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Neural mechanisms of acute stress and trait anxiety in adolescents

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ABSTRACT

Adolescence is a critical period of heightened stress sensitivity and elevated vulnerability for developing mental illness, suggesting a possible association between stress exposure and the etiology of psychiatric disorders. In adults, aberrant neurobiological responses to acute stress relate to anxiety symptoms, yet less is known about the neural stress response in adolescents and how it relates to biological and psychological variables. Here we characterize the neurobiology of stress response in adolescents using multiple modalities, including neuroimaging, subjective stress ratings, heart rate, and cortisol data. We evaluated stress response in adolescents using the Montreal Imaging Stress Task (MIST), an acute psychosocial stressor commonly administered in adult functional magnetic resonance imaging (fMRI) studies but not previously utilized with this population. FMRI data were acquired from 101 adolescents (44 female; 9–16 years) exhibiting varied trait anxiety severity.

The MIST elicited decreased high-frequency heart rate variability and increased heart rate, subjective stress and cortisol. Whole-brain analyses comparing fMRI activity during experimental versus control MIST conditions revealed stress-related activation in regions including the anterior insula, dorsal anterior cingulate cortex, and dorsolateral prefrontal cortex and deactivations in the hippocampus, ventral striatum, and putamen. Region of Interest analyses found that during acute stress (a) hippocampal deactivation corresponded to heightened cortisol release, (b) trait anxiety was associated with increased hippocampal and ventral striatum activation and decreased putamen activity, and (c) males exhibited greater putamen deactivation than females. These results provide novel evidence that the MIST is an effective stressor for adolescents. Associations between the neural acute stress response, other biological factors, and trait anxiety highlight the importance of these neurobiological mechanisms in understanding anxiety disorders.

1. Introduction

Stress exposure is a critical factor in the etiology of mental illness (Romeo, 2017), and adolescents experience increased exposure to daily stressors, heightened biological stress responses (Romeo, 2013; Seiffge-krenke, 2000), and elevated vulnerability for developing psychiatric conditions; half of all lifetime cases of mental illness emerge before individuals turn 14 years old and three quarters occur before age 24 (Kessler et al., 2005). In particular, nearly one third of adolescents have an anxiety disorder, and these adolescents are significantly more likely to present psychiatric conditions in adulthood (Doering et al., 2019; Merikangas et al., 2010). Fronto-limbic cortical regions involved in stress regulation, and known to exhibit abnormal activation in individuals with anxiety disorders, undergo critical neuromaturation during adolescence (Hariri, 2015; National Academies of Sciences, 2019). However, little is known about the neural acute stress response (ASR) in this age range and how it relates to the onset of anxiety disorders (Colich et al., 2015; National Academies of Sciences, 2019; Romeo, 2017; Tottenham and Galván, 2016). Elucidating acute stress neural response mechanisms in adolescents is a critical step in understanding connections between stress, neural and endocrine systems, and anxiety.

Abbreviations: ASR, acute stress response.

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Acute stressors activate the autonomic nervous system and hypothalamic–pituitaryadrenal (HPA) axis, resulting in biological changes such as reduced high-frequency heart rate variability (HF-HRV), increased heart rate (HR), cortisol release, and alterations in neural activity (Li et al., 2013; Noack et al., 2019). HF-HRV represents autonomic nervous system regulation of cardiac vagal tone, reflecting parasympathetic activation (Ernst, 2017; Seddon et al., 2020). Decreased HF-HRV is frequently used as a biomarker of ASR, and adolescents with anxiety exhibit reduced HF-HRV (Paniccia et al., 2017). The HPA axis ASR relies on hormonal communication, which is slower relative to the autonomic response and drives delayed release of cortisol in response to stress. Downstream effects of cortisol release prepare the body for danger through increasing blood glucose levels to provide energy for "flight-fight-or-freeze" responses, in addition to influencing activity of immune, cardiovascular, and cognitive systems (Noack et al., 2019; Stephens and Wand, 2012). During adolescence, the HPA axis becomes increasingly reactive to stress, with teenagers exhibiting greater stress-induced cortisol levels than children (Tottenham and Galván, 2016). Studying cortisol release in this population is critical, because in adolescents aberrant cortisol secretion following acute stress, marked by either increased release or blunted reactivity, can predict development of mental illnesses (Colich et al., 2015; Zorn et al., 2017). Furthermore, activation of fronto-limbic regions involved in stress regulation is modulated by cortisol, and neural and endocrine systems undergo major development during adolescence (Tottenham and Galván, 2016). Therefore, it is necessary to study the relationship between neural and hormonal responses to stress to elucidate how neurobiology may drive the onset of anxiety disorders.

Neural substrates of ASR can be evaluated through psychosocial stress tasks during functional magnetic resonance imaging (fMRI) scans which measure stress-related changes in blood oxygen level dependent (BOLD) signaling in the brain. The Montreal Imaging Stress Task (MIST) is a well-validated fMRI task for mapping neural correlates of ASR in healthy adults and clinical populations (Castro et al., 2015; Ming et al., 2017; Noack et al., 2019). The MIST induces increased cortisol and HR, as well as alters activity in neural networks associated with salience detection, cognition, emotional response, and reward (Noack et al., 2019; van Oort et al., 2017). Neural response to the MIST stress condition correlates with anxiety severity in adults, as reflected by increased activity in the medial prefrontal cortex, posterior cingulate cortex (PCC), and insula (Wheelock et al., 2016) during stress. As such, the MIST is particularly valuable for acute stress research related to anxiety. However, no published work has used the MIST with adolescents, and far less is known about the impact of acute stress on neural activation during adolescence. Existing fMRI studies of ASR in adolescents predominantly include older teenagers, do not directly examine neural activation during exposure to an acute stressor, and/or do not collect physiological data (Elsey et al., 2015; Ordaz and Luna, 2012; Tottenham and Galván, 2016; Uy and Galván, 2017). To our knowledge, this is the first study using the MIST with an adolescent population, providing novel insight into ASR in this age range across multiple neurobiological systems.

