Changes in self-reported distress across experimental sessions, in people with psychosis, are predicted by changes in activations of salience network nodes

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ABSTRACT

Rather than being designed to attenuate psychosis symptoms directly, psychosocial interventions in schizophrenia spectrum disorders (SSDs) are often designed to reduce the distress associated with symptoms. Despite our growing understanding that people with SSDs are distinguished from other people with psychotic-like experiences by the distress associated with their symptoms, and that treatments like Cognitive Behavioral Therapy for Psychosis (CBTp) are often successful in reducing distress, the neural correlates of these reductions in distress have not been established. Using images from the International Affective Pictures Set (IAPS; Lang et al., 2005), our goal was to examine how both immediate and delayed responses to pleasant, aversive, and neutral stimuli related to self-reports of symptoms related to distress. In order to investigate how changes in responses to pleasant, aversive, and neutral stimuli related to changes in self-reports of symptoms related to distress, we had participants perform the Emotional Experience Task (EET; Ursu et al., 2011) twice, on separate study days (once 10 minutes after presentation of an acute stressor, once 10 minutes after a control task). We hypothesized that changes in self-reported distress across experimental sessions, in people with psychosis, would be predicted by changes in activations of the anterior insula (AI) and other salience network nodes.

In our study, 52 patients with schizophrenia spectrum disorders (SZ) and 32 healthy volunteers (HVs) performed the EET twice, at least a week apart. The Cold Pressor Task (CPT; Schwabe et al., 2008) was used as the acute stressor. In the stress condition, participants submerged their non-dominant arm in a bucket of ice water for up to three continuous minutes. The control condition used warm water. During performance of the EET, subjects viewed 72 IAPS picture stimuli (24 pleasant, 24 unpleasant, 24 neutral) in four runs of 18 trials each. On each trial, subjects were asked to rate both the "positivity" and "negativity" of the emotion experienced during the presentation of a picture, on a 5-point scale, by means of a four-button response unit. In both sessions, between the second and third runs of the task, participants were prompted to report their subjective feelings on a 7-point scale along dimensions such as "stress", "pressure", "sadness", and "paranoia". Changes in subjectively-rated feelings between sessions ranged from -6 to +6.

We observed that changes in self-reported distress across experimental sessions, in people with psychosis, correlated significantly with changes in evoked activations to unpleasant pictures in left AI (r=0.314; p=0.034) and right AI (r=0.353; p=0.016). Changes in self-reported distress across experimental sessions, in people with psychosis, correlated significantly with changes in delayed activations to both pleasant (r= 0.300; p=0.043) and unpleasant pictures (r=-0.320; p=0.030) in dorsomedial prefrontal cortex (dmPFC). Changes in self-reported feelings of being "under pressure", across experimental sessions, correlated significantly with changes in delayed activations to pleasant pictures (r=0.355; p=0.016) in left AI. Finally, changes in self-reported feelings of "suspiciousness", across experimental sessions, correlated significantly with changes in evoked activations to unpleasant pictures in ventromedial prefrontal cortex (vmPFC; r=0.342; p=0.020).

We observed that changes in self-reported distress across experimental sessions, in people with psychosis, correlated significantly with changes in activations of the anterior insula, bilaterally, dmPFC, and vmPFC. These relationships between changes in brain activations and changes in reports of subjective experience may represent a neural correlate of distress that is impacted by psychosocial interventions such as CBTp. The ability to improve the lives of people with psychotic illness would benefit from an improved understanding of how both pharmacological and psychosocial interventions attenuate symptoms and the distress associated with symptoms.

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DISCLOSURES

James Waltz: Nothing to declare.
Maahee Patel: Nothing to declare.
Julia Sheffield: Nothing to declare.
Jacob Nudelman: Nothing to declare.
Olivia Hutchinson: Nothing to declare.
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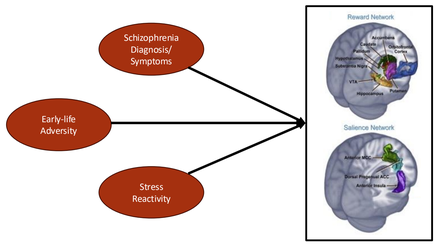
INTRODUCTION

- Rather than being designed to attenuate psychosis symptoms directly, psychosocial interventions in schizophrenia spectrum disorders (SSDs) are often designed to reduce the distress associated with symptoms.
- Despite our growing understanding that people with SSDs are distinguished from other people with psychotic-like experiences by the distress associated with their symptoms, and that treatments like Cognitive Behavioral Therapy for Psychosis (CBTp) are often successful in reducing distress, the neural correlates of these reductions in the distress associated with psychotic symptoms have not been established.
- Psychotic illness, early-life adversity, and acute stress are known to impact dopamine neurons and their targets in the reward and salience networks, such as ventral striatum (VS)/nucleus Accumbens, ventromedial prefrontal cortex (vmPFC), anterior insula (AI) and dorsomedial prefrontal cortex (dmPFC)/anterior mid-cingulate cortex (MCC).



