A. OVERALL COVER PAGE

Project Title: Neuroimaging of Resilience in World Trade Center Responders: A Focus on Emotional Processing, Reward and Social Cognition	
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Program Director/Principal Investigator Information: ADRIANA FEDER , MD **Phone Number:** 2125854670 **Email:** adriana.feder@mssm.edu	**Recipient Organization:** ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI 1 GUSTAVE L. LEVY PL NEW YORK, NY 100296574 **DUNS:** 078861598 **UEI:** C8H9CNG1VBD9 **EIN:** 1136171197A1 **RECIPIENT ID:**
Change of Contact PD/PI: NA	
Administrative Official: AMANDA AMESCUA One Gustave L. Levy Place, Box 1075 New York, NY 100296574 **Phone number:** 646-605-8659 **Email:** amanda.amescua@mssm.edu	**Signing Official:** AMANDA AMESCUA One Gustave L. Levy Place, Box 1075 New York, NY 100296574 **Phone number:** 646-605-8659 **Email:** amanda.amescua@mssm.edu
Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Specific Aims: Psychological resilience is defined as the ability of an individual to adapt successfully to severe stress, trauma or adversity. Three of the most widely replicated and potentially modifiable protective factors linked to psychological resilience are: (1) emotion regulation, (2) positive emotions, and (3) the ability to harness social support. (1) Emotion regulation is a key component of psychological resilience, and has been associated with greater executive function.1, 2 Optimal emotion regulation skills underlie adaptive coping strategies such as active coping and planning during stressful times, which characterize resilient individuals.3, 4 (2) Positive emotions, closely linked to reward system function,5, 6 also promote resilience to stress. Positive emotions enhance social connectedness and adaptive coping,7 enable more flexible psychological responses,8, 9 and facilitate efficient physiological recovery following exposure to stress.10 (3) The ability to establish and nurture a supportive social network is a critical factor linked to resilience. Resilient individuals report high levels of social support, which functions as a safety net in stressful situations.4, 11 Competent social cognition, defined as "the capacity to perceive, interpret and generate responses to the intentions, dispositions and behavior of other people",12 is critical to developing and maintaining a supportive social network. Conversely, a recent meta-analysis revealed pronounced deficits in social cognition (i.e., emotion recognition, mentalizing) in individuals with posttraumatic stress disorder (PTSD),12 which may contribute to functional impairment in this population. While a large body of work has helped identify these three core psychological domains associated with resilience, little is known about the function of neural circuits underlying these three domains in resilient individuals. To address this gap, we propose to characterize brain function in neural circuits subserving (1) implicit (automatic) emotion regulation, (2) reward processing, and (3) social cognition in a sample of highly resilient World Trade Center (WTC) responders, who have remained resilient despite enduring severe WTC-related exposures, in comparison to two groups of WTC responders: (a) a "symptomatic" group with chronic, clinically significant WTC-related PTSD symptoms, and (b) a "low WTC-exposed control" group without psychiatric disorder, who experienced significantly lower levels of WTC-related exposures. Elucidating the function of neural circuits underlying core psychological domains associated with resilience is critical to informing the etiology of resilience, and to developing personalized prevention and treatment approaches designed to promote resilience in WTC responders and other trauma survivors. The proposed study will capitalize on the existence of a unique and well-characterized sample of over 300 WTC responders who have been evaluated in-depth by our team (NIOSH-funded U01 grants OH010407 and OH010986), and whose WTC-related PTSD symptom trajectories range from highly resilient to chronically symptomatic.

Specific Aim 1: To examine brain function in neural circuits subserving automatic emotion regulation in a sample of highly resilient WTC responders compared to symptomatic and low WTC-exposed control groups. Hypothesis: Highly resilient WTC responders will demonstrate significantly greater rostral anterior cingulate cortex (rACC) activation during emotional conflict (incongruent condition) than during the congruent condition, while the low WTC-exposed control group will show a smaller difference in rACC activation across these two conditions and the symptomatic group will not show modulation of rACC activation across conditions.13

Specific Aim 2: To examine brain function in neural circuits mediating reward responses during reward anticipation in highly resilient WTC responders compared to symptomatic and low WTC-exposed control groups. Hypothesis: During the anticipation phase, highly resilient WTC responders will not demonstrate differential activation in reward-processing regions [ventral striatum and ventromedial prefrontal cortex (vmPFC)] between the high-reward and no-reward conditions, while the low WTC-exposed control group will show greater activation in reward-processing regions during the high-reward vs. no-reward conditions.14 The symptomatic group will have the lowest activation in reward processing regions during the high-reward condition compared to the other groups.

Specific Aim 3: To examine brain function in neural circuits involved in social cognition in highly resilient WTC responders compared to symptomatic and low WTC-exposed control groups. Hypothesis: Highly resilient WTC responders will show greater activation in brain regions involved in social cognition (mentalizing) (medial PFC [mPFC], inferior frontal gyrus, precuneus, temporoparietal junction) compared to the low WTC-exposed group.15, 16 The symptomatic group will have the lowest activation compared to the other groups.

Exploratory analyses will probe for between-group differences in resting-state functional connectivity between our a priori regions of interest and the rest of the brain.

Specific Aim 4: To use density-based spatial clustering to identify heterogeneous patterns of brain function in neural circuits subserving the three psychological domains evaluated in Aims 1, 2, and 3. Hypothesis: Resilience is a heterogeneous

phenotype. On a region-by-region basis, across individuals, brain activations in the highly resilient group will evidence common and distinct neural mechanisms underlying emotion regulation, reward processing, and social cognition that are indicative of distinct pathways to resilience.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

Final Progress Report

Neuroimaging of Resilience in World Trade Center Responders: A Focus on Emotional Processing, Reward and Social Cognition

(U01OH011473)

Centers for Disease Control and Prevention

07/01/2017 – 06/30/2023

Final Report

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Principal Investigators:

Adriana Feder, M.D.

Professor, Icahn School of Medicine at Mount Sinai

1399 Park Avenue

New York, NY, 10029

adriana.feder@mssm.edu

212-585-4670

Maria De Las Mercedes Perez Rodriguez, M.D., Ph.D.

Associate Professor, Icahn School of Medicine at Mount Sinai

Icahn Medical Institute L4-53

New York, NY 10029

mercedes.perez@mssm.edu

(212) 241-9775

Robert H. Pietrzak, Ph.D., M.P.H.

Professor, Yale University School of Medicine

National Center for Posttraumatic Stress Disorder

VA Connecticut Healthcare System

950 Campbell Avenue 151E

West Haven, CT, 06516

rhpietrzak@gmail.com

Co-Investigators:

Saren Seeley, Ph.D.

Agnes Norbury, Ph.D.

Cindy Aaronson, Ph.D., M.S.W.

Leah Cahn, L.C.S.W

Laurel Morris, Ph.D.

James W. Murrough, M.D., Ph.D.

Dennis S. Charney, M.D.

Consultants:

Clyde Schechter, M.D., M.A.

Emily Stern, Ph.D.

Lisa Shin, Ph.D.

Prantik Kundu, Ph.D.

Erno Hermans, Ph.D.

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List of Terms and Abbreviations

These are included in the text for ease of reading.

Abstract

Background. Psychological resilience is defined as the ability to adapt successfully to severe stress, trauma, or adversity. A large body of work identifies three core psychological factors associated with resilience[1,2]. *(1)* Emotion regulation, which supports adaptive coping[3]; *(2)* positive emotions, linked to reward system function,[4,5] and *(3)* the ability to harness social support, via competent social cognition[6]. However, little is known about the corresponding neural circuits in resilient individuals. This study aimed to address this gap by characterizing brain activity subserving *(1)* implicit (automatic) emotion regulation, *(2)* reward processing, and *(3)* social cognition, in a sample of highly resilient World Trade Center (WTC) responders, in comparison to a symptomatic group with WTC-related posttraumatic stress disorder (PTSD), and a lower WTC-exposed control group.

Methods. A total of 98 eligible participants (aged ≤65 years), recruited from the WTC Health Program General Responder Cohort, were classified into three groups based on number of potentially traumatic WTC-related exposures (range 0-10) and WTC-related PTSD diagnostic status: (1) a *"highly resilient"* group (n=33, ≥4 exposures, no lifetime DSM-5 disorders), (2) a *"lower WTC-exposed"* group (n=32, ≤3 exposures, no lifetime DSM-5 disorders) and (3) and a *"PTSD*" group (lifetime DSM-5 WTC-related PTSD *and* persistent past-month full or subthreshold PTSD). Exclusion criteria included lifetime psychosis or bipolar disorder; unstable medical illness; central nervous system disorder or head injury; substance use disorder in prior 3 months; and Montreal Cognitive Assessment score < 23. On Visit 1, participants completed clinician-administered and self-report measures, including the Structured Clinical Interview for DSM-5 (SCID-5) and the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). On Visit 2, participants completed an fMRI scan, including an emotional face-word Stroop task, the Incentive Flanker Task, and the Reading the Mind in the Eyes Test (RMET). On Visit 3, participants completed additional cognitive and behavioral tasks on a computer.

Results. We compared BOLD activation within a priori regions of interest (per task) across the three groups. The highly resilient group demonstrated the greatest activation in key regions of interest involved in automatic emotion regulation (rostral anterior cingulate) and response to reward (ventral striatum) compared to the PTSD group. The lower WTC-exposed group appeared to engage both regions in a similar manner to the highly resilient group, but not to a sufficient extent to significantly differ from either highly resilient or PTSD groups. Region of interest analyses did not identify any significant differences on the social cognition task. However, preliminary results from the whole brain analysis suggest that the PTSD group did not effectively engage a canonical social cognition region (not one of the planned ROIs) compared to the other two groups. Further analyses are ongoing and aim to examine how task-related brain activity patterns may relate to heterogeneous resilience trajectories. Other exploratory analyses will examine resilience-linked differences in brain structure, resting state functional connectivity, and performance on Visit 3 tasks.

Conclusions. These findings contribute to our understanding of the neural instantiation of psychological factors that enable some individuals to be highly resilient despite high trauma exposure burden.

SECTION 1

Significant or Key Findings

This was, to our knowledge, the first fMRI study to investigate emotion regulation, reward responsivity, and social cognition as putative resilience mechanisms underlying psychological factors widely linked to resilience to trauma, in a sample of World Trade Center (WTC) rescue and recovery workers, some of whom also survived the 9/11/2001 attacks. This unique sample allowed us to compare the most highly resilient WTC responders ("highly resilient" responders, with no lifetime psychiatric disorders despite high levels of potentially traumatic WTC-related exposures) to two groups of WTC responders*:* resilient responders with lower WTC-exposures ("lower WTC-exposed control" group) and symptomatic responders with lifetime WTC-related PTSD and persistent clinically significant PTSD symptoms approximately two decades after the 9/11 attacks ("PTSD" group).

Significant and key findings include the following:

1. Highly resilient WTC responders reacted to incongruent emotional stimuli by engaging the rostral anterior cingulate cortex (rACC), whereas symptomatic responders (PTSD group) did not appear to engage the rACC. Lower WTC-exposed control responders showed lesser emotional conflict-related rACC activation than the highly resilient group, but more than the PTSD group. This finding suggests that emotion regulation capacity in highly resilient individuals is supported by greater recruitment of key brain regions involved in conflict resolution and automatic emotion regulation, such as the rACC *(**Specific Aim 1**)*.

