Gibbon M and Williams J (1996). *Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Non-patient Edition*. New York State Psychiatric Institute: New York, NY.

Forbes EE and Dahl RE (2012) Research review: altered reward function in adolescent depression: what, when and how? *Journal of Child Psychology and Psychiatry* **53**, 3–15.

Forbes EE, Olino TM, Ryan ND, Birmaher B, Axelson D, Moyles DL and Dahl RE (2010). Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. *Cognitive, Affective and Behavioral Neuroscience* **10**, 107–118.

Gilbert SJ, Spengler S, Simons JS, Steele JD, Lawrie SM, Frith CD and Burgess PW (2006). Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. *Journal of Cognitive Neuroscience* **18**, 932–948.

Glaser J-P, van Os J, Portegijs PJM and Myin-Germeys I (2006). Childhood trauma and emotional reactivity to daily life stress in adult frequent attenders of general practitioners. *Journal of Psychosomatic Research* **61**, 229–236.

Goff B, Gee DG, Telzer EH, Humphreys KL, Gabard-Durnam L, Flannery J and Tottenham N (2013). Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. *Neuroscience* **249**, 129–138.

Gooding HC, Milliren CE, Austin SB, Sheridan MA and McLaughlin KA (2016). Child abuse, resting blood pressure, and blood pressure reactivity to psychosocial stress. *Journal of Pediatric Psychology* **41**, 5–14.

Gorka AX, Hanson JL, Radtke SR and Hariri AR (2014). Reduced hippocampal and medial prefrontal gray matter mediate the association between reported childhood maltreatment and trait anxiety in adulthood and predict sensitivity to future life stress. *Biology of Mood and Anxiety Disorders* **4**, 12.

Green JG, McLaughlin KA, Berglund PA, Gruber MJ, Sampson NA, Zaslavsky AM and Kessler RC (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. *Archives of General Psychiatry* **67**, 113–123.

Haber SN and Knutson B (2009). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* **35**, 4–26.

Haglund MEM, Nestadt PS, Cooper NS, Southwick SM and Charney DS (2007). Psychobiological mechanisms of resilience: relevance to prevention and treatment of stress-related psychopathology. *Development and Psychopathology* **19**, 889–920.

Hammen C, Henry R and Daley SE (2000). Depression and sensitization to stressors among young women as a function of childhood adversity. *Journal of Consulting and Clinical Psychology* **68**, 782–787.

Hanson JL, Albert D, Iselin A-MR, Carré JM, Dodge KA and Hariri AR (2016). Cumulative stress in childhood is associated with blunted reward-related brain activity in adulthood. *Social Cognitive and Affective Neuroscience* **11**, 405–412.

Hanson JL, Hariri AR and Williamson DE (2015*a*). Blunted ventral striatum development in adolescence reflects emotional neglect and predicts depressive symptoms. *Biological Psychiatry* **78**, 598–605.

Hanson JL, Knodt AR, Brigidi BD and Hariri AR (2015*b*). Lower structural integrity of the uncinate fasciculus is associated with a history of child maltreatment and future psychological vulnerability to stress. *Development and Psychopathology* **27**, 1611–1619.

Harkness KL, Bruce AE and Lumley MN (2006). The role of childhood abuse and neglect in the sensitization to stressful life events in adolescent depression. *Journal of Abnormal Psychology* **115**, 730–741.

Heim C, Newport DJ, Mletzko T, Miller AH and Nemeroff CB (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology* **33**, 693–710.

Herts KL, McLaughlin KA and Hatzenbuehler ML (2012). Emotion dysregulation as a mechanism linking stress exposure to adolescent aggressive behavior. *Journal of Abnormal Child Psychology* **40**, 1111–1122.

Kim J and Cicchetti D (2010). Longitudinal pathways linking child maltreatment, emotion regulation, peer relations, and psychopathology. *Journal of Child Psychology and Psychiatry* **51**, 706–716.

Kumar P, Slavich GM, Berghorst LH, Treadway MT, Brooks NH, Dutra SJ, Greve DN, Donovan AO, Bleil ME, Maninger N and Pizzagalli DA (2015). Perceived life stress exposure modulates reward-related medial prefrontal cortex responses to acute stress in depression. *Journal of Affective Disorders* **180**, 104–111.

Kumar S, Hultman R, Hughes D, Michel N, Katz BM and Dzirasa K (2014). Prefrontal cortex reactivity underlies trait vulnerability to chronic social defeat stress. *Nature Communications* **5**, 4537.

Leitzke BT, Hilt LM and Pollak SD (2015). Maltreated youth display a blunted blood pressure response to an acute interpersonal stressor. *Journal of Clinical Child and Adolescent Psychology* **44**, 305–313.

McLaren DG, Ries ML, Xu G and Johnson SC (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *NeuroImage* **61**, 1277–1286.

McLaughlin KA, Conron KJ, Koenen KC and Gilman SE (2010). Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. *Psychological Medicine* **40**, 1647–1658.

McLaughlin KA, Koenen KC, Hill ED, Petukhova M, Sampson NA, Zaslavsky AM and Kessler RC (2013). Trauma exposure and posttraumatic stress disorder in a national sample of adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry* **52**, 815–830.e14.