- Using images from the International Affective Pictures Set (IAPS; Lang et al., 2005), our goal was to examine how both immediate and delayed neural responses to pleasant, aversive, and neutral stimuli related to self-reports of symptoms related to distress and psychosis.
- To investigate how changes in responses to pleasant, aversive, and neutral stimuli related to changes in self-reports of symptoms related to distress, we had participants perform the Emotional Experience Task (EET; Ursu et al., 2011) twice, on separate study days (once 10 minutes after presentation of an acute stressor, once 10 minutes after a control task).
- We hypothesized that differences in self-reported distress across experimental sessions following the presence and absence of a psychosocial stressor, in people with psychosis, would be predicted by changes in activations of nodes of the reward and salience networks.

GENERAL METHODS

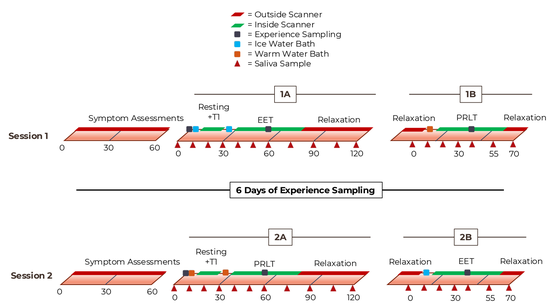


Figure 1. Participants performed the Emotional Experience Task twice, once after being administered an acute stressor (the Socially-evaluated Cold Pressor Task/SECPT; Schwabe et al., 2008), and once after not being stressed. During MRI scanning sessions, saliva samples were taken every 10-15 minutes.

ACUTE STRESS MANIPULATION

The Socially Evaluated Cold Pressor Test (SECPT)

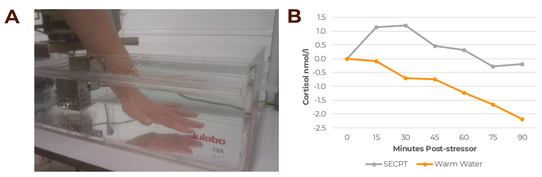


Figure 2. A. In the stress condition of the SECPT, participants submerged their non-dominant arm up to the wrist joint, in a tub of ice water (1°-4° C) until the pain became unbearable (up to for 3 minutes), while being filmed by an unsympathetic confederate. Participants were told to not make a fist or place their hand on the bottom of the tub. The control condition used warm water. **B.** Performance of the SECPT was associated with clear elevations in salivary cortisol up to 45 minutes after administration of the stressor.

PARTICIPANTS

Table 1. Participant demographic information.

Domain/Measure	SZ (N=58)	HV (N=37)	Inferential Statistic	Significance
Demographics				
Age (Years)	39.28 (10.09)	42.30 (13.82)	t_{93} = 1.148	p = 0.255
Sex at Birth	18 F, 40 M	16 F, 21 M	χ^2 = 1.465	p = 0.226
Race	28 W, 30 NW	25 W, 12 NW	χ^2 = 3.409	p = 0.065
Ethnicity	1 Hispanic, 57 Non-Hisp.	7 Hispanic, 30 Non-Hisp.	χ^2 = 8.660	p = 0.003
Tobacco User	14 Yes, 44 No	5 Yes, 32 No	χ^2 = 1.594	p = 0.207
Education				
Subject Education	13.55 (2.09)	15.44 (2.02)	t_{82} = 4.326	p < 0.001
Mother's Education	14.86 (3.16)	14.46 (3.25)	t_{84} = 0.578	p = 0.565
Father's Education	15.08 (3.05)	14.63 (3.73)	t_{83} = 0.613	p = 0.542

Abbreviations: SZ, schizophrenia patients; HV, healthy volunteers; F, female; M, male; W, white; NW, nonwhite.