The goals of this project are to evaluate utility of the MIST as a stressor for adolescents as indexed by subjective, autonomic, and endocrine measures, examine if neural ASR in this age range corresponds to adult findings, and analyze the modulation of neural ASR by sex, age, cortisol, and trait anxiety. Considering current understanding of neural stress circuitry and results of the most relevant MIST studies (Hariri, 2015; Hermans et al., 2014; Lago et al., 2017; Noack et al., 2019; Pruessner et al., 2008), we hypothesize that the MIST will elicit: (a) increased self-reported stress ratings, cortisol, and HR and decreased HF-HRV; (b.1) activation of regions related to salience and cognitive control, including the anterior insula (AI), dorsal anterior cingulate cortex (dACC), and dorsolateral prefrontal cortex (dlPFC), (b.2) increased activity in the PCC and precuneus due to their roles in self-evaluation and social cognition, (b.3) activation of limbic areas implicated in emotional responses including the amygdala and hippocampus, and (b.4) deactivation in reward system regions including the ventral striatum (VS), putamen, ventromedial prefrontal cortex (vmPFC), and orbitofrontal cortex (OFC); (c) differential fMRI activation related to cortisol response and anxiety severity. While this analysis of the influence of cortisol and anxiety on neural ASR is exploratory and lacks a specific hypothesis, examining these relationships may provide critical insight into the enhanced biological vulnerability of these systems during adolescence and the phenomena underlying the etiology of anxiety disorders.

2. Methods and materials

2.1. Participants and clinical measures

106 adolescents aged 9–16 years completed the MIST. After 5 subjects were excluded due to MRI signal dropout, 101 subjects (44 female, age $M = 13.3$, $SD = 2.3$) were included in the final analysis. Participants were recruited using a stratified recruitment strategy to maximize a dimensional range of psychiatric symptomatology in accordance with the Research Domain Criteria (RDoC) framework (Insel et al., 2010). This strategy aimed to produce a heterogenous sample of adolescents with a range of stress-regulation profiles. To allow for this variability, participants were only excluded if they had a neurological disorder, history of head injury, chronic medical condition that could impact stress systems or imaging, lifetime or current DSM-IV-TR Axis I psychotic disorder, current major depressive disorder, post-traumatic stress disorder, bipolar disorder, and/or substance dependence. Legal parents/guardians provided consent and subjects gave assent, and the study was approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill and Duke University.

Trained clinicians assessed presence of DSM-IV Axis I disorders via the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1995) and confirmed diagnoses via electronic health records when applicable. The State-Trait Anxiety Inventory Trait scale (STAIT) (Spielberger, 2010) measured trait anxiety. 45% of the sample met diagnostic criteria for a DSM-IV disorder. Conditions included attention-deficit/hyperactivity disorder (ADHD), generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive–compulsive disorder, and adjustment disorder. 30% of participants were on psychotropics known to impact brain activity (stimulants, non-stimulant ADHD medication, antidepressants, antipsychotics, and 1 case of an anticonvulsant). Further sample demographic information can be found in Table 1.

2.2. Montreal Imaging Stress Task paradigm

The MIST was conducted similarly to existing work studying adults (Khalili-Mahani et al., 2010; Kogler et al., 2015; Pruessner et al., 2008), using a block design with 3 runs of the task, each lasting 6 min. Each run included 3 sets of rest, control, and experimental conditions presented in a semi-randomized order. During rest conditions, participants focused

Table 1
Sample Characteristics.

Characteristic	
Demographics	
Total (N)	101
Sex (% Female)	44%
Age (Years)	13.3 (2.3)
Race (% White)	76%
Diagnosis	
On Medication	30%
DSM-IV Diagnosis	45%
STAIT*	32.8 (6.8)

DSM, Diagnostic and Statistical Manual of Mental Disorders; STAIT, State-Trait Anxiety Inventory – Trait Scale. *for the STAIT N = 97.

on a screen displaying a static task dial image. For control conditions, participants rotated the dial to complete math problems and were told their performance was not being recorded. During experimental conditions, researchers instructed participants to complete the math problems as quickly as possible within the allotted response time window.

The program used for this task was adapted for adolescents from code used for the original computerized MIST (Dedovic et al., 2005) courtesy of Dr. Jens Pruessner. Appropriate starting math difficulty level was assessed by examining subjects' accuracy on a practice MIST run before they entered the scanner. The MIST for adults has 6 levels of difficulty, and during the practice task these adolescents completed problems that had up to a "level 3" difficulty, where the most difficult math problems had the following formats: a/b + c - d = e, a/b - d = e, or a/b - c - d = e (where participants had to solve for e). If participants had below 50% accuracy on the practice task, problem difficulty in the scanner was reduced to a maximum of "level 2" difficulty, where the most difficult problems had the formulas: a × b + c = d, a × b - c = d, or a × b = d (where participants had to solve for d). In the scanner, time per problem in the stress condition was programmed to adjust dynamically between blocks based on subjects' performance to ensure that participant accuracy was low, but the task was not so impossible that they would give up. During each experimental block, the difference between number of correct and incorrect responses a participant made was recorded, and this difference was used to determine task speed; if a participant provided more correct than incorrect responses (greater than 50% correct), time allotted per problem was reduced to make the task harder, but if there were more incorrect responses (less than 50% correct) participants were given more time to complete each question.

For the experimental condition, a stressful rising tone was played during the response window using MRI-compatible headphones to emphasize the importance of answering quickly. After entering their responses, participants were presented with written feedback on their performance ("incorrect," "correct," or "timeout") indicating that it was "recorded." Participants were instructed that the bar at the top of the screen showed their performance relative to others, but in reality a participant could never do better than the average performance, which elicits the "achievement stress" aspect of the MIST. Between each run, experimenters provided negative feedback, telling subjects that their performance was below average and that it was important they try their best during the experimental condition. After the conclusion of the experiment, participants were debriefed about the nature of the questions and informed that the task was designed to induce stress and they actually performed well. Subjects completed resting state scans both before and after the MIST, enabling comparison of cardiac response during the MIST versus HR and HF-HRV at rest. See Fig. S1 for examples of the user interface for the MIST and Fig. S2 for the paradigm timeline for a testing day.

