Abnormal Anterior Cingulate Activation Revealed by a Novel Ankle-Shock Stress Task in Schizophrenia and Association With Depression and Psychosis

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Introduction

- Stress and abnormal stress response are associated with many psychiatric illnesses including schizophrenia spectrum disorder (SSD), but the brain mechanisms linking stress to psychiatric disorders remain unclear.
- Brain areas and cellular pathways responsible for the evaluation of and response to stress have been implicated in psychotic disorders and are themselves vulnerable to stress and are associated with worsened functional capacity and positive symptom burden.
- One potential mechanism by which a high cumulative burden of stress is converted to psychotic experience may be through aberrant salience representation or misattributed threat operationalized as paranoia or delusion in daily experience.
- In animal studies, the threat of electric foot shock is a classic approach to study mechanisms related to stress. A similar fMRI-based task in healthy human participants has used a shock threat to engage salience network and limbic activation (McMenamin et al., 2014, *J. Neuroscience*).
- Here, we used a stress-based neuroimaging task, reverse-translated from preclinical studies of stress in participants with SSD and community controls.

Hypothesis

Abnormal corticolimbic processing of stressful threat anticipation contributes to psychosis and affective symptoms in patients with SSD

Methods

Subjects: Eighteen participants with SSD (10M/8F) and twelve community controls (CC, 9M/3F)

Clinical items:
- **Brief Psychiatric Rating Scale**
- **BPRS psychosis subscale:** suspiciousness, hallucinatory behavior, conceptual disorganization * unusual thought content individual items
- **Maryland Trait and State Depression Scale:** frequency of depressive symptoms over the lifetime (trait) and over the previous two weeks (state)

Ankle-Shock Task (AST)
- Electrode affixed to ankle, attached to battery-powered shock device (Transcutaneous Aversive Stimulator, Coulborne Instruments)
- *Sensitivity testing:* Performed prior to scan to identify stimulation threshold of a static-electric shock to mild pain
- Participants instructed that one signal would mean they would receive random shocks, while another would indicate safety.
- Inside scanner, there were 3 conditions: i) Shock signal shown, and a shock is delivered randomly ii) Safety signal shown, and no shock is delivered and iii) shock signal is shown to generate anticipated threat, but no shock delivered.
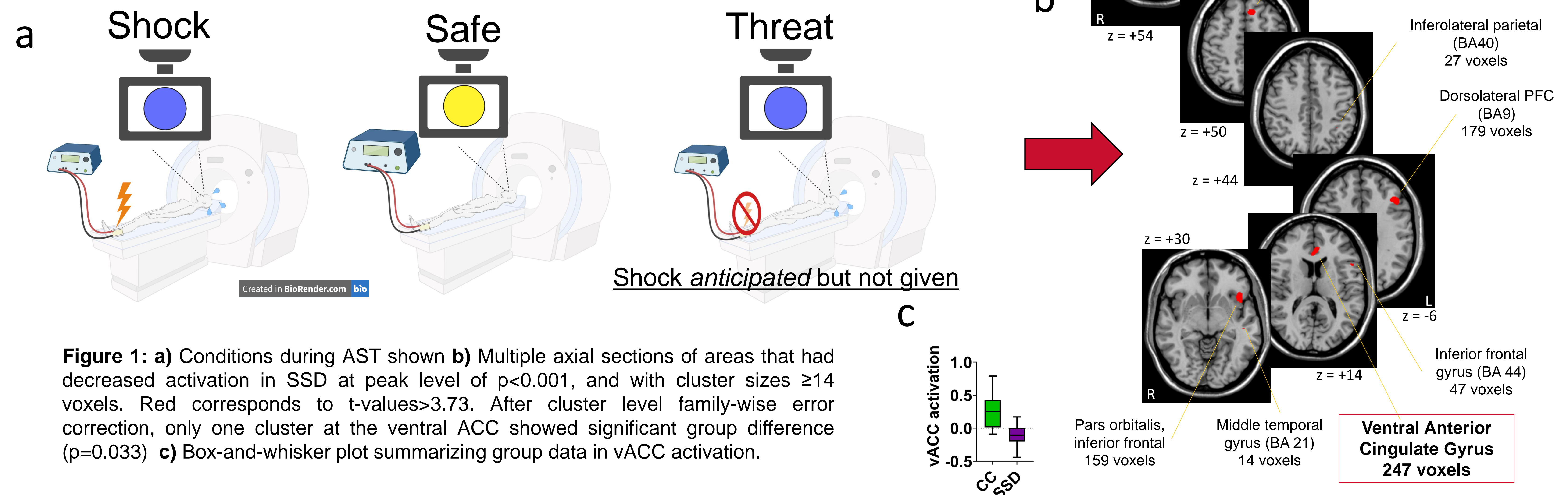
MRI analysis
- fMRI data was collected using a 3-T Siemens Prisma scanner and 64-channel coil. Whole brain EPI was collected using the Human Connectome Project (HCP) multi-band fMRI protocol, with the following parameters: 2 mm isotropic, TR/TE=720/33.1ms, flip angle = 52 degrees, FOV=208x108 mm (RO x PE), Matrix=1-4x90 (RO x PE), slice thickness = 2 mm, multiband factor=8, AP/PA encoding, echo spacing = 0.58 ms, and 2290 Hz/Px. Images were slice timing corrected, volume registered, linearly detrended, normalized into MNI standard space, and spatially smoothed (FWHM=8mm) using SPM12.
- First level models were developed for each subject by entering all the volumes into a single analysis regressing the "shock", "threat" and "safe" conditions. The contrast of interest was the threat - safe condition, to study brain processing the anticipatory threat of the unpleasant shock but without the interference of the actual shock.
- This contrast was further investigated in the second level group analysis. Statistical significance of voxel-wise whole brain analysis activations followed by family-wise error correction were computed using SPM Marsbar with a peak value of p<0.001 and cluster-wise FWE α<0.05.