BEHAVIORAL PARADIGM

The Emotional Experience Task (EET)

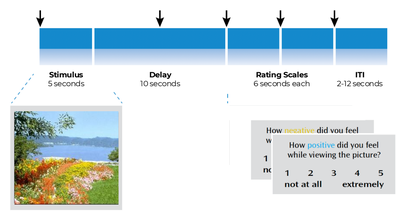


Figure 3. During performance of the EET, subjects viewed 72 IAPS images (24 pleasant, 24 unpleasant, 24 neutral) in four runs of 18 trials each. On each trial, subjects were asked to rate both the "positivity" and "negativity" of the emotion experienced, during the presentation of a picture, on a 5-point scale, by means of a three-button response unit. Halfway through each MRI session (after 2 runs of the task), participants were prompted with 28 probes about general feelings and symptoms related to mood and psychotic-like experiences, taken from the experience sampling surveys they completed in the 6 days between MRI scanning days. Examples included: "I feel cheerful", "I feel anxious", "I feel stressed", "I feel lonely", "I can concentrate well", "I feel like I am under pressure", "I feel like I can do this well", "I feel suspicious", and "I feel judged". Subjects used the button box to rate the feeling experienced on a 7-point scale.

RESULTS: EFFECTS OF ACUTE STRESS AND DIAGNOSIS

Effects of Acute Stress and Diagnosis on Symptoms

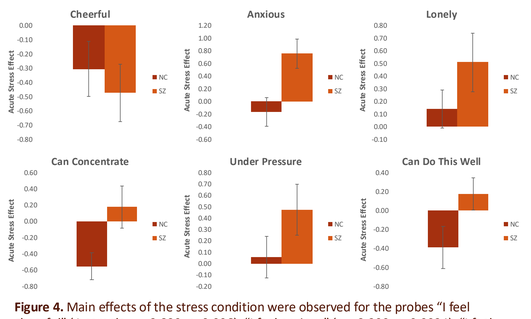


Figure 4. Main effects of the stress condition were observed for the probes "I feel cheerful" (1-sample t_{92}=2.829, p=0.006), "I feel anxious" (t_{92}=2.290, p=0.0024), "I feel lonely" (t_{92}=2.370, p=0.020), and "I feel like I am under pressure" (t_{92}=2.000, p=0.048). Between-group differences in acute stressor effects were observed for the probes "I feel anxious" (2-sample t_{91}=2.667, p=0.009), "I can concentrate well" (t_{91}=2.075, p=0.041), and "I feel like I can do this well" (t_{91}=2.046, p=0.044).

Effects of Acute Stress and Diagnosis on Picture Ratings

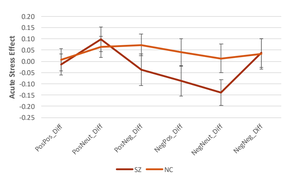


Figure 5. We observed a main effect of the stress condition on positive ratings of neutral pictures (1-sample t_{83}=2.229, p=0.028). We observed a trend toward a significant difference in the effect of the acute stressor on negative ratings of neutral pictures, with patients showing a greater change in negative ratings of neutral pictures, relative to controls (2-sample t_{82}=1.743, p=0.085).

Effects of Acute Stress and Diagnosis on Brain Responses

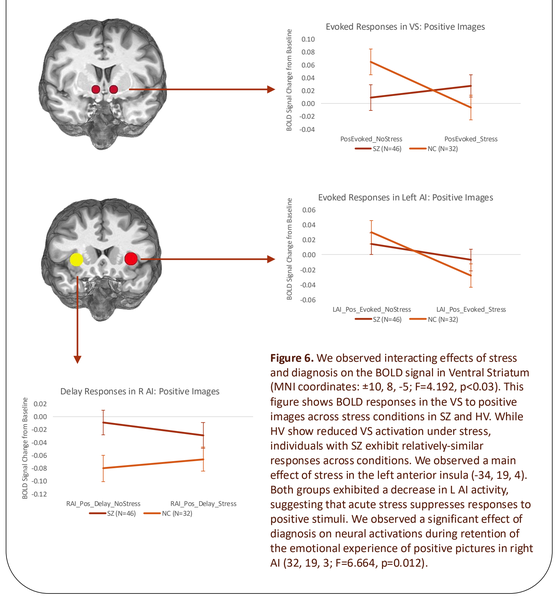


Figure 6. We observed interacting effects of stress and diagnosis on the BOLD signal in Ventral Striatum (MNI coordinates: ±10, 8, -5; F=4.192, p<0.03). This figure shows BOLD responses in the VS to positive images across stress conditions in SZ and HV. While HV show reduced VS activation under stress, individuals with SZ exhibit relatively-similar responses across conditions. We observed a main effect of stress in the left anterior insula (-34, 19, 4). Both groups exhibited a decrease in L AI activity, suggesting that acute stress suppresses responses to positive stimuli. We observed a significant effect of diagnosis on neural activations during retention of the emotional experience of positive pictures in right AI (32, 19, 3; F=6.664, p=0.012).