2.3. Heart rate collection and processing

A Biopac pulse oximeter measured HR data, which was converted to interbeat interval format and passed to Kubios HRV software (Niskanen et al., 2004; Tarvainen et al., 2014) for automated artifact correction. A single trained rater inspected accuracy of the selected peaks, and files with abnormal or biologically implausible peaks were manually edited in CardioEdit (Brain Body Center, 2007; Porges and Bohrer, 1990) and rerun in Kubios. Files with greater than 5% artifacts were excluded from analysis. After this quality control process, 78 subjects had usable resting state and MIST heart rate data. HF-HRV was defined within a 0.12–0.4 Hz band, which is an appropriate range for an adolescent population (Cui et al., 2015; McLaughlin et al., 2015), and analyzed in Kubios using fast Fourier transformations.

2.4. Salivary cortisol and subjective stress collection

Five salivary samples were collected in Salivettes to assess the cortisol stress response following a Salimetrics protocol (Salimetrics, 2019). Participants were instructed not to eat or drink 30 min prior to the study to minimize external factors affecting salivary content and flow rate. Samples were collected immediately before (t = 0) and after the MIST (t = 20), 15 min after (t = 35) the conclusion of the stressor, at the conclusion of the scan (t = 55), and 30 min after the scan's completion (t = 85). Self-reported stress ratings were measured at each of the five salivary collection points, during which researchers asked participants to verbally respond to a five-item Likert affect scale, indicating the degree to which they felt: "Stressed, Worried, or Nervous," "Happy, Relaxed, or Comfortable," "Irritated, Annoyed, or Mad," "Sad, Down, or Unhappy," and "Overwhelmed, Unable to Control Things, or Discouraged."

Due to missing salivary samples from participants that either did not complete all runs or had too little saliva to process, we used multiple imputation via the MICE package in R (van Buuren and Groothuis-Oudshoorn, 2011) to give the best estimate of missing cortisol concentrations based on both the sample population average and the individual's cortisol trajectory. Each sample timepoint contained less than 5% missing values, and there were 15 missing samples across all 5 timepoints (reflecting 3% of the total 500 samples), with 13 subjects missing data. This method is widely used in the literature (Graham, 2008; Walker et al., 2010) and is necessary as area under the curve with respect to increase (AUCi) analyses are intolerant of missing data. Because raw cortisol values were skewed and cortisol levels have a circadian rhythm, cortisol values were log transformed and then regressed against collection time. The residuals, representing time of day corrected cortisol concentrations, were then used in subsequent analyses. Salivary cortisol AUCi was calculated using a trapezoidal formula to represent changes in cortisol over time and the sensitivity of response (Pruessner et al., 2003).

2.5. Stress induction statistical analysis

Paired sample t-tests examined changes in HF-HRV and HR during the MIST and differences in subjective stress and cortisol before and after the MIST. HR and HF-HRV during the MIST were compared with their resting state scan values prior to and after the task. While HR was predicted to increase and HF-HRV to decrease during the MIST, both measures were expected to return to baseline levels after stress. Subjective stress ratings given immediately before and after the MIST were compared, whereas to account for the slower time course of the HPA axis response cortisol values before the MIST and 35 min after stressor onset were contrasted. All statistical analyses were run in R v3.6.1 (R Core Team, 2019).

2.6. Imaging procedures

2.6.1. FMRI acquisition

Subjects were scanned on a 3T GE MR750 scanner at the Duke Brain Imaging and Analysis Center. For anatomical images, a 3D fast spoiled-gradient-recalled sequence generated a high-resolution T1-weighted image (TR = 8.2 ms; TE = 3.22 ms; FA, 12°; FOV, 240x240x166 mm^2; matrix size, 256x256x166; slice thickness, 1.0 mm). MIST functional imaging series were collected with an 8-channel head-coil using a spiral-in sensitivity encoding interleaved sequence (TR/TE = 2000/30 ms, flip angle = 60°, field of view = 24 cm, acquisition matrix = 64x64, slice thickness = 4 mm, number of slices = 34). Each functional run began with four discarded acquisitions to allow for steady-state equilibrium of the MR signal.

2.6.2. FMRI preprocessing

Results included in this manuscript come from preprocessing performed using *fMRIPprep* v1.2.4 (Esteban et al., 2019b, 2019a), which is based on *Nipype* 1.1.6 (Gorgolewski et al., 2011, 2017). Each T1-weighted (T1w) volume was corrected for intensity non-uniformity

using N4BiasFieldCorrection v2.1.0 (Tustison et al., 2010) and skull-stripped using *antsBrainExtraction.sh* v2.2.0 (using the OASIS template). Brain surfaces were reconstructed using recon-all from FreeSurfer v6.0.1 (Dale et al., 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (Klein et al., 2017). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template v2009c (Fonov et al., 2009) was performed through nonlinear registration with the *antsRegistration* tool of ANTs v2.2.0 (Avants et al., 2008), using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid, white-matter and gray-matter was performed on the brain-extracted T1w using *fast* (Zhang et al., 2001).

Functional data was slice time corrected using *3dTshift* from AFNI v16.2.07 (Cox, 1996) and motion corrected using *mcflirt* (FSL v5.0.9) (Jenkinson et al., 2002). This was followed by co-registration to the corresponding T1w using boundary-based registration (Greve and Fischl, 2009) with nine degrees of freedom, using *bbregister* (FreeSurfer v6.0.1). Motion correcting transformations, field distortion correcting warp, BOLD-to-T1w transformation and T1w-to-template (MNI) warp were concatenated and applied in a single step using *antsApplyTransforms* (ANTs) using Lanczos interpolation. Physiological noise regressors were extracted applying CompCor (Behzadi et al., 2007). Frame-wise displacement (Power et al., 2014) was calculated for each functional run using the implementation of Nipype. Automatic removal of motion artifacts using independent component analysis (ICA-AROMA (Pruim et al., 2015)) was performed on the preprocessed BOLD on MNI space time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6 mm full-width half-maximum (Pruim et al., 2015). Further processing steps utilized FSL (v5.0.10) fsl_regfilt (Jenkinson et al., 2012) to regress out white matter and cerebrospinal fluid from the global signal.