2. Highly resilient WTC responders showed the greatest degree of anticipatory *de*activation of the ventral striatum, a key reward region, when presented with a cue indicating a potential monetary loss (vs. neutral or gain cues), compared to both the PTSD and lower WTC-exposed groups. Number of WTC-related exposures appeared to modulate ventral striatum activation in responders with no lifetime psychiatric disorders, such that the lower WTC-exposed group showed a smaller decrease in ventral striatum activation than the highly resilient group in response to loss cues. The PTSD group did not demonstrate differential ventral striatum *de*activation during anticipation of potential reward, loss, or neutral outcomes *(**Specific Aim 2**)*. Analysis of consummatory loss- and reward-related activation in reward-related regions of interest (ROIs) is currently in progress.

3. In our preliminary region of interest (ROI) analysis of a social cognition task, we did not identify any significant group differences in recruitment of multiple key brain regions involved in social processes or in task performance. However, exploratory whole-brain analysis pointed to a social cognition-related region that was not one of our ROIs – the posterior superior temporal sulcus –, with stronger activation in both resilient groups compared with the PTSD group during the task condition that required Theory of Mind decisions *(**Specific Aim 3**)*.

4. Density-based spatial clustering analysis is ongoing, with the aim of identifying resilience subgroups based on heterogeneous patterns of neural activity across the three fMRI tasks (***Specific Aim 4***). This could provide insight into individual differences in resilience and adaptation after trauma exposure.

5. Exploratory analyses are ongoing, including analysis of the structural and resting state neuroimaging data and behavioral data from ancillary out-of-scanner tasks measuring social, affective, and reward processes. We are also examining the differential impact that specific exposures (e.g., encountering human remains; being injured in the attacks or during the WTC recovery effort) may have on vulnerability to adverse psychological outcomes in WTC responders.

Translation of Findings

Findings from this novel neuroimaging study of resilience to trauma exposure in WTC responders suggest that the most resilient individuals (e.g., good psychological functioning without any lifetime psychiatric disorders despite high levels of potentially traumatic WTC-related exposures) exhibit differential functioning in neural circuitry involved in automatic emotion regulation, anticipation of reward and loss, and potentially social cognition – from both resilient WTC responder controls with lower levels of WTC-related exposures, and from symptomatic WTC responders with persistent clinically significant PTSD symptoms approximately two decades after the events of 9/11/2001.

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Research Outcomes/Impact

These findings add to our understanding of how specific psychological factors that enable some individuals to be highly resilient even in the face of severe trauma exposure are instantiated in the brain. Knowledge gained from the study of neural function in highly resilient individuals can be harnessed to develop novel approaches to help prevent the development of trauma-related psychopathology or to mitigate psychopathology in those already experiencing posttraumatic stress symptoms, among WTC populations as well as future disaster survivors and responders.

SECTION 2

Scientific Report

Background

Psychological resilience is defined as the ability of an individual to adapt successfully to severe stress, trauma, or adversity. Three of the most widely replicated and potentially modifiable protective factors linked to psychological resilience are *(1)* emotion regulation, *(2)* positive emotions, and *(3)* the ability to harness social support. *(1)* Emotion regulation is a key component of psychological resilience and is associated with greater executive function.[7,8] Optimal emotion regulation skills underlie adaptive coping strategies such as active coping and planning in response to stress or trauma exposure, which characterize resilient individuals.[3,9] *(2)* Positive emotions, closely linked to reward system function,[4,5] also promote resilience to stress. Positive emotions enhance social connectedness and adaptive coping,[10] enable more flexible psychological responses,[11,12] and facilitate efficient physiological recovery following exposure to stress.[13] *(3)* The ability to establish and nurture a supportive social network is a critical factor linked to resilience. Resilient individuals report high levels of social support, which functions as a safety net in stressful situations.[3,6] Competent social cognition, defined as "the capacity to perceive, interpret and generate responses to the intentions, dispositions and behavior of other people",[14] is critical to developing and maintaining a supportive social network. Conversely, studies have revealed significant deficits in social cognition (i.e., emotion recognition, mentalizing) in individuals with PTSD, which may contribute to functional impairment in this population[15].

While a large body of work has helped identify these three core psychological factors associated with resilience, little is known about the function of neural circuits underlying these three factors in resilient individuals. The present study aimed to address this gap by characterizing brain function in neural circuits subserving ***(1) implicit (automatic) emotion regulation***, ***(2) reward processing***, and ***(3) social cognition*** in a sample of ***highly resilient*** World Trade Center (WTC) responders, who have remained resilient (with no lifetime DSM-5 psychiatric disorders) despite high levels of WTC-related exposures (≥ 4 exposures), in comparison to two groups of WTC responders: *(a)* a ***"PTSD"*** group with lifetime DSM-5 WTC-related PTSD and persistent clinically significant WTC-related PTSD symptoms in the past month, and *(b)* a ***"lower WTC-exposed control"*** group with no lifetime DSM-5 psychiatric disorders, who experienced lower levels of WTC-related exposures (≤ 3 exposures). Elucidating the function of neural circuits underlying core psychological factors associated with resilience is critical to informing the etiology of resilience, and to developing personalized prevention and treatment approaches designed to promote resilience and recovery in WTC responders and other trauma survivors.

Specific Aims

Specific Aim 1: To examine brain function in neural circuits subserving automatic emotion regulation in a sample of highly resilient WTC responders compared to PTSD and lower WTC-exposed control groups. ***Hypothesis:*** Highly resilient WTC responders will demonstrate *significantly greater* rostral anterior cingulate cortex (rACC) activation during emotional conflict (incongruent condition) than during the congruent condition, while the lower WTC-exposed control group will show a *smaller difference* in rACC activation across these two conditions and the symptomatic (PTSD) group will *not* show modulation of rACC activation across conditions.[16]

Specific Aim 2: To examine brain function in neural circuits mediating reward responses during reward anticipation in highly resilient WTC responders compared to symptomatic (PTSD) and low WTC-exposed control groups. ***Hypothesis:*** During the anticipation phase of the incentive flanker task[17], highly resilient WTC responders will *not* demonstrate differential activation in reward-processing regions [ventral striatum and ventromedial prefrontal cortex (vmPFC)] between the high-reward and no-reward conditions, while the low WTC-exposed control group will show *greater* activation in reward-processing regions during the *high-reward* vs. no-reward conditions.[18] The symptomatic (PTSD) group will have the lowest activation in reward processing regions during the high-reward condition compared to the other groups.

Specific Aim 3: To examine brain function in neural circuits involved in social cognition in highly resilient WTC responders compared to symptomatic (PTSD) and low WTC-exposed control groups. ***Hypothesis:*** Highly resilient WTC responders will show *greater* activation in brain regions involved in social cognition (mentalizing) (medial PFC [mPFC], inferior frontal gyrus, precuneus, temporoparietal junction) compared to the low WTC-exposed group.[19,20] The symptomatic (PTSD) group will have the lowest activation compared to the other groups.

Exploratory analyses will probe for between-group differences in resting-state functional connectivity between our *a priori* regions of interest and the rest of the brain.

Specific Aim 4: To use density-based spatial clustering to identify heterogeneous patterns of brain function in neural circuits subserving the three psychological domains evaluated in Aims 1, 2, and 3. ***Hypothesis:*** Resilience is a heterogeneous phenotype. On a region-by-region basis, across individuals, brain activations in the highly resilient group will evidence common and distinct neural mechanisms underlying emotion regulation, reward processing, and social cognition that are indicative of distinct pathways to resilience.

Methodology

Recruitment and Eligibility

Participants were recruited from the WTC Health Program General Responder Cohort (WTC-HP GRC) in collaboration with the WTC-HP GRC Data Center. Data Center staff initially provided de-identified data, collected longitudinally at all five WTC-HP Clinical Centers of Excellence during periodic monitoring visits and housed at the Data Center, from WTC-HP GRC members who had provided written consent to be contacted for future studies – to determine provisional eligibility. The Data Center then provided lists of names and contact information from selected groups of responders who met provisional eligibility, so that the study team could reach out to them.

WTC-HP GRC members were also recruited by contacting WTC responders who had previously participated in NIOSH-funded studies led by Dr. Feder (U01 OH010986 and U01 OH010407) and had provided written consent to be contacted for future studies by the study team. For the PTSD group, some WTC-HP GRC members were referred by their clinicians at the WTC Mental Health Program at Mount Sinai, if they expressed interest in being evaluated for study participation.

Eligible male and female responders, aged ≤ 65 years, were recruited into three groups (see **Table 1** for participant characteristics): *(1) highly resilient* responders, who remained psychologically resilient (i.e., with no lifetime DSM-5 psychiatric disorders) despite exposure to ≥ 4 WTC-related exposures out of a total of 10 potentially traumatic WTC-related exposures (e.g., participated in search and rescue, exposed to human remains, experienced death of a colleague or loved one); *(2) lower WTC-exposed control* responders with no lifetime DSM-5 psychiatric disorders, who had experienced ≤ 3 WTC-related exposures; and *(3)* symptomatic responders, who met DSM-5 criteria for lifetime WTC-related PTSD on the CAPS-5 and persistent past-month full or subthreshold PTSD *(PTSD* group).

Data about potentially traumatic WTC-related exposures, already collected on the full cohort of WTC responders on their first WTC-HP health monitoring visit, was provided by the WTC-HP GRC Data Center and supplemented with data collected by the study team during the present study.

Key exclusion criteria included lifetime history psychotic or bipolar disorder; any unstable medical disorder likely to involve central nervous system functioning; history of significant head injury; meeting DSM-5 criteria for alcohol and/or substance use disorder within the prior 3 months; current treatment with opioid medication, benzodiazepines or mood stabilizers; score < 23 on the Montreal Cognitive Assessment (MoCA); estimated full scale IQ < 80, positive urine toxicology for drugs of abuse; currently pregnant; and non-proficiency in English.

Study Procedures

Potential study participants were initially sent an invitation letter by the study team, via mail or email, followed by phone calls. Interested potential participants initially completed a phone screen, administered by a member of the study team, to confirm preliminary eligibility for the study.

WTC responders who were found to be preliminarily eligible based on the phone screen were scheduled for the first study visit.

During **Visit 1**, potential participants first completed informed consent procedures, administered by a member of the study team, with ample opportunity to ask any questions or voice any concerns. After the onset of the COVID pandemic, participants had the option to complete this study visit remotely via HIPAA-compliant Zoom video platform approved by Mount Sinai. Participants signed the study consent form either in person or

electronically. After providing signed consent, participants were administered the Montreal Cognitive Assessment (MoCA)[21] and the Wechsler Test of Adult Reading (WTAR)[22] by a member of the study team. Participants were then asked to complete several self-report questionnaires, including demographic characteristics, a checklist of diagnosed medical problems, scales to assess lifetime traumas – the *Traumatic Life Events Questionnaire (TLEQ)*[23] and the *Childhood Trauma Questionnaire (CTQ)*[24]*,* the *PTSD Checklist for DSM-5 (PCL-5)*[25] the *Beck Depression Inventory – Version II (BDI-II)*[26], and additional scales to assess psychological traits associated with resilience (e.g., trait optimism, positive emotions, perceived social support).

A study clinician (licensed Masters- and PhD-level clinical social workers, postdoctoral fellow with a PhD in clinical psychology, supervised by Dr. Feder), then met with the participant to conduct a full assessment, starting by reviewing the participant's WTC-related exposures, and then administering the *Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)*[27] and the *Structured Clinical Interview for DSM-5 (SCID-5)*[28] to determine participant eligibility into one of the three study groups and to characterize symptom severity. Available electronic medical records, as well as the participant's reported medical history, current medical problems, and current medications were reviewed by the study team in consultation with MPIs Drs. Feder and Perez-Rodriguez.