Mies GW, Van den Berg I, Franken IHA, Smits M, van der Molen MW and Van der Veen FM (2013). Neurophysiological correlates of anhedonia in feedback processing. *Frontiers in Human Neuroscience* **7**, 96.

Morgan JK, Shaw DS and Forbes EE (2014). Maternal depression and warmth during childhood predict age 20 neural response to reward. *Journal of the American Academy of Child and Adolescent Psychiatry* **53**, 108–117.e1.

Nestler EJ and Carlezon WA Jr (2006). The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry* **59**, 1151–1159.

Nikolova YS, Bogdan R, Brigidi BD and Hariri AR (2012). Ventral striatum reactivity to reward and recent life stress interact to predict positive affect. *Biological Psychiatry* **72**, 157–163.

Nikolova YS, Knodt AR, Radtke SR and Hariri AR (2016). Divergent responses of the amygdala and ventral striatum predict stress-related problem drinking in young adults: possible differential markers of affective and impulsive pathways of risk for alcohol use disorder. *Molecular Psychiatry* **21**, 348–356.

Northoff G and Hayes DJ (2011). Is our self nothing but reward? *Biological Psychiatry* **69**, 1019–1025.

O'Reilly JX, Woolrich MW, Behrens TEJ, Smith SM and Johansen-Berg H (2012). Tools of the trade: psychophysiological interactions and functional connectivity. *Social Cognitive and Affective Neuroscience* **7**, 604–609.

Quevedo K, Ng R, Scott H, Kodavaganti S, Smyda G, Diwadkar V and Phillips M (2017). Ventral striatum functional connectivity during rewards and losses and symptomatology in depressed patients. *Biological Psychology* **123**, 62–73.

Reuben A, Moffitt TE, Caspi A, Belsky DW, Harrington H, Schroeder F, Hogan S, Ramrakha S, Poulton R, Danese A (2016). Lest we forget: comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. *Journal of Child Psychology and Psychiatry* **57**, 1103–1112.

Richard JM, Castro DC, DiFeliceantonio AG, Robinson MJF and Berridge KC (2013). Mapping brain circuits of reward and motivation: in the footsteps of Ann Kelley. *Neuroscience and Biobehavioral Reviews* **37**, 1919–1931.

Romens SE, Casement MD, McAloon R, Keenan K, Hipwell AE, Guyer AE and Forbes EE (2015). Adolescent girls' neural response to reward mediates the relation between childhood financial disadvantage and depression. *Journal of Child Psychology and Psychiatry* **56**, 1177–1184.

Russo SJ, Murrough JW, Han M-H, Charney DS and Nestler EJ (2012). Neurobiology of resilience. *Nature Neuroscience* **15**, 1475–1484.

Scher CD, Stein MB, Asmundson GJ, McCreary DR and Forde DR (2001). The childhood trauma questionnaire in a community sample: psychometric properties and normative data. *Journal of Traumatic Stress* **14**, 843–857.

Shapero BG, Black SK, Liu RT, Klugman J, Bender RE, Abramson LY and Alloy LB (2013). Stressful life events and depression symptoms: the effect of childhood emotional abuse on stress reactivity. *Journal of Clinical Psychology* **70**, 209–223.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R and Dunbar GC (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* **59**, 22–33.

Shepherd GMG (2013). Corticostriatal connectivity and its role in disease. *Nature Reviews Neuroscience* **14**, 278–291.

Smoski MJ, Felder J, Bizzell J, Green SR, Ernst M, Lynch TR and Dichter GS (2009). fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *Journal of Affective Disorders* **118**, 69–78.

Swartz JR, Knodt AR, Radtke SR and Hariri AR (2015). A neural biomarker of psychological vulnerability to future life stress. *Neuron* **85**, 505–511.

Tarullo AR and Gunnar MR (2006). Child maltreatment and the developing HPA axis. *Hormones and Behavior* **50**, 632–639.

Tricomi EM, Delgado MR and Fiez JA (2004). Modulation of caudate activity by action contingency. *Neuron* **41**, 281–292.

Van Harmelen A-L, Hauber K, Gunther Moor B, Spinhoven P, Boon AE, Crone EA and Elzinga BM (2014). Childhood emotional maltreatment severity is associated with dorsal medial prefrontal cortex responsivity to social exclusion in young adults. *PLoS One* **9**, e85107.

Wang M, Perova Z, Arenkiel BR and Li B (2014). Synaptic modifications in the medial prefrontal cortex in susceptibility and resilience to stress. *Journal of Neuroscience* **34**, 7485–7492.

Wang Y, Liu WH, Li Z, Wei XH, Jiang XQ, Geng FL, Zou LQ, Lui SSY, Cheung EFC, Pantelis C and Chan RCK (2016). Altered corticostriatal functional connectivity in individuals with high social anhedonia. *Psychological Medicine* **46**, 125–135.

Wildeman C, Emanuel N, Leventhal JM, Putnam-Hornstein E, Waldfogel J and Lee H (2014). The prevalence of confirmed maltreatment among US children, 2004 to 2011. *JAMA Pediatrics* **168**, 706–713.