2.7. Image processing

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) v6.00 (Jenkinson et al., 2002; Jenkinson and Smith, 2001). The following pre-statistics processing was applied: non-brain removal using BET (Smith, 2002), highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s), and prewhitening. Second-level analyses combined MIST runs within each subject. Group-level thresholding was carried out using a gray matter mask and FSL's randomize for non-parametric permutations with 5000 permutations and a voxel-wise FWE-corrected threshold of $p < .05$ (Winkler et al., 2014).

2.8. Whole brain voxel-wise analysis

To more comprehensively examine fMRI activation during the MIST in adolescents and determine whether regions of activation mapped onto the adult activation patterns, we conducted a whole-brain analysis. The contrasts of this third-level analysis included identification of regions showing (a) greater activation during the experimental condition (EC) compared to the control condition (CC), and (b) less activation in the EC compared to the CC.

2.9. Region of Interest analysis

To probe neural ASR and its relationships with physiological and psychological measures, 11 5 mm spherical Regions of Interest (ROIs) were selected for analysis based on existing acute stress literature (Dedovic et al., 2014; Noack et al., 2019; Pruessner et al., 2008). Coordinates of these ROIs were defined by the center of mass coordinates of corresponding clusters in the whole-brain analysis. For the purposes of this paper, regions were considered to be "activated" during stress if they exhibited greater mean BOLD signal during the EC than during the CC and "deactivated" during stress if CC mean BOLD signal was greater than during the EC. 97 subjects with complete neural, cortisol, and STAIT data were included in the ROI analysis. Using the R *robustbase* library (Maechler et al., 2020), 11 robust linear models using Bonferroni corrections for multiple comparisons were run to characterize the relationship between fMRI activity in each ROI and sex, age, cortisol, and trait anxiety. Because 30% of participants were on some form of psychotropic medication known to impact neural activity, to determine if medication may have significantly impacted ROI activation, these 11 robust linear models were repeated in supplementary analyses which included medication status as an additional binary variable.

3. Results

3.1. Subjective, autonomic, and endocrine stress response

Standard measures used to determine stressor efficacy – including self-reported stress rating, heart rate changes, and cortisol release – suggest that the MIST elicited a stress response in our adolescent sample consistent with current literature (Noack et al., 2019). Subjects self-reported higher stress ratings directly after completing the MIST than they did immediately before ($t(96) = 8.16$, $p < .001$) (Fig. 1A). In accordance with the expected heart rate response to acute stress, average MIST HR was greater than resting state HR both before ($t(77) = 7.21$, $p < .001$) and after ($t(73) = 6.12$, $p < .001$) the MIST (Fig. 1B), while average MIST HF-HRV was less than resting state HF-HRV both before ($t(77) = 2.55$, $p = .013$) and after ($t(73) = 2.16$, $p = .034$) (Fig. 1C). As anticipated, post-MIST peak cortisol was greater than pre-MIST ($t(99) = -2.12$, $p = .037$) across all subjects (Fig. 1D).

3.2. FMRI results

3.2.1. Stress-induced whole brain activation

Whole-brain analysis identified 14 clusters that were more activated during the MIST EC as compared to the CC, including the right precuneus, right dACC, right AI, and right dlPFC (FWE-corrected $p < .05$, Fig. 2A, Table 2A). 9 clusters were less active in the EC relative to the CC, including the left vmPFC, both the left and right VS, left PCC, left OFC, right putamen, and left hippocampus (FWE-corrected $p < .05$, Fig. 2B, Table 2B).

3.2.2. Associations between ROI activation and sex, age, cortisol release, and anxiety

Cortisol AUCi was negatively correlated with left hippocampal activity during stress ($B = -0.65$, $t(92) = -3.50$, $p < .001$, Fig. 3A), signifying that greater release of cortisol after stress was associated with stronger hippocampal deactivation. There was a main effect of trait anxiety during the MIST such that during the EC as compared to the CC, higher trait anxiety was associated with increased left hippocampal ($B = 0.45$, $t(92) = 2.93$, $p = .004$, Fig. 3B) and left VS ($B = 0.82$, $t(92) = 3.51$, $p < .001$, Fig. 3C) activity and decreased activation of the right putamen ($B = -0.89$, $t(92) = -5.41$, $p < .001$, Fig. 3D). Males exhibited less right putamen activity ($M = -6.62$, $SD = 11.8$, $N = 55$) during stress than females ($M = -5.73$, $SD = 11.1$, $N = 42$) ($B = 8.98$, $t = 4.28$, $p < .001$, Fig. 3E) indicating the putamen was more deactivated during stress in males. No other relationships between fMRI activation and sex, age, cortisol, and anxiety were evident (Table S1). Importantly, supplementary models that included use of psychotropic medication as an additional variable did not indicate a significant relationship between medication status and activation of any ROI (Table S2).

4. Discussion

To our knowledge, this is the first study to investigate the neurobiological ASR in adolescents using the MIST. Our results demonstrate that the MIST is an effective stressor for adolescents, as indicated by