Eligible participants based on the Visit-1 assessments and clinical evaluation were scheduled for Visit 2, in person.

During **Visit 2**, participants completed the study MRI scan, including three fMRI tasks: the Trauma-unrelated Emotional Interference Task (FaceStroop), the Incentive Flanker Task (IFT), and a modified version of the Reading the Mind in the Eyes Task (RMET).

During the FaceStroop task[16], participants view black and white photographs of 10 faces (5 male), each displaying one happy and one fearful expression, with either the word "happy" or "afraid" superimposed on each face. Participants are instructed to use a button box to indicate whether faces are happy or afraid. In the congruent condition (low interference), the superimposed word matches the facial expression. In the incongruent condition (high interference), the superimposed word does not match the facial expression.

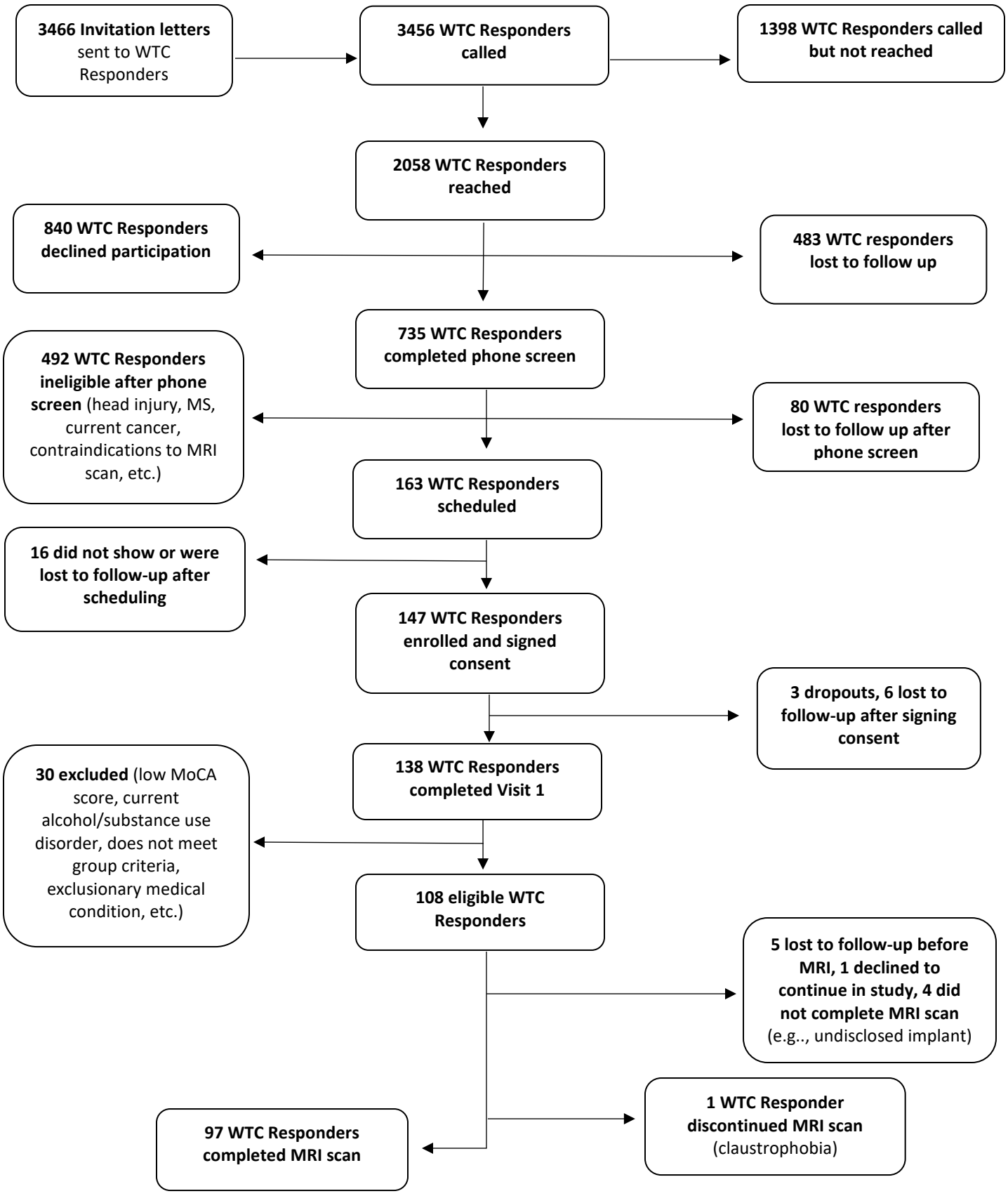
The Incentive Flanker Task (IFT)[17] is a variant of the Monetary Incentive Delay (MID) task. Cues presented prior to letter stimuli designate the monetary value for each trial: *(1)* "gain" cues indicate that participants earn 50 cents with a correct response (and fail to gain with an error); *(2)* "loss" cues indicate that participants can avoid a loss of 50 cents with a correct response (and lose money with an error); and *(3)* "neutral" cues indicate that no money is at stake. Two-thirds of all cues are followed by the letter stimuli. Immediately after the participant response, outcome feedback is presented, followed by a blank inter-trial interval. Letter stimuli (flanker portion of the task): during the flanker portion, participants are asked to press the left response button for target letters S/K and the right button for letters H/C. Target letters are flanked by letters associated with the same button press (low conflict) or different button press (high conflict).

During the modified version of the Reading of the Mind in the Eyes Task (RMET),[29] participants are asked to choose which out of two words best describes the emotion expressed in a picture of the eye region of an individual. Participants respond by pressing one of two buttons with the right index or middle finger to select the left or right word respectively. Thirty-six pictures of the eye region are presented (18 male and 18 female). In a control condition ("gender", a sex discrimination task), for the same 36 pictures of eyes, the participants have to judge whether the eyes belong to a man or woman.

During **Visit 3** (participants had the option to complete this visit remotely via HIPAA-compliant Zoom video platform after the onset of the COVID pandemic), several behavioral tasks were administered outside the scanner to supplement fMRI data, including the Dot Probe Task[30], the Probabilistic Reward Task (PRT),[31] the Movie for the Assessment of Social Cognition (MASC),[32] and the unmodified Reading of the Mind in the Eyes (RMET)[19] outside the scanner.

A total of 97 (out of 98) participants completed the MRI scan: 33 in the *highly resilient group,* 32 in the *PTSD* group, and 32 in the *lower WTC-exposed* group. One participant from the latter group was unable to complete the MRI session due to claustrophobia but did return for study Visit 3 to complete the tasks outside the scanner. A total of 89 (out of 98) participants completed the ancillary behavioral tasks administered outside the scanner (Visit 3).

Figure 1. *Study Recruitment and Enrollment*



MRI Acquisition

MRI data were acquired using a Siemens Skyra 3T scanner at the Icahn School of Medicine at Mount Sinai's Biomedical Engineering and Imaging Institute (BMEII).

The T1-weighted MRI sequence parameters included an isotropic spatial resolution of 320 x 320 x 0.8 mm^3 voxels, slice thickness 0.8 mm, TR of 2400ms, TE of 2.07ms, 8º flip angle, and 319 phase encoding steps. Inversion time (TI) was set to 1 second for improved tissue contrast. The imaging frequency was 123.249 MHz, and the pixel bandwidth was 240 Hz/pixel. Parallel imaging with a reduction factor of 2 was utilized for improved acquisition speed. The acquisition matrix in the phase-encoding direction was 320, and 32 reference lines were acquired for phase encoding.

The fMRI acquisition used a muti-echo EPI sequence with the following parameters: 3mm slice thickness, 240mm FOV, 59 phase encoding steps, 45º flip angle, and TR of 0.882 seconds. There were four echoes acquired for each MRI volume, TEs = (.011, .0297, 0.0484, 0.0671) seconds. The phase encoding was performed in the anteroposterior direction (j-) to minimize susceptibility artifacts. Total acquisition time varied depending on the specific task. To accelerate the acquisition, parallel imaging was used with a reduction factor of 2 in the in-plane direction. The fMRI data were acquired using multiband acceleration with a factor of 5, allowing simultaneous acquisition of multiple slices.

Data Analysis

Neuroimaging Data

fMRI Preprocessing

fMRI data preprocessing used fMRIPrep 21.0.2 to generate individual motion-, susceptibility distortion-, and slice timing-corrected echoes. These partially preprocessed echoes were subsequently denoised using TE-dependent independent components analysis (TEDANA 0.0.12): multi-echo data were optimally combined using the T2* combination method, and principal component analysis followed by the 'stabilized' Kundu component selection decision tree was applied to the optimally combined data to identify BOLD (TE-dependent), non-BOLD (TE-independent), and uncertain (low-variance) components. The denoised optimally combined images for each task and run were smoothed with a 6-mm FWHM Gaussian kernel before single-subject and group-level analysis in SPM12.

fMRIPrep leverages preprocessing modules from different fMRI software programs (e.g., ANTs, AFNI, Freesurfer, FSL) that have different strengths in particular aspects of preprocessing. The T1w (anatomical) preprocessing pipeline in fMRIPrep 21.0.2 includes steps for skull-stripping, segmentation, brain surface reconstruction, intensity non-uniformity correction, and spatial normalization to the MNI152NLin2009cAsym template via nonlinear registration. fMRIPrep 21.0.2 functional data preprocessing includes steps correcting for inhomogeneities in the gradient field using the echo-1 *B0*-nonuniformity fieldmaps (susceptibility distortion correction; SDC), slice timing correction to 0.382s (0.5 of slice acquisition range 0s-0.765s), and co-registration to the T1w image. If fieldmaps were not available to perform SDC using Phase Encoding POLARity (PEPOLAR) techniques or PEPOLAR failed, SDC was applied using a fieldmap-less method of correction via nonlinear registration, as implemented in fMRIPrep's SyN-SDC option. SyN-SDC was applied to selected tasks from two participants: one whose FaceStroop, IFT, and resting state fieldmaps were acquired with wrong phase encoding direction, and another participant whose RMET fieldmaps were missing entirely (likely accidentally skipped during the scan session).

fMRI Analysis

fMRI analyses were conducted using Matlab batch script implementations of utilities from SPM12. The default SPM AR(1) algorithm may underestimate temporal autocorrelation in multiband EPI data, due to its higher temporal resolution, so address this potential issue, we used the FAST algorithm for autocorrelation correction [33]. For two of the three tasks (FaceStroop and RMET), neural responses to stimulus onsets were modeled using a variable duration (trial duration = reaction time on that trial), convolved with a hemodynamic response function. For the IFT "anticipation/cue" onsets, the hemodynamic response function was convolved with stimulus presentation duration as participants only viewed the cue and did not make any responses. The IFT flanker onsets were modeled using a variable duration based on reaction time. A general linear model with OLS was applied to all runs of the task(s) to obtain individual contrast images per subject. These first-level

contrast images were aggregated at the group level in a whole brain 1-sample T test to assess task effects (e.g., Incongruent > Congruent) at a familywise error (FWE)-corrected $p = .05$ threshold for statistical significance.

Region of interest (ROI) analyses involved extracting each participant's contrast parameter estimates within binary masks of a priori ROI(s), using Marsbar 0.45. Estimated BOLD activation within the ROI(s) served as dependent variable(s) for subsequent statistical analyses in R.

