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Linking Salience Signaling With Early Adversity and Affective Distress in Individuals at Clinical High Risk for Psychosis: Results From an Event-Related fMRI Study

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Evidence suggests dysregulation of the salience network in individuals with psychosis, but few studies have examined the intersection of stress exposure and affective distress with prediction error (PE) signals among youth at clinical high-risk (CHR). Here, 26 individuals at CHR and 19 healthy volunteers (HVs) completed a monetary incentive delay task in conjunction with fMRI. We compared these groups on the amplitudes of neural responses to surprising outcomes—PEs without respect to their valence—across the whole brain and in two regions of interest, the anterior insula and amygdala. We then examined relations of these signals to the severity of depression, anxiety, and trauma histories in the CHR group. Relative to HV, youth at CHR presented with aberrant PE-evoked activation of the temporoparietal junction and weaker deactivation of the precentral gyrus, posterior insula, and associative striatum. No between-group differences were observed in the amygdala or anterior insula. Among youth at CHR, greater trauma histories were correlated with stronger PE-evoked amygdala activation. No associations were found between affective symptoms and the neural responses to PE. Our results suggest that unvalenced PE signals may provide unique information about the neurobiology of CHR syndromes and that early adversity exposure may contribute to neurobiological heterogeneity in this group. Longitudinal studies of young people with a range of risk syndromes are needed to further disentangle the contributions of distinct aspects of salience signaling to the development of psychopathology.

Key words: clinical high risk/psychosis/salience network/prediction error/adversity/affective symptoms

Introduction

Learning to accurately predict the occurrence of rewarding or aversive outcomes using available information is critical for flexible responding to environmental stimuli. In the typically-developing brain, mismatches between expectations and outcomes, called prediction errors (PEs), are signaled by rapid, phasic burst firing of dopamine and serotonin neurons projecting to nodes of the brain's reward and salience networks.^{1,2} Whereas reward networks are centered on the ventral striatum and ventromedial prefrontal cortex,³ the salience network connects the amygdala, anterior insula (AI), dorsal anterior cingulate cortex (dACC), and temporoparietal junction.^{4,5} Prediction error signals within these networks play a key role in directing attention, assigning meaning, and integrating internal information with external stimuli, thereby supporting the development and updating of one's "internal model" of the environment.⁶ Considerable evidence implicates abnormal PE signaling and related deficits in learning and decision making in psychotic disorders such as schizophrenia.⁷ These findings support the possibility that abnormalities in the acquisition or retention of cue-outcome associations—and the neural circuits subserving these operations—may be involved in the initial formation of symptoms in individuals with psychosis.^{8,9}

Although findings of abnormal salience signaling and learning are common in the psychosis literature,¹⁰ recent work from cognitive neuroscience demonstrates that reward PEs may actually embody at least two distinct

but interactive components.¹¹ One of these components encodes the valence, sign, or direction of the error—positive following better than expected outcomes, and negative following worse than expected outcomes—and is used to reinforce or extinguish a particular behavior. The other component encodes the extent to which the outcome is surprising or unexpected and is represented as the “unsigned” or absolute value of the mismatch. This surprise signal, which originates in the amygdala and projects to the dACC, insula, and other salience network structures, is used to gate the amount of attention paid to the valence signal, thereby modulating its strength or “associability”.^{12,13} Together, signed and unsigned PEs are believed to interact dynamically across a distributed set of neural circuits to steer attention, form associations, and integrate external stimuli with internal information.¹⁴

The vast majority of evidence supporting abnormal PE signaling in psychosis comes from studies probing signed PE signaling in adults with established illness. These studies report abnormal encoding of rewarding or aversive outcomes in key brain structures such as the ventral striatum,¹⁵ dACC,¹⁶ amygdala,¹⁷ and insula,¹⁸ alongside corresponding deficits in reinforcement learning.^{19,20} Similar abnormalities are observed in those with depressive,²¹ anxiety,²² and stress-related disorders,²³ suggesting that salience network dysfunction may be a transdiagnostic contributor to psychopathology.²⁴