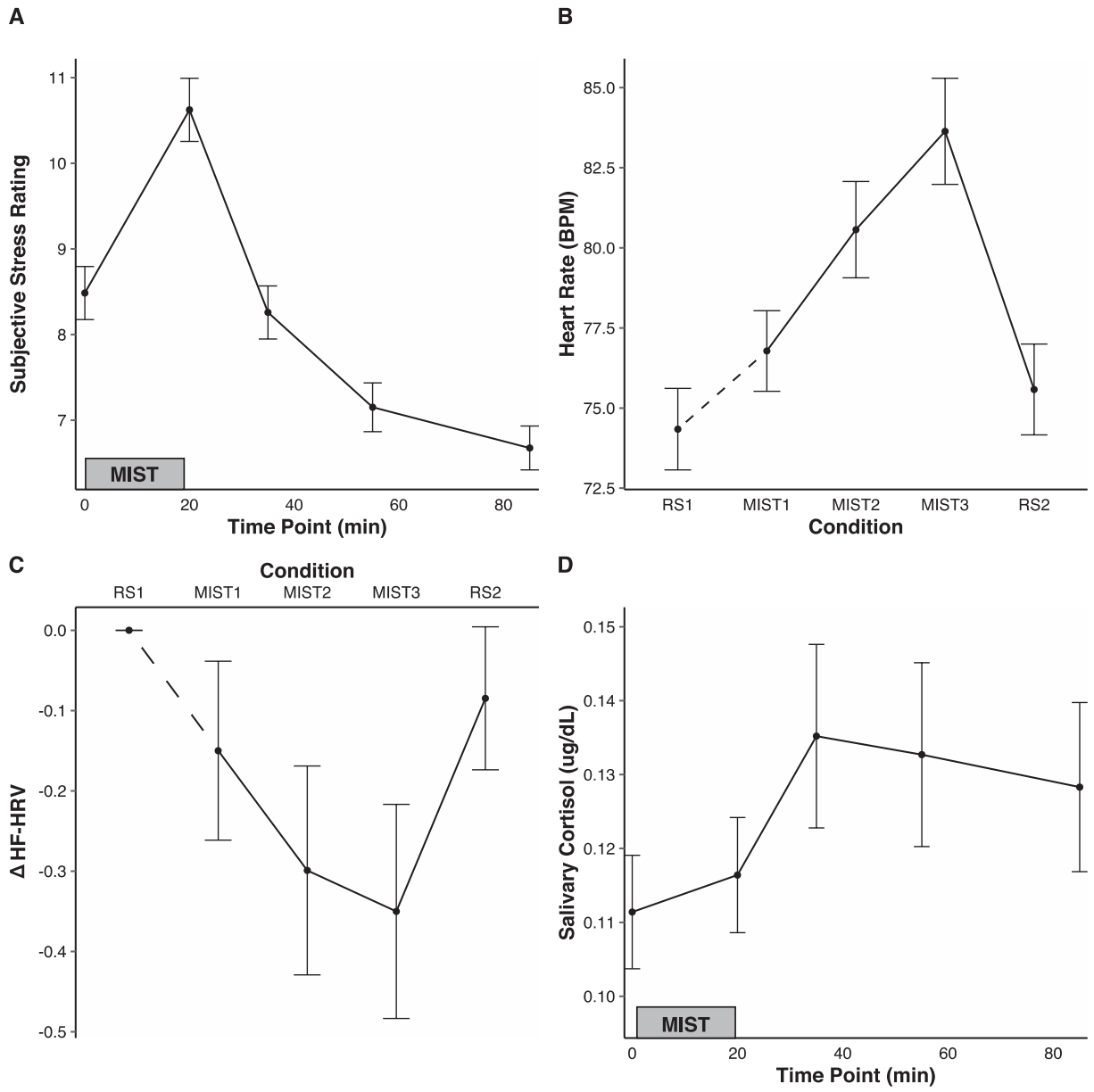

Fig. 1. Psychological and physiological response to the Montreal Imaging Stress Task (MIST) is indicated by (A) increased self-reported subjective stress ratings, (B) increased heart rate in beats per minute (BPM) compared to resting state (RS) values (C) decreased high frequency heart rate variability (HF-HRV) compared to rest, and (4) increased salivary cortisol release. Error bars shown are SEM.

increased subjective stress, cortisol, and HR, decreased HF-HRV, and changes in fMRI activation in regions implicated in salience, cognitive control, social cognition, emotional response, and reward. ROI analyses indicated relationships between cortisol release and hippocampal activation, trait anxiety and activity in mesolimbic regions, and sex and putamen activity. Results from this study support that the MIST can be reliably used in neuroimaging research of stress in adolescents.

4.1. Adolescents exhibit psychological, autonomic, and endocrine stress responses to the MIST

Perceived stress levels relate to biomarkers of the stress response, coping strategies, and anxiety (de Rooij et al., 2010; Hager and Runtz, 2012; Stutts et al., 2018), and measuring perceived stress along with biological markers is critical for connecting the biological changes that occurred during the MIST to the psychological construct of stress. Consistent with previous studies (Noack et al., 2019), subjective stress increased across the MIST, indicating participants felt stressed during this paradigm. During the MIST, subjects also exhibited increased HR and decreased HF-HRV, indexing activation of the autonomic nervous system. Heightened cortisol seen following the MIST signified HPA axis activation. Together, these findings provide evidence across multiple systems indicating that the MIST is an effective stressor for adolescents, as it elicits subjective stress and activation of both the faster-acting autonomic nervous system and the slower-acting HPA axis.

4.2. FMRI activity during psychosocial stress

The MIST activated regions related to salience detection and cognitive control including the AI, dACC, and dlPFC, supporting our hypothesis. As part of the salience network, which supports focused attention on task-relevant stimuli, the AI has been identified as the site of convergence for somatosensory and interoceptive cues and identification of significant salient stimuli, while the dACC drives subsequent