Behavioral Data

For all tasks, behavioral data were cleaned following established procedures (e.g., aggregating trial-level data from each participant to create summary scores, applying any quality control criteria based on task performance identifying and addressing extreme values) from previously published studies for that task. Specific analysis details are reported below in the Results section for each Aim. Broadly, preliminary behavioral analyses focused on testing for group differences in task performance using mixed ANOVAs with one between-subjects factor with three levels (group) and varying levels of one or more within-subjects factor (e.g., condition, run). Variables that differ between groups will be entered as fixed factors or covariates in the final analyses – namely, responder type, gender, and lifetime trauma (including childhood trauma).

Results

Demographic and Clinical Characteristics

The majority of the sample (N = 98) were White, later-middle aged men who had been employed in a traditional responder role, such as NYPD officer, at the time of the 9/11 attacks on the World Trade Center. The three groups were generally well-matched in terms of demographics, estimated full-scale IQ, and handedness (**Table 1**).

Table 1. Demographic and Clinical Characteristics of the Sample

	Lower WTC-exposed (N=33)	PTSD (N=32)	Highly resilient (N=33)	Overall (N=98)	*p value*
Age					.621
Mean (± SD)	53 (± 6.0)	54 (± 6.4)	54 (± 4.6)	54 (± 5.7)	
Sex					.445
Male	25 (76 %)	26 (81 %)	29 (88 %)	80 (82 %)	
Female	8 (24 %)	6 (19 %)	4 (12 %)	18 (18 %)	
Race					.412
Asian	0 (0 %)	2 (6 %)	2 (6 %)	4 (4 %)	
Black	1 (3 %)	4 (12 %)	4 (12 %)	9 (9 %)	
White	28 (85 %)	20 (62 %)	21 (64 %)	69 (70 %)	
Unspecified	4 (12 %)	6 (19 %)	6 (18 %)	16 (16 %)	
Ethnicity					.602
Non-Hispanic	29 (88 %)	26 (81 %)	26 (79 %)	81 (83 %)	
Hispanic	4 (12 %)	6 (19 %)	7 (21 %)	17 (17 %)	
Employment					.062
Disabled (not WTC-related)	1 (3 %)	3 (9 %)	2 (6 %)	6 (6 %)	
Disabled (WTC-related)	0 (0 %)	4 (12 %)	0 (0 %)	4 (4 %)	
Full time	14 (42 %)	16 (50 %)	19 (58 %)	49 (50 %)	
Part time	6 (18 %)	3 (9 %)	5 (15 %)	14 (14 %)	
Retired	11 (33 %)	4 (12 %)	7 (21 %)	22 (22 %)	
Unemployed or Other	1 (3 %)	2 (6 %)	0 (0 %)	3 (3 %)	
Highest level of education					.289
High school degree	1 (3 %)	6 (19 %)	4 (12 %)	11 (11 %)	
Some college	5 (15 %)	5 (16 %)	8 (24 %)	18 (18 %)	
Two-year college degree	4 (12 %)	5 (16 %)	2 (6 %)	11 (11 %)	
Four-year degree	17 (52 %)	7 (22 %)	11 (33 %)	35 (36 %)	
Some graduate or professional	2 (6 %)	1 (3 %)	1 (3 %)	4 (4 %)	
Graduate or professional degree	4 (12 %)	8 (25 %)	7 (21 %)	19 (19 %)	
Estimated full-scale IQ					
Mean (SD)	110 (± 9.3)	110 (± 11)	110 (± 9.3)	110 (± 10)	.151
Missing	0 (0%)	1 (3.1%)	0 (0%)	1 (1.0%)	

Responder type					**<.001**
Non-traditional	5 (15 %)	19 (59 %)	3 (9 %)	27 (28 %)	
Traditional (e.g., police, fire, EMS)	28 (85 %)	13 (41 %)	30 (91 %)	71 (72 %)	
Number of WTC exposures					**<.001**
Mean (SD)	2.5 (± 0.97)	5.4 (± 2.4)	5.5 (± 1.2)	4.5 (± 2.1)	
Right-handed					.442
No	3 (9 %)	3 (9 %)	6 (18 %)	12 (12 %)	
Yes	30 (91 %)	29 (91 %)	27 (82 %)	86 (88 %)	
CAPS-5 - Past Month					**<.001**
Mean (SD)	0.94 (± 1.4)	28 (± 10)	0.94 (± 1.1)	9.9 (± 14)	
CAPS-5 – Worst Month					**<.001**
Mean (SD)	2.4 (± 2.6)	42 (± 14)	2.4 (± 2.4)	15 (± 20)	
Beck Depression Inventory-II					**<.001**
Mean (SD)	1.2 (± 2.0)	20 (± 12)	0.69 (± 1.4)	7.0 (± 11)	
Missing	0 (0%)	1 (3.1%)	1 (3.0%)	2 (2.0%)	

Note: Participants with 'Unspecified' race provided ethnicity but not race, due to survey design of this question. BDI-II total is missing for two participants because they provided no response on one or more items. Missing data will be addressed by multiple imputation in final analyses. CAPS-5 = Clinician-Administered PTSD Scale for DSM-5. BDI-II = Beck Depression Inventory – Version II. P values from chi square (categorical variables) or F (numeric variables) tests.

Table 2. Prevalence of Other DSM-5 Psychiatric Diagnoses (Current and Lifetime) in the PTSD Group

SCID-5 diagnosis	*Current*	*Lifetime*
Major depressive disorder	10 (31.3%)	19 (59.4%)
Persistent depressive disorder	7 (21.9%)	12 (37.5%)
Other specified depressive disorder	-	1 (3.1%)
Generalized anxiety disorder	3 (9.4%)	3 (9.4%)
Panic disorder	5 (15.6%)	9 (28.1%)
Social anxiety disorder	4 (12.5%)	4 (12.5%)
Substance use disorder	-	14 (43.8%)

Note: Participants with lifetime alcohol or substance use disorder(s) were eligible for the study only if they had not met DSM-5 criteria for alcohol or substance use disorder diagnosis within the past 3 months. SCID-5 = Structured Clinical Interview for DSM-5.

Specific Aim 1: Neuroimaging of Implicit Emotion Regulation in Resilient and Symptomatic World Trade Center Responders

Quality Control and Processing

fMRI data. See sections under *Methods* and *Data Analysis* (above) for details of fMRI acquisition and preprocessing. Ninety-six of 98 participants completed the FaceStroop task (one did not have time to complete the FaceStroop during his scan session, and one opted to discontinue Visit 2 due to claustrophobia before any imaging data had been collected). FaceStroop fMRI data from 6 participants was excluded due to excessive motion in the scanner (n = 5) or technical error in MRI acquisition (n = 1).

Behavioral data. An additional 5 participants were excluded based on conventional quality control thresholds for FaceStroop performance (<25% missed trials and >75% accuracy[16]). After excluding trials with conditions of no interest (fixation cross display; trials with “XXX” overlaid instead of a word) and/or errors of commission or omission as is typical for this task, all trials had reaction times <2000ms. In keeping with established methods, we also dropped any trials on which reaction time was <200ms, as very brief response latencies typically reflect “misfires” rather than an intentional response.

Preliminary Findings for Aim 1

FaceStroop analyses included data from 85 participants: *n*=31 *highly resilient* responders *n* = 26 *lower WTC-exposed* responders, and *n* = 28 *symptomatic* responders (PTSD group).

Task performance. Individual trial-level reaction times were aggregated within the following levels: participant, task run (1 or 2), condition (incongruent or congruent), and emotion valence of the target (happy or afraid face). Task accuracy was calculated over all trials on which participants responded, as well as accuracy within condition (incongruent or congruent). There was no significant effect of group in separate mixed 3 (Group) x 2 (Emotion) x 2 (Condition) ANOVAs: Mean RT $F(2,83) = 1.23$, $p = .299$, Accuracy $F(2,83) = 2.38$, $p = .099$. There were no significant interactions between group and the other factors. As typically for this and similar tasks, participants on the whole were slower to respond and less accurate on incongruent trials: Mean RT $F(1,83) = 144.87$, $p < .001$, Accuracy $F(1,83) = 202.09$, $p < .001$. These results are consistent with the prior FaceStroop study where there were no significant differences in task performance between trauma-exposed controls vs. individuals with PTSD[16].

Region of interest analysis. To test our a-priori region of interest hypotheses, we created an 8-mm sphere around the rostral ACC peak coordinates reported in Offringa et al. (2013) [x=16, y=36, z=34] and extracted participants' *Incongruent > Congruent* BOLD activation estimates within the spherical mask. Consistent with our prediction, we observed an overall effect of group, $F(2,82) = 3.20$, $p = .046$, such that the highly resilient group showed the greatest rACC response to emotional conflict, followed by the lower WTC-exposed group, with minimal to no rACC activation in the PTSD group (**Figure 2**). Linear contrast results supported our specific directional hypotheses: rACC in Highly Resilient > PTSD ($b = 0.17$, SE = 0.70, $t(82) = 2.48$, $p = .015$), Highly Resilient > Lower WTC-Exposed ($b = 0.05$, SE = 0.07, $t(82) = 0.72$, $p = .48$), and Lower WTC-Exposed > PTSD ($b = 0.12$, SE = 0.13, $t(82) = 1.67$, $p = .098$). Effects were similar when using the combined bilateral subgenual and pregenual ACC masks from the Automated Anatomical Labeling Atlas (AAL3) to define the rACC region of interest. Though the overall effect of group was no longer statistically significant using the atlas-defined rACC mask, $F(1,82) = 2.11$, $p = .128$, the linear contrast results supported the same conclusion: Highly Resilient > PTSD ($b = 0.26$, SE = 0.13, $t(82) = 2.03$, $p = .046$), Highly Resilient > Lower WTC-Exposed ($b = 0.09$, SE = 0.13, $t(82) = .67$, $p = .504$), and Lower WTC-Exposed > PTSD ($b = 1.70$, SE = 0.13, $t(82) = 1.29$, $p = .202$).

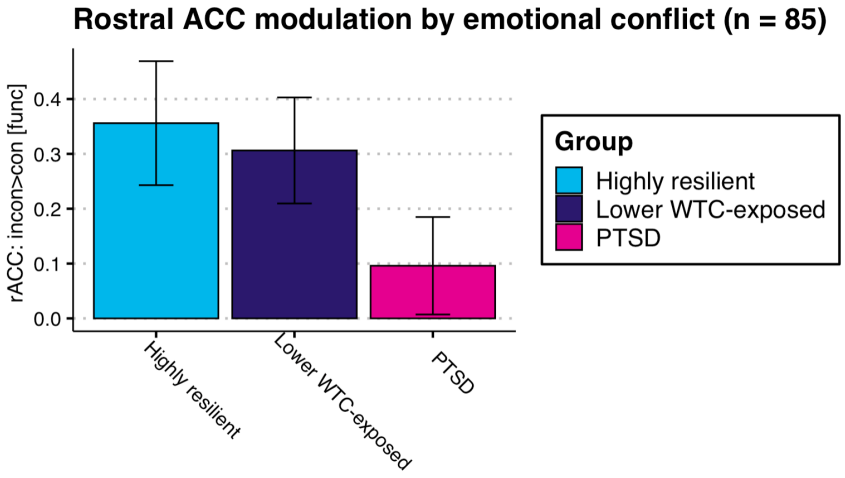


Figure 2. *Rostral ACC Modulation by Emotional Conflict.*

Mean (and standard error) in each group: rostral anterior cingulate BOLD activation from the *Incongruent > Congruent* contrast, representing engagement during implicit emotion regulation.

Analyses in progress and planned analyses. Analyses in progress will examine "emotional conflict adaptation" (i.e., response to post-incongruent incongruent trials vs. post-incongruent congruent trials), linked in previous studies to rACC functioning, as an additional index of implicit emotion regulation[34].