Ethical Considerations
- Written, informed consent, evaluation of capacity
- Participants able to withdraw at any time
- Emergency button given during task to stop at any point
- Approved by the University of Maryland Baltimore Institutional Review Board

Anticipated threat task reveals lower ventral anterior cingulate (vACC) activation in SSD

Figure 1: a) Conditions during AST shown **b)** Multiple axial sections of areas that had decreased activation in SSD at peak level of p<0.001, and with cluster sizes ≥14 voxels. Red corresponds to t-values>3.73. After cluster level family-wise error correction, only one cluster at the ventral ACC showed significant group difference (p=0.033) **c)** Box-and-whisker plot summarizing group data in vACC activation.

vACC activation during anticipated threat is associated with greater symptom burden, most strongly with BPRS psychosis measures

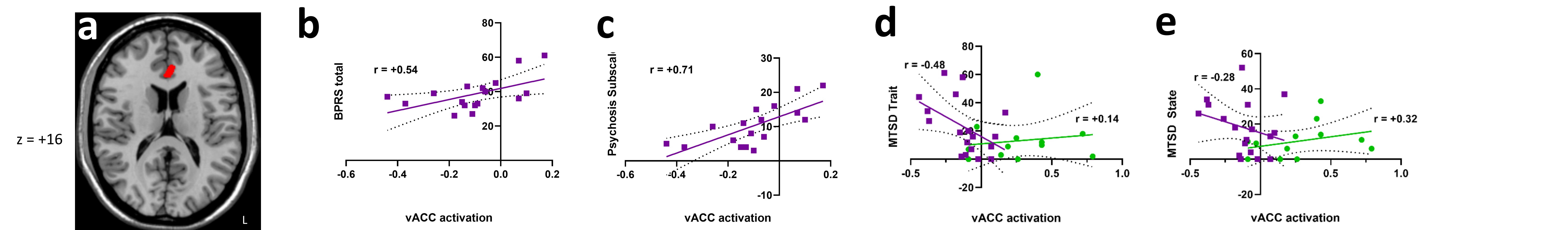**Figure 2: a)** Cluster activation during threat-safe comparison, with 274-voxel cluster located in ventral ACC. AST task-based vACC activation is associated with **(b)** BPRS ratings (p=0.024) and **(c)** BPRS psychosis subscale (p=0.001). **d)** ACC activation during ankle-shock threat task (threat-safe condition) vs. trait and state depression measures in SSD patients (purple) and community controls (green). Trait quantitative depression scores were significantly associated with vACC activation (p=0.043) in patients with SSD but not in controls (p=0.7). **e)** State depression scores were not significantly correlated with vACC activation (SSD p>0.25, CC p>0.31). Linear regressions shown with 95% confidence interval, with r values indicated.

Conclusions

- This novel translational stress-based task can engage and reveal deficient activation in SZ in the vACC, a region known to be associated with error-monitoring, social-emotional evaluation, and other reward and affective processing.
- Our findings of aberrant vACC activation are consistent with others implicating abnormal stress responses as well as salience network dysfunction in SSD.
- Deficient activation in vACC under the stress of an anticipated threat may lead to aberrant interpretation of such threat, which may contribute to overrepresentation of stress and the threat attributed to everyday experiences. This could represent a neurobiological substrate for psychosis (i.e. in generating paranoia and abnormal thought content) and propagate mood symptoms in SSD.
- This experimental paradigm has translational potential and may be useful to identify circuitry-level mechanisms of stress-related mental illness, leading to more targeted treatment.

Acknowledgements