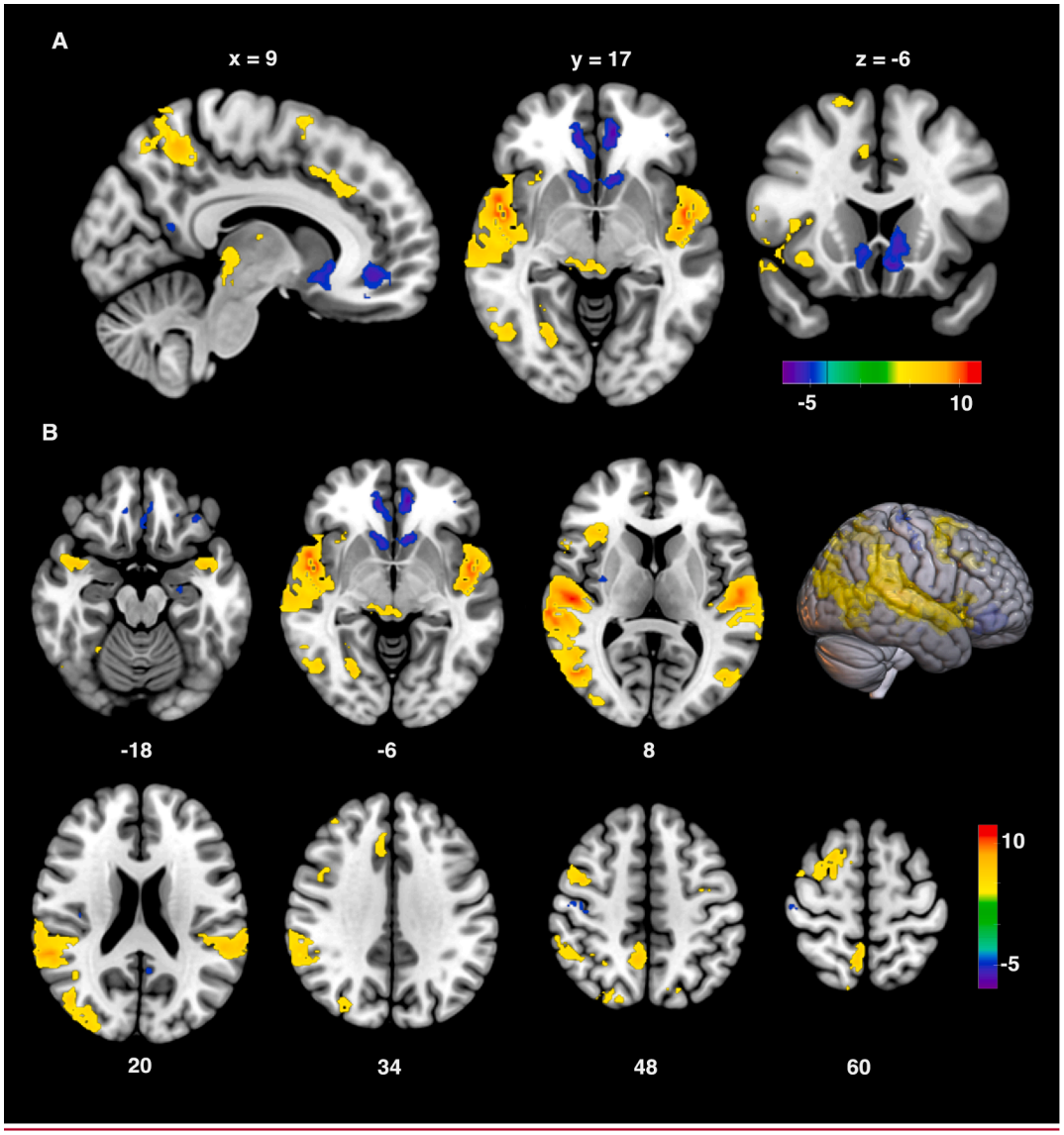

Fig. 2. FMRI activation during the Montreal Imaging Stress Task displaying Z-scores of activation thresholded at $p < .05$ FWE-corrected. Positive values represent the experimental > control contrast, and negative values represent the control > experimental contrast. Results are presented (A) centered at the right ventral striatum region of interest (MNI coordinates: $x = 9, y = 17, z = -6$) and (B) as axial slices.

Table 2A
Regions Activated During Acute Stress (Experimental > Control Contrast).

Cluster size (k)	*AAL Region*	*MNI coordinates*			*Z-score*
		x	y	z	
5670	Superior Temporal Gyrus – R	52.3	–33.3	9.24	12.20
2476	Superior Temporal Gyrus – L	−51.9	–22.7	6	11.30
491	Precuneus – R	9.43	−56.5	54	9.92
398	Superior Frontal Gyrus – R	20.7	6.3	62	8.34
251	Precentral Gyrus – R	43.3	2.63	47	7.62
159	Fusiform Gyrus – R	25.9	−63.2	−9.85	7.68
147	Brainstem – R	7.43	−27.6	−2.93	7.77
112	Mid Cingulate Gyrus – R	7.44	22.6	36.4	5.84
75	Insula – R	32	20.3	−10.3	6.88
56	Mid Occipital Lobe – L	−27.2	−82.1	26.4	5.88
22	Inferior Parietal Gyrus – R	32	−50.1	45.3	5.30
14	Inferior Frontal Gyrus, orbital – R	56	15.9	9.84	5.09
13	Superior Parietal Gyrus – R	−16.7	−70.3	48	5.65
12	Mid Frontal Gyrus – R	36.5	41.7	35.7	5.58

Table 2B
Regions Deactivated During Acute Stress (Control > Experimental Contrast).

Cluster size (k)	*AAL Region*	*MNI coordinates*			*Z-score*
		x	y	z	
373	Mid Frontal Gyrus, Orbital – L	−1.78	39	−8.82	7.80
165	Caudate – L	−8.14	17.8	−6.17	6.83
105	Caudate – R	9.42	17.2	−6.16	6.52
61	Precuneus – L	−5.59	−56.5	15	5.98
58	Precentral Gyrus – R	44.5	−17.3	51.1	5.32
52	Inferior Frontal Gyrus, Orbital – R	−34.9	34.2	−14.1	5.73
32	Precentral Gyrus – R	30.7	−27.8	68.6	6.99
27	Putamen – R	31.5	−7.83	4.98	5.83
8	Hippocampus – L	−24.2	−13.5	−17	5.35

action selection (Menon, 2015). Critically, this AI-dACC circuit triggers activation of regions implicated in cognitive control related to salience evaluation, including the dlPFC (Geng et al., 2016). Co-activation of these regions may reflect induction of a "hypervigilant state" during