Specific Aim 2: Neuroimaging of Reward Responsivity in Resilient and Symptomatic World Trade Center Responders

Quality Control and Processing

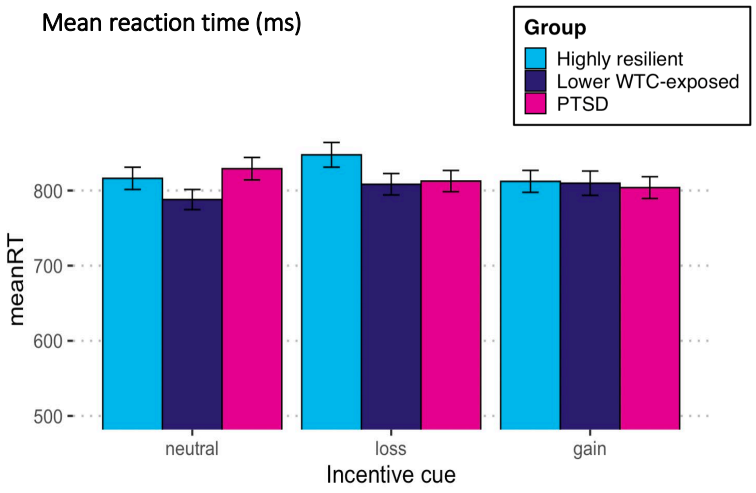
fMRI data. See sections under *Methods* and *Data Analysis* (above) for details of fMRI acquisition and preprocessing. Ninety seven of 98 participants completed the IFT (one opted to discontinue Visit 2 due to claustrophobia before any imaging data had been collected). fMRI data from 3 participants were excluded due to excessive motion in the scanner ($n = 1$), issues with temporal syncing between the scanner and behavioral data (n = 1) or technical error in MRI acquisition ($n = 1$).

Behavioral data. After excluding missed trials, individual trial-level reaction times (RTs) were aggregated within the following strata: participant, flanker interference (high/incongruent or low/congruent), incentive condition (gain cue, null cue, loss cue), incentive outcome (gain, null, or lose money), and feedback (positive or negative). Trial-level RTs ranged from 200-1700ms. Because of the stringent upper limit on RTs, no trials were

discarded as outliers. Task accuracy (*n* correct / total trials with a response) was calculated within participant, incentive condition, and flanker interference, as well as overall trials.

Preliminary Findings for Aim 2

IFT analyses included data from 93 participants: *n* = 31 highly resilient, *n* = 31 lower WTC-exposed, and *n* = 31 responders with PTSD.



Task performance. There was no significant effect of group in separate mixed 3 (Group) x 2 (Interference) x 3 (Incentive Cue) ANOVAs for Mean RT $F(2,90) = .03$, $p = .739$ and Accuracy $F(2,90) = 2.04$, $p = .136$. Accuracy on high-interference flanker trials was lower than on low-interference trials, $F(1,90) = 46.25$, $p < .001$ (averaged across incentive cues and group). Mean RTs on high-interference trials were slower than on low-interference trials, $F(1,90) = 16.24$, $p < .001$. There was an interaction between group and incentive cue, $F(4,180) = 3.71$, $p = .006$. Pairwise contrasts with Holm correction for multiple comparisons indicated that in the highly resilient and lower WTC-exposed groups, null incentive trials were faster than loss incentive trials. In the highly resilient group only, loss incentive trials were slower than gain incentive trials. There were no significant RT differences by incentive cue in the PTSD group (**Figure 3**).

Whole brain analysis. After obtaining single-subject T contrast images, a 1-sample T contrast at the group level was used to examine the effect of reward anticipation (*Gain cue* > *Loss cue*) across the whole brain. Relative to Loss cues, Gain cues elicited greater activation in visual and spatial attention areas (FWE-corrected $p < .05$, $k = 20$), as well as additional regions at a lower statistical threshold (uncorrected $p < .001$, $k = 20$), including the dorsal and ventral striatum, thalamus, dorsal and ventral ACC, and medial prefrontal cortex. We identified two clusters corresponding to our vmPFC and ventral striatum ROIs, one within the medial orbital area of the superior frontal gyrus (x=-4, y=56, z=-2) and the other overlapping with nucleus accumbens and olfactory tubercle (i.e., ventral striatum, x=-18, y=10, z=-14), respectively (**Figure 4**).

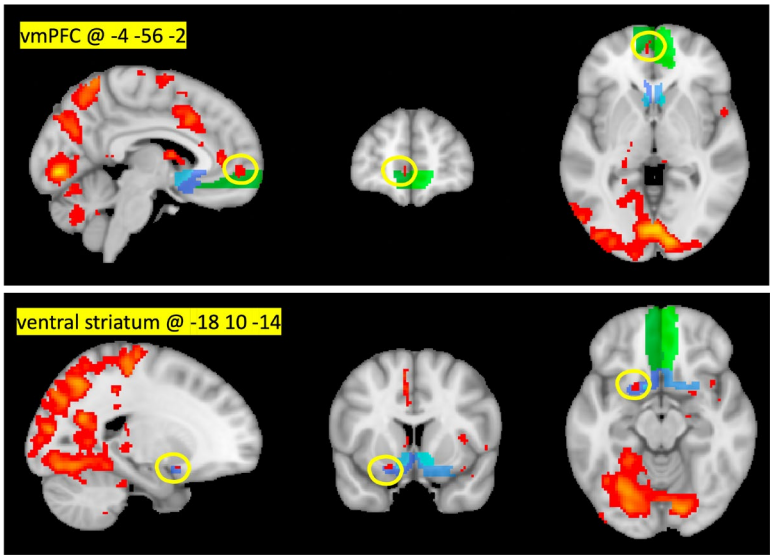


Figure 4. *Incentive Flanker Task ROIs*

Red activation map illustrates brain regions showing an effect of reward vs. loss anticipation (*Gain Cue > Loss Cue*, thresholded at $T = 3.09$, $p = .001$, $k = 10$). Yellow circles indicate clusters corresponding to the vmPFC and ventral striatum. Green and blue-shaded underlays indicate, respectively, atlas-defined vmPFC (AAL3 #21, 22) and ventral striatum. (AAL3 #156, 157, 17, 18) and their overlap with the vmPFC and ventral striatum functionally defined ROIs.

Region of interest analysis. To test our a priori region of interest hypotheses about the IFT anticipation phase, we created "functionally defined" masks of the vmPFC and ventral striatum based on the two clusters that corresponded to vmPFC and ventral striatum from the 1-sample T test of *Gain Cue* > *Loss Cue* across the whole brain, and then extracted participants' parameter estimates within each of the two ROIs.

Using the functionally defined ROIs, there was no significant overall effect of group on reward anticipation-related vmPFC activation, $F(2,90) = .27$, $p = .762$, nor the ventral striatum, $F(2,90) = 1.93$, $p = .151$ (i.e., Gain Cue > Loss Cue contrast). However, for the ventral striatum, the direction of linear contrast results supported our directional hypotheses: highly resilient > PTSD ($t(90) = 1.95$, $p = .054$), highly resilient > lower WTC-exposed ($t(90) = 0.76$, $p = .45$), and lower WTC-exposed > PTSD ($t(90) = 1.19$, $p = .237$) (**Figure 5**).

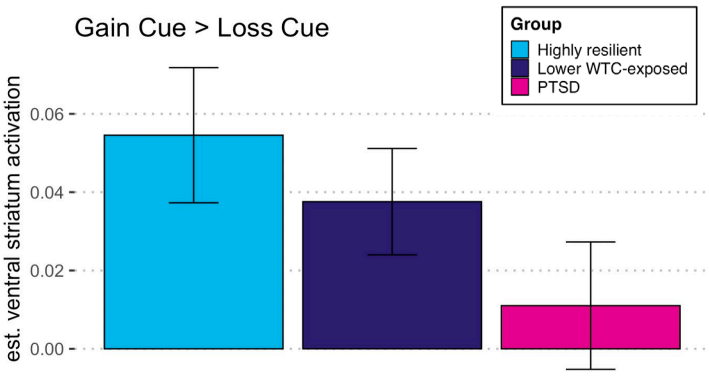


Figure 5. *Ventral Striatum Modulation by Reward Anticipation (vs. Loss).*

Mean (and standard error) in each group: parameter estimates for ventral striatum at -18 10 -14 during reward (vs. loss) anticipation.

Interestingly, examining ventral striatum parameter estimates when Gain and Loss Cues were each contrasted with the Neutral Cue clarified that that the Gain Cue > Loss Cue effect in the highly resilient group was driven by ventral striatum *deactivation* in the Loss Cue > Neutral Cue contrast (**Figure 6**). In other words, it appears that the highly resilient group on average exhibited similar ventral striatum activation to Gain and Neutral Cues, that was substantially greater than their ventral striatum response to Loss Cues. In contrast, ventral striatum activation in the PTSD group appeared not to significantly differ across anticipation of reward, loss, or neutral monetary outcome. The lower WTC-exposed group showed similar ventral striatum effects to the highly resilient group but the difference between lower WTC-exposed and the other two groups was not statistically significant. Loss Cue > Neutral Cue linear contrast results: highly resilient > PTSD ($t(90) = -2.24$, $p = .023$), highly resilient > lower WTC-exposed ($t(90) = -0.78$, $p = .433$), and lower WTC-exposed > PTSD ($t(90) = -1.45$, $p = .150$).

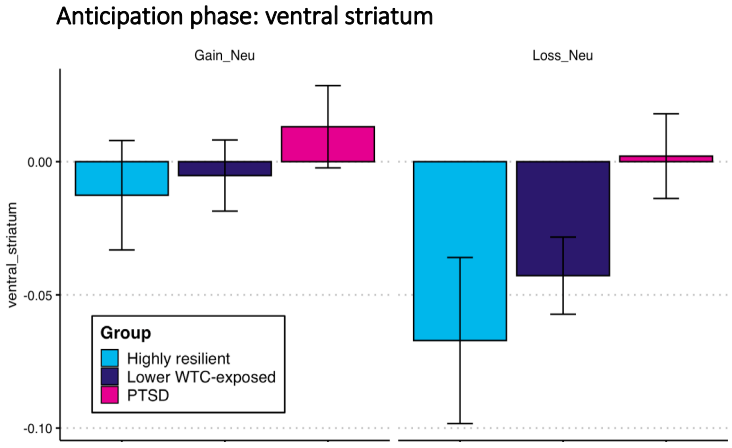


Figure 6. *Ventral Striatum Modulation by Reward and Loss Anticipation (vs. Neutral).*

Ventral striatum (-18 10 -14) mean parameter estimates by group, for gain cue > neutral cue and loss cue > neutral cue.

Analyses in progress and planned analyses. Analyses in progress will investigate whether neural responses to receiving (rather than anticipating) monetary reward also varies by group. Future exploratory analyses will examine the flanker data as an index of executive functioning and cognitive control. We are also exploring different modeling strategies to avoid potential issues with collinearity between regressors and to test the linear effect of cue condition more directly (e.g., modeling "condition" as a parametric modulator of the main "cue" regressor, rather than three separate regressors).

Specific Aim 3: Neuroimaging of Social Cognition in Resilient and Symptomatic World Trade Center Responders

Quality Control and Processing

fMRI data. See sections under *Methods* and *Data Analysis* (above) for details of MRI acquisition and preprocessing. Ninety-seven of 98 participants completed the RMET (one opted to discontinue Visit 2 due to claustrophobia before any imaging data had been collected). fMRI data from four participants were excluded due to excessive motion in the scanner ($n = 4$) or technical error in MRI acquisition ($n = 1$).