Despite evidence of salience network abnormalities in those with psychosis, very few studies have examined the possibility that unsigned PE signaling may contribute to salience network dysfunction, particularly among adolescents or young adults who have not developed psychosis yet but may be at imminent risk. A small but growing body of work suggests multiple subtle reward or salience system abnormalities in youth with clinical high-risk (CHR) syndromes, including disrupted functional connectivity of the salience network^{25,26} and reduced striatal, insula, and medial prefrontal cortex activity during reward anticipation or PE signaling.^{27–29} The results of behavioral studies provide corroborating evidence of impaired reinforcement learning,²⁸ reduced effort-cost expenditure,³⁰ and a tendency to assign salience to task-irrelevant stimuli.^{31,32} Importantly, a recent study found that unsigned PE signals were detectable in the dACC and supported learning among youth at CHR,³³ suggesting that more research is needed to understand the contributions of surprise (ie, unvalenced) signaling to salience network function in this population.

Interpretation of salience network abnormalities in individuals at CHR is complicated by the transdiagnostic nature of reward system impairment and the observation that most such individuals present with cooccurring symptoms of depression and anxiety.^{34,35} Little attention has been paid to the intersection between affective symptoms and salience or reward network dysfunction in youth at CHR, despite the possibility that at least

some of the observed impairments are attributable to these dimensions of illness^{36,37} and considerable evidence in support of an affective pathway to first episode psychosis.³⁸ The few studies addressing the relation between salience network abnormalities and affective disturbances in CHR youth have reported that depressive or anxiety symptom severity was uniquely associated with reduced neural differentiation of rewarded vs unrewarded,³⁹ expected vs unexpected,²⁸ and aversive vs neutral or pleasant outcomes^{40,41} within the salience or reward network. Importantly, youth with psychosis risk symptoms have also been found to show elevated amygdala activity during emotion processing,^{42,43} a key observation given the amygdala’s central role in aversive and associative learning,⁴⁴ its functional impairment in anxiety and depressive disorders,⁴⁵ and the fact that the unsigned error signal is thought to originate in this structure.¹² Thus, abnormal surprise signaling may contribute to multiple important symptom dimensions outside the classical psychotic symptoms in individuals at CHR.

Finally, if salience network dysfunction contributes to depressive, anxiety, and psychosis outcomes in young people, an important question is whether such dysfunction is also associated with environmental risk factors that are shared across these disorders. A relation between known risk factors for psychiatric disorders and nonspecific salience network impairment may suggest a pathway through which symptoms develop, elucidating both etiological and neurodevelopmental aspects of illness and highlighting targets for intervention. Childhood trauma exposure represents a promising area of inquiry in this context. Early-life adversity is among the most potent risk factors for affective and psychotic disorders^{46,47} and impacts multiple aspects of salience processing, including the signaling of signed^{48,49} and unsigned PEs⁵⁰ and the ability to learn from previously rewarded outcomes.⁵¹ Importantly, the amygdala and insula are among the structures most commonly implicated in studies of trauma-related brain changes.⁵² Thus, it is possible that prior trauma exposure plays a key role in determining the nature of neural salience system activity in youth at CHR.

This study examined the intersection between affective symptoms, trauma exposure, and PE signaling of the salience network in youth at CHR for psychosis. In a cross-sectional design, help-seeking young people at CHR completed clinical interviews and symptom surveys plus a monetary reward task that elicited PEs in conjunction with fMRI. We focused our analyses on the amygdala and AI, given evidence of their involvement in salience signaling, stress response, and psychotic and affective psychopathology, but supplemented with whole-brain analyses given the known relevance of additional regions such as the temporoparietal junction and other insular subfields.^{4,5,14,53} In addition, we paid special attention to effects of violent trauma exposures on salience signaling,

given that such exposures are likely to have especially pathogenic effects on the development of this brain network.^{52,54,55} We operationalized unvalenced surprising outcomes in two complementary ways: parametrically, quantified as the magnitude of the unsigned PE, or degree of mismatch between expectation and outcome irrespective of its direction; and nonparametrically, as the binary presence (vs absence) of a mismatch between the expected and unexpected outcome. We refer to these related definitions collectively as PEs or surprising outcomes. We hypothesized that relative to healthy volunteers (HVs), individuals at CHR would present with altered salience signaling—stronger activation or weaker deactivation—within the salience network, and that altered signals evoked by unexpected outcomes would be associated with the severity of depressive symptoms, anxiety symptoms, and trauma history.