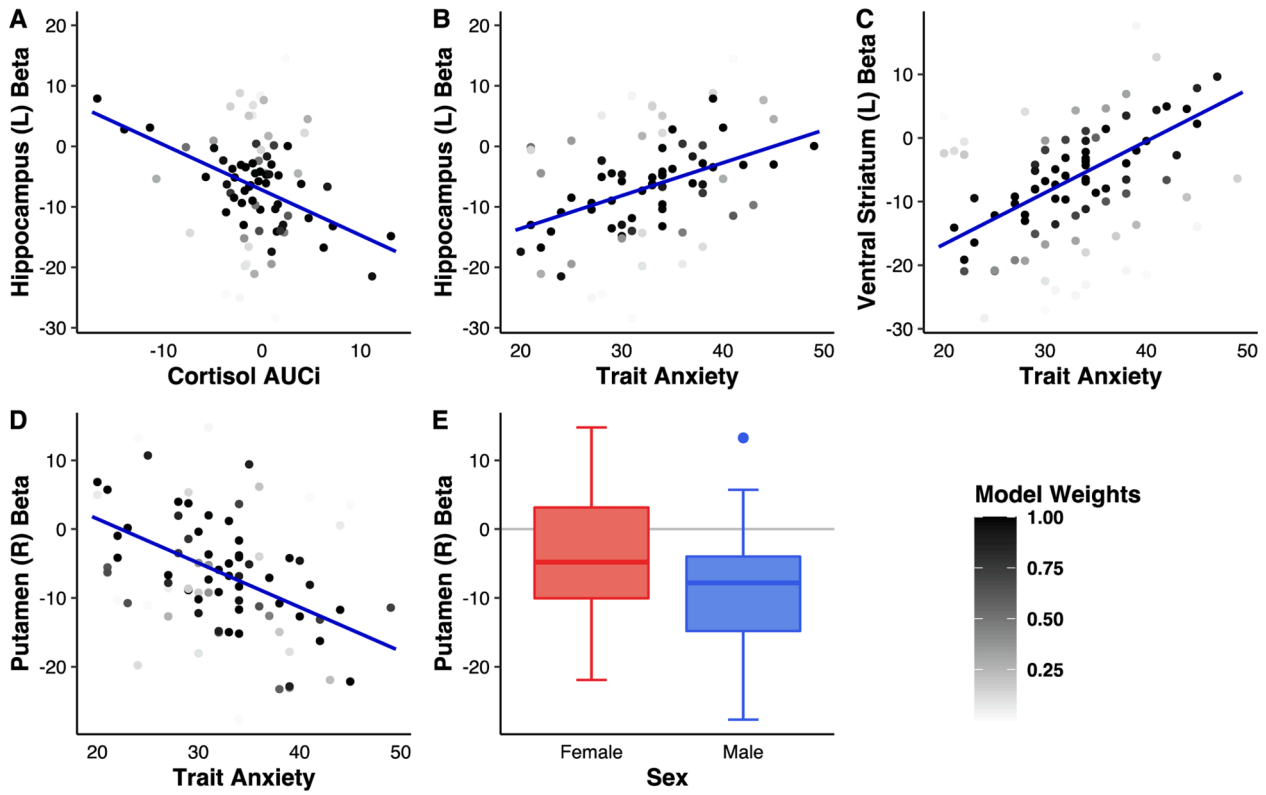

Fig. 3. During the experimental condition of the Montreal Imaging Stress Task as compared to the control condition, (A) cortisol AUCi (area under the curve with respect to increase) was negatively associated with left hippocampal activity. Trait anxiety (as measured by the State-Trait Anxiety Inventory Trait scale) was positively associated with left hippocampal (B) and left ventral striatum (C) activity and negatively associated with right putamen (D) activation. (E) Males exhibited greater putamen deactivation during stress than females. Shading on graphs A-D represents the weight of each data point in the full robust linear model. Values identified as outliers by the model and weighted to zero are not pictured.

acute stress whereby cognitive effort is focused on salient information, with heightened threat detection and reduced sensitivity to other stimuli like pain or reward (van Oort et al., 2017). During the MIST, this neural adaptation may occur when participants attempt to redirect attention from negative feedback to completing the arithmetic task.

Additionally, a complex activation pattern emerged in regions implicated in a variety of processes, including social cognition and evaluation of information relevant to self and others; the precuneus was activated during the MIST, however the PCC exhibited deactivation. Precuneus activation is a consistent result across MIST studies and may reflect its role in self-focused processing in response to the negative social feedback participants received (Ashare et al., 2016; Dedovic et al., 2014; Lederbogen et al., 2011; Ming et al., 2017). The PCC has been implicated in attention, emotional salience, consciousness, and memory processing (Brewer and Garrison, 2014; van Oort et al., 2017), and its deactivation has been associated with focused attention during demanding tasks and processing emotional stimuli (Kennedy et al., 2006; Leech and Sharp, 2014). Disparate activations in the PCC and precuneus may occur, because PCC activation is associated with general emotional evaluation, while precuneus activation has been uniquely associated with self-attribution (Cabanis et al., 2013). During the MIST, precuneus activation may reflect such self-attribution mechanisms, with participants attributing their poor performance to their perceived math abilities, while PCC deactivation may reflect attempts to shift focus from that personal failure to improving performance on the task.

Contrary to our hypothesis that the MIST would drive limbic activation, acute stress correlated with decreased hippocampal activity and was not associated with amygdala activation. While some studies have found increases in hippocampal and amygdala activity during the MIST (Chung et al., 2016a), others have found no changes in activation (Inagaki et al., 2016) or even limbic deactivation during the task (Pruessner et al., 2008). Inconsistencies in reported limbic activation may reflect the influence of other biological systems or variations in clinical symptomatology across study populations. The impact of these factors on hippocampal activation is further discussed below in the context of individual differences in cortisol response and trait anxiety.

As hypothesized, acute stress was associated with deactivation of reward-related striatal regions including the VS and putamen, as well as associated frontal regions including the vmPFC and OFC. The VS and putamen contribute to reward processing, learning, and encoding valence; receiving a reward has been associated with increased activity in these regions, while negative feedback and punishment have been associated with their deactivation (Jiang et al., 2014; Mattfeld et al., 2011). Thus, the negative feedback subjects receive during the MIST may drive deactivation in the striatum. Relatedly, the vmPFC and OFC are highly-connected ventral PFC regions that integrate input from across the brain to encode value and goal-directed behavior, and their deactivation is also associated with negative feedback and punishment (Helfinstein et al., 2011; O'Doherty et al., 2001). Together, these PFC regions provide awareness of internal and external factors and focus attention on relevant stimuli for value learning, and their deactivation during the MIST may be a response to receiving negative social and visual feedback (Walton et al., 2015).

4.3. *Hippocampal deactivation is correlated with cortisol release*

Subjects with higher cortisol following the MIST experienced greater hippocampal deactivation during stress, consistent with the findings of Pruessner et al. (2008). They attribute this relationship to the role of the hippocampus in regulating the HPA axis; within the corticolimbic circuit, the hippocampus provides negative feedback to the HPA axis to terminate its response through inhibiting the paraventricular nucleus

(PVN) of the hypothalamus. As the PVN discharges corticotropin-releasing hormone into the anterior pituitary gland to initiate the HPA axis response, inhibition of the PVN ultimately reduces cortisol release and stops the endocrine ASR (Hariri, 2015). Within this analysis, subjects with lower hippocampal activation may have less PVN inhibition, ultimately driving greater release of cortisol. Understanding this pathway is important, because the relationship between hippocampal activation and cortisol is implicated in emotional memory performance in depressed individuals, and efficacy of psychosocial therapy could theoretically be enhanced via pharmacological agents that alter corticosteroid receptors (Abercrombie et al., 2011).