Behavioral data. Individual trials on which reaction time was above or below three standard deviations from the mean of all trials across the sample were dropped. After filtering out missed and outlier trials, individual trial-level reaction times were aggregated within the following strata: participant, task run (1 or 2), and condition (social or non-social decision). Task accuracy was calculated over all trials on which participants responded, as well as accuracy within condition.

Preliminary Findings for Aim 3

RMET analyses included data from 93 participants: *n* = 32 in the highly resilient group, *n* = 30 in the lower WTC-exposed group, and *n* = 31 in the PTSD group.

Task performance. Individual trial-level reaction times were aggregated within the following strata: participant, task run (1 or 2), and condition (social decision or non-social decision). Task accuracy was calculated over all trials on which participants responded, as well as within condition. All three groups were slower to respond and less accurate on social trials: Mean RT $F(1,90) = 263.0$, $p < .001$, Accuracy $F(1,90) = 255.51$, $p < .001$ (**Figure 7**). In two separate mixed 3 (Group) x 2 (Condition) ANOVAs for mean RT and accuracy, there was no significant effect of group: Mean RT $F(2,90) = 2.28$, $p = .108$, Accuracy $F(2,90) = 0.91$, $p = .407$. There were no significant interactions between group and condition. However, linear contrasts comparing groups identified that the lower WTC-exposed group was significantly faster to respond (across both conditions) vs. the PTSD group, b = 103.5, SE = 51.3, t(90) = 2.02, p = .046. Performance in the highly resilient group did not significantly differ from either the PTSD or lower WTC-exposed groups.

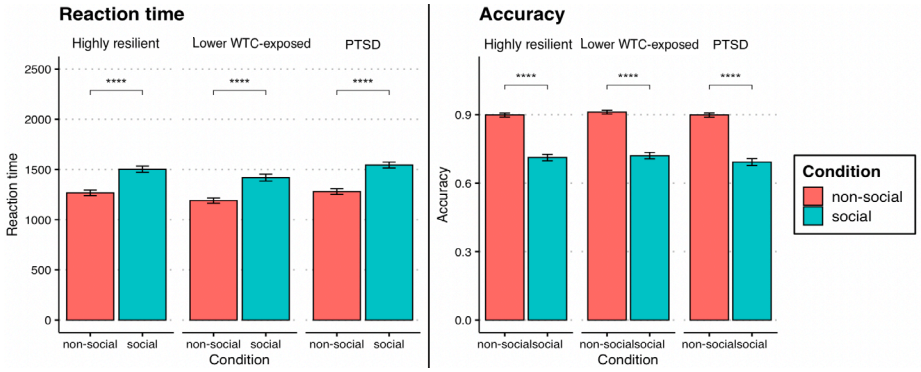


Figure 7. *Reading the Mind in the Eyes: Task Performance by Group.*

Across all three groups, participants were significantly slower to respond and less accurate on social vs. non-social decision trials (pairwise comparisons p < .001).

Whole brain analysis. Because of the relatively high difficulty of the social condition in this version of the RMET and the fact that incorrect trials still required the participant to make a judgement using social cognition, error trials were not modeled separately from correct trials. After obtaining single-subject T contrast images, a 1-sample T contrast at the group level was used to examine the effect of *Social* > *Non-social* across the whole brain. The whole brain analysis showed a robust task effect where the Social condition elicited greater activation in regions typically involved in social cognition and theory of mind[20] (FWE-corrected p < .05, k = 20). Peak coordinates corresponding to our a-priori ROIs were located in the left (-50, 30, -2) and right (46, 32, -2) inferior frontal gyri, right temporoparietal junction (46, -34, 4), left dmPFC (-6, 60, 30 and -10, 32, 58) and right (4, 62, 26) dmPFC, and right temporal pole (50, 16, -32). Other brain regions that showed an effect of Social vs. Non-social included the posterior cingulate (-2, -48, 30), middle cingulate (-8, 14, 66), and supplementary motor area (-8, 14, 66) (**Figure 8**).

Region of interest analysis. To test our a priori region of interest hypotheses, we created masks of the ROIs described above from the 1-sample T test of *Social* > *Non-social* across the whole brain, and then extracted participants' parameter estimates from within each of these. Contrary to hypotheses, there was no statistically significant effect of group on any of the ROIs: right IFG $F(2,90) = .02$, left IFG $F(2,90) = .40$, TPJ $F(2,90) = .72$, right dmPFC $F(2,90) = .09$, left dmPFC $F(2,90) = .09$, right temporal pole $F(2,90) = .19$ (all *p*'s >.50) (**Figure 9**).

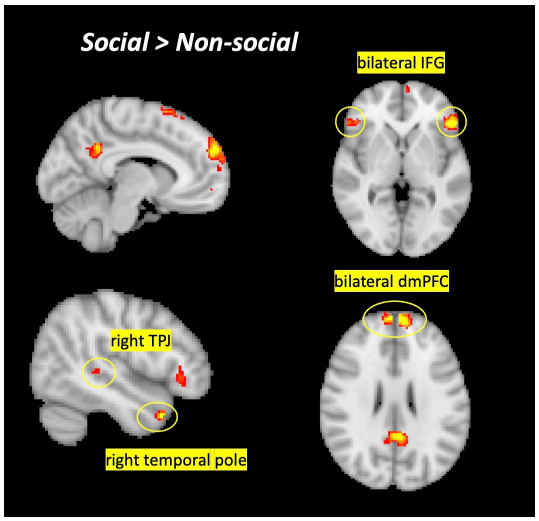


Figure 8. *RMET Social Cognition ROIs.*

Red activation map illustrates brain regions showing an effect of social cognition (*Social > Non-social*) thresholded at $T = 4.51$, pFWE = .05, k = 20). Yellow circles indicate clusters corresponding to a priori regions of interest for the RMET.

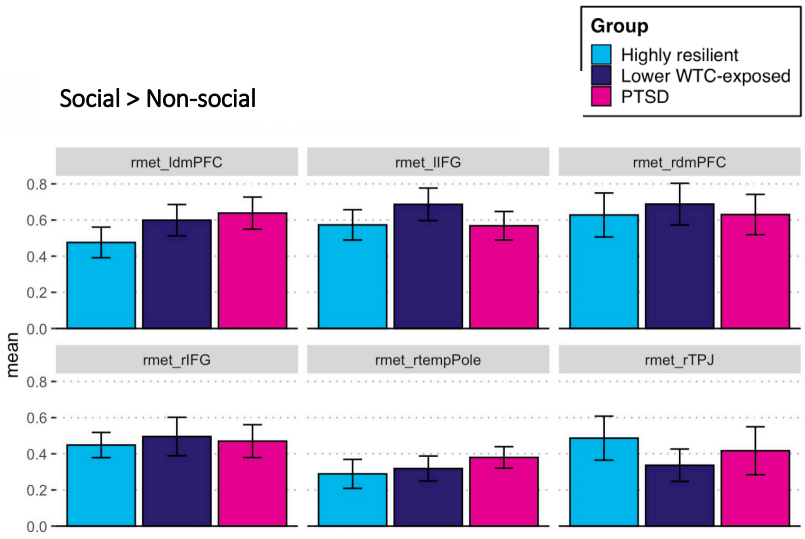


Figure 9. *RMET ROIs by Group.*

Mean parameter estimates for Social > Non-social within each of the ROIs (bilateral inferior frontal gyri, bilateral dmPFC, right temporoparietal junction, right temporal pole).

In progress and planned analyses. Analyses in progress are investigating potential relationships between social cognition-related BOLD activation, self-report measures of social functioning, and/or performance on the out-of-scanner original version of the Reading the Mind in the Eyes Test. Further, an F-test for the effect of group across the whole brain identified a posterior superior temporal sulcus cluster with greater activation in both the highly resilient and lower WTC-exposed groups versus the PTSD group (albeit at an uncorrected statistical threshold, $p < .001$, k = 10). The posterior superior temporal sulcus is consistently linked to social cognition in healthy adults, as well as poor social cognition in disorders including schizophrenia and autism. We intend to follow up on this exploratory finding.

Specific Aim 4: Identifying Heterogeneous Patterns of Brain Activity linked to Resilience via Density-based Spatial Clustering.

In progress and planned analyses. Resilience is a heterogeneous phenotype. On a region-by-region basis, across individuals, we hypothesize brain activations in the highly resilient group will evidence common and distinct neural mechanisms underlying emotion regulation, reward processing, and social cognition that are indicative of distinct pathways to resilience. Analyses for Aim 4 will be completed after finalizing the analyses from Aims 1-3.

Future Work

Exploratory analyses will probe for between-group differences in resting-state functional connectivity between our a-priori regions of interest and the rest of the brain. We will also use group independent components analysis to examine functional network connectivity among large-scale brain networks implicated in psychopathology and resilience, including default, cognitive control, and salience networks. Analyses of behavioral data from Visit 3 (out-of-scanner RMET, MASC, Dot Probe, PRT) are currently underway.

Discussion

Insights derived from the study of functional neural mechanisms in highly resilient rescue and recovery workers are essential to informing the etiology of resilience, and for the development of novel preventive and treatment interventions for WTC and other disaster responders, as well as other populations of trauma survivors.[25-28] This was, to our knowledge, the first study to investigate key neural circuits for emotion regulation, reward processing, and social cognition hypothesized to facilitate resilience to trauma exposure in a sample of WTC responders, who all experienced the same potentially traumatic event (albeit differing in exposure severity) but show markedly different trajectories of psychological functioning over 20 years since the September 11th, 2001 attacks. Importantly, we were able to recruit a sample of *highly resilient* WTC responders who have remained psychologically well with no lifetime psychiatric disorder, despite having endured severe WTC-related exposures ("highly resilient"). We compared these highly resilient individuals to two groups, the first being WTC responders who were also resilient (no lifetime psychiatric disorder) *but* had lower severity of WTC-related exposures ("lower WTC-exposed"), and the second being WTC responders who developed WTC-related PTSD and are still experiencing clinically significant, chronic PTSD symptoms as a result of their involvement in the 9/11 rescue and recovery efforts. Existing functional neuroimaging studies have primarily focused on individuals with PTSD, without further characterizing the resilient group (trauma-exposed control group) when included. Further, the vast majority of studies compared neural responses in PTSD patients to either trauma-exposed or unexposed controls – not accounting for the fact that trauma exposure is not equally distributed across individuals.

In the present study, highly resilient WTC responders exhibited higher BOLD activation in a-priori regions of interest related to implicit or automatic emotion regulation (rostral anterior cingulate; rACC) (***Specific Aim 1***) as well as reward anticipation (ventral striatum) (***Specific Aim 2***), compared to both symptomatic and non-symptomatic comparison groups. Notably, in both Aims 1 and 2, findings were consistent with the hypothesized linear effect of resilience (highly resilient > lower WTC-exposed > PTSD groups), such that the difference between highly resilient and PTSD groups was statistically significant, while the difference in activation between the lower WTC-exposed group vs. the other two groups was not.

Our findings extend previous work implicating reward responsivity and emotion regulation in the ability to avoid negative psychological effects of trauma and adversity[2]. For example, a prior study found diminished rACC response to the same affective FaceStroop task we used in the present study, in individuals with PTSD compared to trauma-exposed controls[16]. We replicated the finding that rACC engagement during automatic emotional conflict regulation is modulated by PTSD, further elaborating on this effect by showing that higher vs. lower trauma exposure burden also modulates rACC activation in resilient individuals (***Specific Aim 1***). The rACC plays a key role in regulating emotional conflict, via functional connectivity with the amygdala[34], and our finding is consistent with the idea that greater ability to inhibit limbic reactivity by engaging the medial prefrontal cortex represents a resilience-promoting adaptation after trauma exposure (e.g., Chen et al 2018)[35].