RESULTS: CORRELATION ANALYSES

Correlations between Acute Stress Effects on Evoked Activations and Self-reported Symptoms

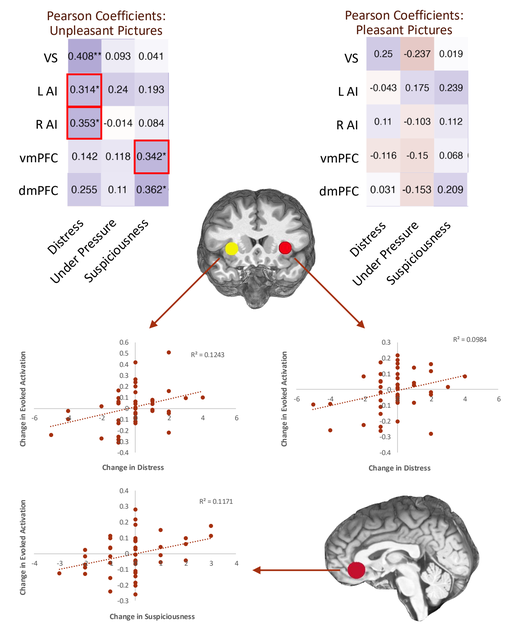


Figure 7. We observed that changes in self-reported **distress** across experimental sessions, in people with psychosis, correlated significantly with changes in evoked activations to unpleasant pictures in left AI (r=0.314; p=0.034) and right AI (r=0.353; p=0.016). Acute stress effects on self-reported feelings of "**suspiciousness**" correlated significantly with acute stress effects on evoked activations to unpleasant pictures in vmPFC (3, 35, -5; r=0.342; p=0.020).

Correlations between Acute Stress Effects on Delay Activations and Self-reported Symptoms

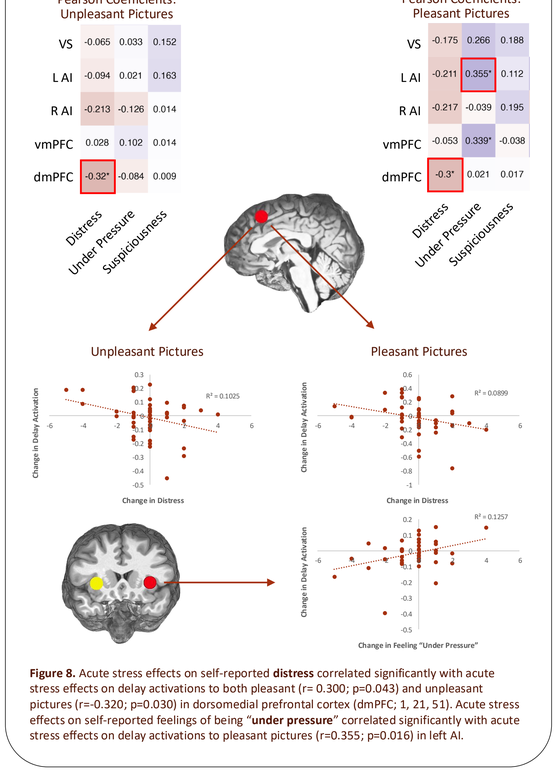


Figure 8. Acute stress effects on self-reported **distress** correlated significantly with acute stress effects on delay activations to both pleasant (r= 0.300; p=0.043) and unpleasant pictures (r=-0.320; p=0.030) in dorsomedial prefrontal cortex (dmPFC; 1, 21, 51). Acute stress effects on self-reported feelings of being "**under pressure**" correlated significantly with acute stress effects on delay activations to pleasant pictures (r=0.355; p=0.016) in left AI.

DISCUSSION

- We observed that changes in self-reported distress across experimental sessions, in people with psychosis, correlated significantly with changes in activations of the anterior insula, bilaterally, and in dmPFC and vmPFC.
- These relationships between changes in brain activations and changes in reports of subjective experience may represent a neural correlate of distress that is impacted by psychosocial interventions such as CBTp.
- The ability to improve the lives of people with psychotic illness would benefit from an improved understanding of how both pharmacological and psychosocial interventions attenuate symptoms and the distress associated with symptoms.