4.4. Trait anxiety is associated with greater hippocampal and ventral striatum activity and reduced putamen activation

Trait anxiety was associated with greater hippocampal and left VS activation and less putamen activity during stress, possibly reflecting their roles in anticipating and processing potential threats, which is at the heart of anxiety symptomatology. The hippocampus and striatum are functionally connected regions implicated in the onset of anxiety disorders. However, the literature relating their activation during acute stress to trait anxiety has not reached a clear consensus (Lago et al., 2017). Hippocampal hyperactivation has been found across anxiety disorders in the majority of current research, but some work reported blunted hippocampal response to novel stimuli in individuals with higher trait anxiety (Lago et al., 2017; Pedersen et al., 2017). Work using a variation of the MIST found that trait anxiety was correlated with increased activation of clusters which included the hippocampus and putamen (Wheelock et al., 2016). These divergent results may arise from differences in experimental design and study populations, but they also may reflect the complexity of anxiety itself; neural activation can significantly differ between the anxiety related to the anticipation of a stressful task versus anxiety experienced during the threatening situation (Lyons and Beilock, 2012). Further studies designed to separately measure fMRI activation when anticipating versus experiencing a stress task may explain inconsistencies in the current acute stress literature and more clearly elucidate the relationship between anxiety and ASR.

4.5. Males exhibited greater putamen deactivation during stress

During the MIST, the putamen was more deactivated in males than females. Overall, current publications detailing the influence of sex on the neurobiological ASR have generated mixed results, with some studies finding greater stress-related activation in males and others reporting greater activation in females (Noack et al., 2019). Specific to the putamen, while Wang et al. found that females but not males exhibited putamen activation during stress, Kogler, Gur & Derntl found that males exhibited greater putamen activation during the MIST than females (Kogler et al., 2015; Wang et al., 2007). This analysis did not find sex-related activation differences in any other ROIs, but other work using the MIST has reported sex-related differences in a variety of regions including the dlPFC, VS, and insula (Chung et al., 2016b; Wang et al., 2007). There is limited research into how sex impacts the neural response to acute stress in this age range, and future work is necessary to better understand these relationships.

4.6. Strengths, limitations, and future directions

One strength of this analysis was our heterogenous sample of adolescents who exhibit a range of anxiety symptoms; this dimensional approach follows RDoC principles (Insel et al., 2010) and should make findings more generalizable, rather than applying to only typically-developing adolescents or those with specific diagnoses. However, to obtain this heterogeneity we included participants who were taking psychotropic medication and who had psychiatric diagnoses including ADHD and a range of anxiety disorders. Although it is known that these medications can impact neural activation (Weyandt et al., 2013), when included in cursory ROI models medication status was not significantly associated with activation of any ROI, which supports our findings' validity despite possible confounds. More detailed analyses, which are beyond the scope of this paper, evaluating the impacts of specific medications on neural ASR would be necessary to better characterize how medication use may influence the brain's response to stress in adolescents. Additionally, while inclusion of subjects with clinical diagnoses allows for a more complete dimensional analysis, it is possible that acute stress elicits unique neurobiological responses in adolescents with anxiety conditions versus typically-developing subjects with higher levels of anxiety. Due to high rates of comorbidity, it would be difficult to disentangle the relationship between specific psychiatric diagnoses and the neurobiological ASR with this dataset.

Aspects of this study's experimental design may have unintentionally influenced measured neurobiological changes. During the MIST EC, a rising tone was played to further induce stress, while no sound was played during the CC. This may explain the widespread activations of auditory areas seen in the whole-brain analysis. It is also possible that the MRI environment itself elicited a stress response, but we took several precautions to address this concern; in the hour before the actual study, participants completed a "mock scan," where they entered a decommissioned MRI scanner and listened to examples of sounds made by the scanner to help them acclimate to the environment. Furthermore, the first cortisol and self-reported stress ratings were collected immediately before the start of the MIST after subjects had already been in the scanner for 30–40 min. This provided subjects the opportunity to become desensitized to the MRI environment before the MIST, reducing the likelihood that stress related to being in an MRI scanner influenced findings. Additionally, the working memory tasks completed before and after the MIST may impact cortisol response; for some subjects, cognitive tasks may produce additional stress resulting in prolonged stress exposure and cortisol release, whereas for others these challenges may provide a distraction from ruminating on their MIST performance, instead blunting their cortisol response (Zoccola and Dickerson, 2012).

Finally, additional variables are known to correlate with neural response to the MIST – including childhood trauma exposure, social support, neuroticism, and depression – that were outside the scope of this analysis (Dedovic et al., 2014; Dong et al., 2020; Inagaki et al., 2016; Zhong et al., 2020). Future work should explore relationships between these variables and neurobiological ASR in adolescents to better characterize related pathways. Additional analyses should also examine changes in functional connectivity during stress exposure to understand how acute stress impacts neural networks. To fully explicate the development of neural ASR and its relationship with anxiety disorders, longitudinal studies are needed that follow the same population into adulthood and evaluate how changes in the brain's response to acute stress relate to emergence of anxiety symptoms.

5. Conclusions

Endocrine, autonomic, and subjective stress findings support that the MIST is an effective stressor for adolescents. Acute stress elicited alterations in fMRI activation across the brain, with cortisol release, trait anxiety, and sex impacting some regions. These findings offer novel insight into the ASR in adolescents and provide an important expansion to the literature; few studies have examined neural ASR in this age range, even though adolescents are particularly vulnerable to developing anxiety disorders and in adults anxiety is linked to aberrant ASR. Understanding the neurobiological response to acute stress in adolescents is crucial for understanding the etiology of anxiety disorders, and further studies are needed to comprehensively characterize the complex relationships between ASR and the development of mental illness.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102543.

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