Our findings also add to previous work regarding the role of reward responsivity in resilience to trauma. Lesser reactivity to any motivationally salient stimulus – positive or negative – might allow for greater stability in a changing environment, enabling the individual to maintain focus on goals in the face of salient yet irrelevant cues (e.g., Vythilingam et al 2009)[18]. However, positive emotions and traits such as dispositional optimism are consistently linked to resilience in humans and require intact sensitivity to potential rewards in the environment – in contrast to the anhedonia and blunted reward response commonly seen in individuals with PTSD[1]. In the present study, the highly resilient group showed greater ventral striatum activation while anticipating potential reward vs. loss in a modified monetary incentive delay task, compared to the PTSD group (at a statistically significant level) and the lower-WTC-exposed group (though not statistically significant) (***Specific Aim 2***). This effect was driven by the fact that the highly resilient group exhibited ventral striatum *deactivation* on trials with a potential loss outcome; activation in the ventral striatum was not substantially different in reward anticipation vs. neutral (no potential gain or loss of money) anticipation. In contrast, in both the lower WTC-exposed and PTSD groups ventral striatum response to loss incentive cues varied little from the response to neutral and reward cues. This finding may help explain why we see mixed findings in previous fMRI studies: resilient individuals may appear either more or less responsive to reward depending on the comparison condition used. Lack of difference between reward and neutral conditions may indicate either lesser reward-related activation, or a higher reward response to neutral cues in resilient individuals. The next step in Specific Aim 2 is to

analyze ROI activation during the outcome period of the task, in which participants learn whether they won money, lost money, or neither (consummatory reward).

We also examined social cognition-related regions of interest during a modified Reading the Mind in the Eyes task, including the dorsomedial PFC, temporal pole, temporoparietal junction, and inferior frontal gyri (***Specific Aim 3***). Social cognition is an emerging area of interest in resilience neuroscience[2]; despite few existing neuroimaging studies, the ability to accurately read and respond adaptively to social cues helps individuals maintain supportive the social networks consistently shown to buffer negative effects of trauma exposure. Our preliminary analyses for this aim did not identify any group differences in either behavioral performance on the task, nor social cognition-related activation within any of our regions of interest, despite the task eliciting a robust, canonical pattern of social cognition-related activation across the groups in the whole-brain analysis. However, we did see a potential signal of differential social cognition-related neural functioning in the posterior superior temporal sulcus in the PTSD group vs. both resilient groups, which merits further exploration (currently underway).

Exploratory analyses of the resting state data are currently in progress, as well as are analyses that seek to identify heterogenous neural phenotypes of resilience via density-based spatial clustering (***Specific Aim 4***), a method with potential to illuminate other factors contributing to differential outcomes after trauma exposure. Also in progress are ***exploratory analyses*** of the out-of-scanner behavioral data (social cognition, social navigation, and social controllability, threat bias, and reward learning) and how specific exposures (e.g., being exposed to human remains; being injured in the attacks or during the recovery efforts) may have a differential impact on vulnerability to adverse psychological outcomes after trauma exposure. Finally, ***exploratory analyses*** of the structural brain imaging data are investigating volumetric differences in the three groups and testing putative associations between grey matter volume in key brain regions and behavior (e.g., hippocampus and social navigation behavior).

Conclusion

Findings from this novel neuroimaging study of resilience-linked mechanisms in WTC-exposed individuals who vary both in trauma exposure and PTSD presence/absence suggest that, at least for two of the three hypothesized mechanisms (emotion regulation and reward response), the most resilient individuals also show the greatest engagement within key regions of interest. These findings contribute to our understanding of the neural instantiation of psychological factors that enable some individuals to be highly resilient despite high trauma exposure burden. Knowledge gained from the study of neural function in highly resilient individuals can be harnessed to develop novel approaches to help prevent the development of trauma-related psychopathology in more vulnerable individuals or mitigate trauma-related psychopathology.

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REFERENCES

1. Feder, A., Fred-Torres, S., Southwick, S. M. & Charney, D. S. The Biology of Human Resilience: Opportunities for Enhancing Resilience Across the Life Span. *Biol Psychiatry* **86**, 443–453 (2019).

2. Norbury, A., Seeley, S. H., Perez-Rodriguez, M. M. & Feder, A. Functional neuroimaging of resilience to trauma: convergent evidence and challenges for future research. *Psychol. Med.* **53**, 3293–3305 (2023).

3. Horn, S. R., Charney, D. S. & Feder, A. Understanding resilience: New approaches for preventing and treating PTSD. *Experimental Neurology* **284**, 119–132 (2016).

4. Forbes, E. E. *et al.* Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am J Psychiatry* **166**, 64–73 (2009).

5. Nikolova, Y. S., Bogdan, R., Brigidi, B. D. & Hariri, A. R. Ventral striatum reactivity to reward and recent life stress interact to predict positive affect. *Biol Psychiatry* **72**, 157–163 (2012).

6. Hyde, L. W., Gorka, A., Manuck, S. B. & Hariri, A. R. Perceived social support moderates the link between threat-related amygdala reactivity and trait anxiety. *Neuropsychologia* **49**, 651–656 (2011).

7. Bridgett, D. J., Oddi, K. B., Laake, L. M., Murdock, K. W. & Bachmann, M. N. Integrating and differentiating aspects of self-regulation: Effortful control, executive functioning, and links to negative affectivity. *Emotion* **13**, 47–63 (2013).

8. Sapienza, J. K. & Masten, A. S. Understanding and promoting resilience in children and youth. *Current Opinion in Psychiatry* **24**, 267–273 (2011).

9. Kent, M., Rivers, C. T. & Wrenn, G. Goal-Directed Resilience in Training (GRIT): A Biopsychosocial Model of Self-Regulation, Executive Functions, and Personal Growth (Eudaimonia) in Evocative Contexts of PTSD, Obesity, and Chronic Pain. *Behavioral Sciences* **5**, 264–304 (2015).

10. Ong, A. D., Bergeman, C. S., Bisconti, T. L. & Wallace, K. A. Psychological resilience, positive emotions, and successful adaptation to stress in later life. *J Pers Soc Psychol* **91**, 730–749 (2006).

11. Bar, M. A cognitive neuroscience hypothesis of mood and depression. *Trends Cogn Sci* **13**, 456–463 (2009).

12. Garland, E. L. *et al.* Upward Spirals of Positive Emotions Counter Downward Spirals of Negativity: Insights from the Broaden-and-Build Theory and Affective Neuroscience on The Treatment of Emotion Dysfunctions and Deficits in Psychopathology. *Clin Psychol Rev* **30**, 849–864 (2010).

13. Tugade, M. M. & Fredrickson, B. L. Resilient Individuals Use Positive Emotions to Bounce Back From Negative Emotional Experiences. *J Pers Soc Psychol* **86**, 320–333 (2004).

14. Plana, I., Lavoie, M.-A., Battaglia, M. & Achim, A. M. A meta-analysis and scoping review of social cognition performance in social phobia, posttraumatic stress disorder and other anxiety disorders. *J Anxiety Disord* **28**, 169–177 (2014).

15. Stevens, J. S. & Jovanovic, T. Role of social cognition in post-traumatic stress disorder: A review and meta-analysis. *Genes, Brain and Behavior* **18**, e12518 (2019).

16. Offringa, R. *et al.* Diminished rostral anterior cingulate cortex activation during trauma-unrelated emotional interference in PTSD. *Biol Mood Anxiety Disord* **3**, 1–6 (2013).

17. Stern, E. R. *et al.* Hyperactive Error Responses and Altered Connectivity in Ventromedial and Frontoinsular Cortices in Obsessive-Compulsive Disorder. *Biological Psychiatry* **69**, 583–591 (2011).

18. Vythilingam, M. *et al.* Reward circuitry in resilience to severe trauma: An fMRI investigation of resilient special forces soldiers. *Psychiatry Research: Neuroimaging* **172**, 75–77 (2009).

19. Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y. & Plumb, I. The “Reading the Mind in the Eyes” Test Revised Version: A Study with Normal Adults, and Adults with Asperger Syndrome or High-functioning Autism. *Journal of Child Psychology and Psychiatry* **42**, 241–251 (2001).

20. Schurz, M., Radua, J., Aichhorn, M., Richlan, F. & Perner, J. Fractionating theory of mind: A meta-analysis of functional brain imaging studies. *Neuroscience & Biobehavioral Reviews* **42**, 9–34 (2014).

21. Nasreddine, Z. S. *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695–699 (2005).

22. Wechsler, D. *Wechsler Test of Adult Reading: WTAR.* (The Psychological Corporation., 2001).

23. Kubany, E. S. *et al.* Development and preliminary validation of a brief broad-spectrum measure of trauma exposure: the Traumatic Life Events Questionnaire. *Psychol Assess* **12**, 210–224 (2000).

24. Bernstein, D. P. *et al.* Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American journal of psychiatry* **151**, 1132–1136 (1994).

25. Weathers, F. W. *et al.* The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychological Assessment* **30**, 383–395 (2018).

26. Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. & Erbaugh, J. An inventory for measuring depression. *Arch Gen Psychiatry* **4**, 561–571 (1961).

27. Weathers, F. W. *et al.* Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). (2013).

28. First, M. B., Spitzer, R. L., Gibbon, M. & Williams, J. *Structured clinical interview for DSM-IV-TR Axis I disorders, research version.* (Biometrics Research, 2002).

29. Bos, P. A. *et al.* Testosterone reduces functional connectivity during the ‘Reading the Mind in the Eyes’ Test. *Psychoneuroendocrinology* **68**, 194–201 (2016).

30. Iacoviello, B. M. *et al.* Attention Bias Variability and Symptoms of Posttraumatic Stress Disorder: Attention Bias Variability in PTSD. *Journal of Traumatic Stress* **27**, 232–239 (2014).

31. Pizzagalli, D. A., Iosifescu, D., Hallett, L. A., Ratner, K. G. & Fava, M. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *J Psychiatr Res* **43**, 76–87 (2008).

32. Dziobek, I. *et al.* Introducing MASC: A Movie for the Assessment of Social Cognition. *J Autism Dev Disord* **36**, 623–636 (2006).

33. Bollmann, S., Puckett, A. M., Cunnington, R. & Barth, M. Serial correlations in single-subject fMRI with sub-second TR. *NeuroImage* **166**, 152–166 (2018).

34. Etkin, A., Büchel, C. & Gross, J. J. The neural bases of emotion regulation. *Nat Rev Neurosci* **16**, 693–700 (2015).

35. Chen, F. *et al.* Increased Inhibition of the Amygdala by the mPFC may Reflect a Resilience Factor in Post-traumatic Stress Disorder: A Resting-State fMRI Granger Causality Analysis. *Frontiers in Psychiatry* **9**, 516 (2018).

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Publications

Published Abstracts

Norbury A, Monti E, Diab E, Pietrzak RH, Perez-Rodriguez M, Feder A: Neuroimaging resilience to trauma in World Trade Center rescue and recovery workers [Abstract]. *Biological Psychiatry* 87(9), Supplement, S424, 2020.

Lapolla D, Monti E, Norbury A, Pietrzak R, Perez-Rodriguez M, Feder A: Social cognitive function and trauma related symptom dimensions in 9/11 World Trade Center responders [Abstract] *Biological Psychiatry* 89(9):S220, 2021.

Schreiber Z, Braide B, Zonshayn D, Schafler T, Monti E, Corcoran C, Perez-Rodriguez MM, Pietrzak RH, Feder A: Linguistic markers of chronic PTSD in World Trade Center rescue and recovery workers: A computer-based natural language processing study. [Abstract]. *Neuropsychopharmacology* 46(Suppl 1):50(P98), 2021.

Seeley SH, Schreiber Z, Verghese M, Leska T, Astorino E, Morris LS, Cahn L, Hermans E, Pietrzak RH, Perez-Rodriguez MM, Feder A: Greater social cognition-related right temporal pole activation in World Trade Center responders with PTSD: preliminary evidence. [Abstract]. *Neuropsychopharmacology* 47(Suppl 1):pp 88-88, 2023.

Published manuscripts

Norbury A, Brinkman H, Kowalchyk M, Monti E, Pietrzak RH, Schiller D, Feder A: Latent cause inference during extinction learning in trauma-exposed individuals with and without PTSD. *Psychological Medicine* 2021;8:1-12.

Norbury A*, Seeley SH*, Perez-Rodriguez MM, Feder A: Functional neuroimaging of resilience to trauma: convergent evidence and challenges for future research. *Psychological Medicine* 2023;53(8):3293-3305.

Presentations

Schafer M, Monti E, Feder A, Schiller D: *Social consistency is related to social support and social network size in PTSD*. Poster accepted for presentation at the Social and Affective Neuroscience Society annual meeting, 2020 (meeting canceled due to COVID-19).

Norbury A, Monti E, Diab E, Pietrzak RH, Perez-Rodriguez M, Feder A: *Neuroimaging resilience to trauma in World Trade Center rescue and recovery workers.* Poster accepted for presentation at the Society of Biological Psychiatry (SOBP) annual meeting, 2020 (meeting was canceled due to COVID-19).

Heflin M, Na S, Monti E, Feder A, Gu X: *The Impact of Trauma on Social Adaptation and Control in World Trade Center First Responders*. Poster accepted for presentation at the SOBP annual meeting, 2020 (meeting was canceled due to COVID-19).

Braide B, Cahn L, Monti E, Garg S, Norbury S, Torres D, Aaronson C, Pietrzak RH, Perez-Rodriguez MM, Feder A: *Linguistic Markers of Psychological Resilience in World Trade Center First Responders: A Computer-Based Natural Language Processing Study.* Poster accepted for presentation at the SOBP annual meeting, 2020 (meeting was canceled due to COVID-19).

Lapolla D, Monti E, Norbury A, Pietrzak RH, Perez-Rodriguez MM, Feder A: *Phenotypic heterogeneity of trauma-related psychopathology and social cognition in World Trade Center responders*. Poster presented at the Anxiety and Depression Association of American (ADAA) annual meeting, virtual meeting, 2021.

Lapolla D, Monti E, Norbury A, Pietrzak R, Perez-Rodriguez M, Feder A: *Social cognitive function and trauma-related symptom dimensions in 9/11 World Trade Center responders.* Poster presented at the SOBP annual meeting, virtual meeting, 2021.

Feder A: Symposium presentation, *Neural mechanisms underlying psychological resilience in World Trade Center rescue and recovery workers*, American College of Neuropsychopharmacology (ACNP), hybrid annual meeting, San Juan, Puerto Rico, December 2021.

Schreiber Z, Braide B, Zonshayn D, Schafler T, Monti E, Corcoran C, Perez-Rodriguez MM, Pietrzak RH, Feder A: *Linguistic markers of chronic PTSD in World Trade Center rescue and recovery workers: A computer-based natural language processing study*. Poster presented at the ACNP hybrid annual meeting, San Juan, Puerto Rico, December 2021.

Seeley SH, Schreiber Z, Verghese M, Leska T, Astorino E, Morris LS, Cahn L, Hermans E, Pietrzak RH, Perez-Rodriguez MM, Feder A: *Greater social cognition-related right temporal pole activation in World Trade Center responders with PTSD: preliminary evidence*. Poster presented at the ACNP annual meeting, Phoenix, AZ, December 2022.

Seeley, S.H., Schreiber, Z., Block, A., Astorino, E., Verghese, M., Norbury, A., Morris, L.S., Cahn, L., Murrough, J.W., Shin, L., Pietrzak, R.H., Perez-Rodriguez, M.M. & Feder, A. *Rostral anterior cingulate response to emotional conflict is modulated by trauma exposure burden in resilient World Trade Center responders*. Poster submitted to the annual meeting of the American College of Neuropsychopharmacology, December 2023, Tampa FL.

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Additional Reports

Cumulative Inclusion Enrollment Table (see below)

Inclusion of Gender and Minority Study Subjects

For this study we recruited and enrolled WTC rescue, recovery, and clean-up workers who are members of the WTC-HP GRC. The study sample is composed of WTC responders from both genders, and diverse ethnicity and racial background, broadly reflecting the composition of the WTC-HP GRC.

Inclusion of Children

Children are not included in this study of WTC responders, completed over 20 years after 9/11/2001.

Materials Available for Other Investigators

Data sharing for this study will comply with local, state, and federal laws and regulations, including the Health Insurance Portability and Accountability Act (HIPAA), as well as institutional policies and review. Research data will be made available for sharing in accordance with the CDC/ATSDR Policy on Releasing and Sharing Data.

C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Norbury A, Brinkman H, Kowalchyk M, Monti E, Pietrzak RH, Schiller D, Feder A. Latent cause inference during extinction learning in trauma-exposed individuals with and without PTSD. Psychological medicine. 2021 March 8:1-12. PubMed PMID: 33682653; DOI: 10.1017/S0033291721000647.

Non-compliant Publications Previously Reported for this Project

Public Access Compliance	Citation
N/A: Not NIH Funded	Feder A, Fred-Torres S, Southwick SM, Charney DS. The Biology of Human Resilience: Opportunities for Enhancing Resilience Across the Life Span. Biological psychiatry. 2019 September 15;86(6):443-453. PubMed PMID: 31466561; DOI: 10.1016/j.biopsych.2019.07.012.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
FEDERADRI	Y	Feder, Adriana	MD	PD/PI	3.3	0.0	0.0			NA
PIETRZAK	Y	Pietrzak, Robert H		PD/PI	4.5	0.0	0.0			NA
AARONC10	N	Aaronson, Cindy J	MOTH,PHD,OTH	Co-Investigator	1.1	0.0	0.0			NA
MPEREZRODRIGUEZ	N	Perez Rodriguez, Maria De Las Mercedes	MD,PHD	PD/PI	1.4	0.0	0.0			NA
NORBURYA	N	Norbury, Agnes	PhD	Postdoctoral Scholar, Fellow, or Other Postdoctoral Position	9.6	0.0	0.0			NA
MONTI0001	N	Monti, Elisa		Coordinator	12.0	0.0	0.0			NA
	N	Kowalchyk, Mary		Coordinator	7.6	0.0	0.0			NA
	N	Schreiber, Zoe		Coordinator	5.2	0.0	0.0			NA
	N	Cahn, Leah	LCSW	Clinician	2.2	0.0	0.0			NA

Glossary of acronyms:
S/K - Senior/Key
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RS - Reentry Supplement
DS - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES? Not Applicable
E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE? NOTHING TO REPORT
E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER? Not Applicable
E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)? NOTHING TO REPORT

G. OVERALL SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

File(s) uploaded:
CumulativeInclusionEnrollmentReport.pdf

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE Not Applicable
G.11 PROGRAM INCOME Not Applicable
G.12 F&A COSTS Not Applicable

Cumulative Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

Study Title: Neuroimaging of Resilience in World Trade Center Responders: A Focus on Emotional Processing, Reward, and Social Cognition

Comments:

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	**0**
Asian	0	3	0	0	0	0	0	0	0	**3**
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	**0**
Black or African American	2	5	0	0	0	0	0	0	0	**7**
White	9	59	0	0	0	0	0	0	0	**68**
More Than One Race	2	1	0	1	0	0	0	0	0	**4**
Unknown or Not Reported	0	0	0	4	12	0	0	0	0	**16**
Total	**13**	**68**	**0**	**5**	**12**	**0**	**0**	**0**	**0**	**98**

I. OVERALL OUTCOMES

I.1 What were the outcomes of the award?

This was, to our knowledge, the first fMRI study to investigate emotion regulation, reward responsivity, and social cognition as putative resilience mechanisms underlying psychological factors widely linked to resilience to trauma, in a sample of World Trade Center (WTC) rescue and recovery workers, some of whom also survived the 9/11/2001 attacks. This unique sample allowed us to compare the most highly resilient WTC responders ("highly resilient" responders, with no lifetime psychiatric disorders despite high levels of potentially traumatic WTC-related exposures) to two groups of WTC responders: resilient responders with lower WTC-exposures ("lower WTC-exposed control" group) and symptomatic responders with lifetime WTC-related PTSD and persistent clinically significant PTSD symptoms approximately two decades after the 9/11 attacks ("PTSD" group).

Significant and key findings include the following:
1. Highly resilient WTC responders reacted to incongruent emotional stimuli by engaging the rostral anterior cingulate cortex (rACC), whereas symptomatic responders (PTSD group) did not appear to engage the rACC. Lower WTC-exposed control responders showed lesser emotional conflict-related rACC activation than the highly resilient group, but more than the PTSD group. This finding suggests that emotion regulation capacity in highly resilient individuals is supported by greater recruitment of key brain regions involved in conflict resolution and automatic emotion regulation, such as the rACC (Specific Aim 1).
2. Highly resilient WTC responders showed the greatest degree of anticipatory deactivation of the ventral striatum, a key reward region, when presented with a cue indicating a potential monetary loss (vs. neutral or gain cues), compared to both the PTSD and lower WTC-exposed groups. Number of WTC-related exposures appeared to modulate ventral striatum activation in responders with no lifetime psychiatric disorders, such that the lower WTC-exposed group showed a smaller decrease in ventral striatum activation than the highly resilient group in response to loss cues. The PTSD group did not demonstrate differential ventral striatum deactivation during anticipation of potential reward, loss, or neutral outcomes (Specific Aim 2). Analysis of consummatory loss- and reward-related activation in reward-related regions of interest (ROIs) is currently in progress.
3. In our preliminary region of interest (ROI) analysis of a social cognition task, we did not identify any significant group differences in recruitment of multiple key brain regions involved in social processes or in task performance. However, exploratory whole-brain analysis pointed to a social cognition-related region that was not one of our ROIs – the posterior superior temporal sulcus –, with stronger activation in both resilient groups compared with the PTSD group during the task condition that required Theory of Mind decisions (Specific Aim 3).
4. Density-based spatial clustering analysis is ongoing, with the aim of identifying resilience subgroups based on heterogeneous patterns of neural activity across the three fMRI tasks (Specific Aim 4). This could provide insight into individual differences in resilience and adaptation after trauma exposure.
5. Exploratory analyses are ongoing, including analysis of the structural and resting state neuroimaging data and behavioral data from ancillary out-of-scanner tasks measuring social, affective, and reward processes. We are also examining the differential impact that specific exposures (e.g., encountering human remains; being injured in the attacks or during the WTC recovery effort) may have on vulnerability to adverse psychological outcomes in WTC responders.

Please see "Accomplishments" for a list of published abstracts, a published review paper on neuroimaging of resilience, and conference presentations related to this award.
Manuscripts reporting the main findings from this study are currently in preparation.