Methods

Participants

This study took place within the Maryland Early Intervention Program, an early psychosis identification, treatment, and research collaboration between the University of Maryland School of Medicine and the University of Maryland, Baltimore County. Individuals at CHR (*n* = 26) were referred from community providers. Healthy volunteers (*n* = 19) were recruited from the greater Baltimore community using flyers and advertisements. The sample includes all participants described in a prior report from the same protocol (described below) plus four new participants at CHR. Inclusion criteria were having an age of 12–25 years, being willing and able to provide written consent or assent, and having no contraindication to the MRI environment. HVs must have been receiving no mental health services and have no current psychiatric disorder or history of psychosis, major depressive disorder, bipolar disorder, or psychiatric medication use. The study was approved by the overseeing Institutional Review Boards.

Instruments

Clinical Measures. All clinical interviews were conducted by trained masters or doctoral-level staff and reviewed by an interdisciplinary team of early psychosis experts. CHR status was determined using the Structured Interview for Psychosis-risk Syndromes (SIPS).⁵⁶ To meet SIPS criteria, within the past year participants must have experienced (1) attenuated psychotic symptoms; (2) brief intermittent psychotic symptoms (ie, ≤24 h); or (3) a significant decline in global functioning (measured following standard SIPS protocol with the Global Assessment of Functioning) in the context of schizotypal personality disorder or a family history of psychosis ([Supplementary Methods](#) for detail).

Diagnostic and Statistical Manual (DSM) diagnoses were determined using the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS)⁵⁷ or the Structured Clinical Interview for the DSM, 5th Edition (SCID).⁵⁸ These interviews were also used to identify lifetime exposure to potentially traumatic events. Participants were asked whether they had experienced any of several events that would meet the PTSD criterion A (trauma exposure). Binary scores for each trauma type were recorded and summed to create an index of overall lifetime trauma exposure, consistent with prior research.⁵⁹ We further classified exposures as violent or nonviolent so that we could examine the effects of these trauma dimensions separately. This classification scheme emulates our prior work⁶⁰ and is displayed in [table 1](#). Here, we focused on violent and total trauma exposures, as the nonviolent dimension represents a more heterogeneous set of exposure types and we did not have specific hypotheses about the effects of this dimension on brain functioning. Additional information about the use of the KSADS and SCID in the broader study protocol is provided in the Supplement.

Anxiety and depressive symptom severity was measured using the respective subscales of the Behavioral Assessment System for Children, Second Edition (BASC-2).⁶¹ The BASC-2 is a self-report form capturing a variety of emotional and behavioral indicators of functioning among youth. Items are summed within subscales and converted to T scores with a mean of 50 and standard deviation of 10. See the Supplement for additional psychometric information about the BASC-2 subscales.

Experimental Behavioral Paradigm. To elicit neural PE signals, we used a modified version of the Monetary Incentive Delay task⁶² (MID; [figure 1](#)). In this task, participants saw a cue that indicated they could win money (gain trial), lose money (loss trial), or neither win nor lose money (neutral trial). Participants’ response times to the response prompt partly determined the outcomes: If participants responded within an acceptable time window on gain trials, they would win the cued amount (either \$8 or \$15); otherwise, they would win a nominal amount (\$1). If participants responded within

Table 1. Classification Scheme for Trauma Exposures Coded During the Clinical Interview

| Violent Trauma | Nonviolent Trauma |
|--|------------------------------------|
| Witnessing domestic violence | Being in a car accident |
| Witnessing another violent crime | Being in another serious accident |
| Being the victim of a violent crime | Being in a fire |
| Being physically abused by a caregiver | Being in a natural disaster |
| Being sexually assaulted | Hearing traumatic news |
| Another violent trauma exposure | Another nonviolent trauma exposure |

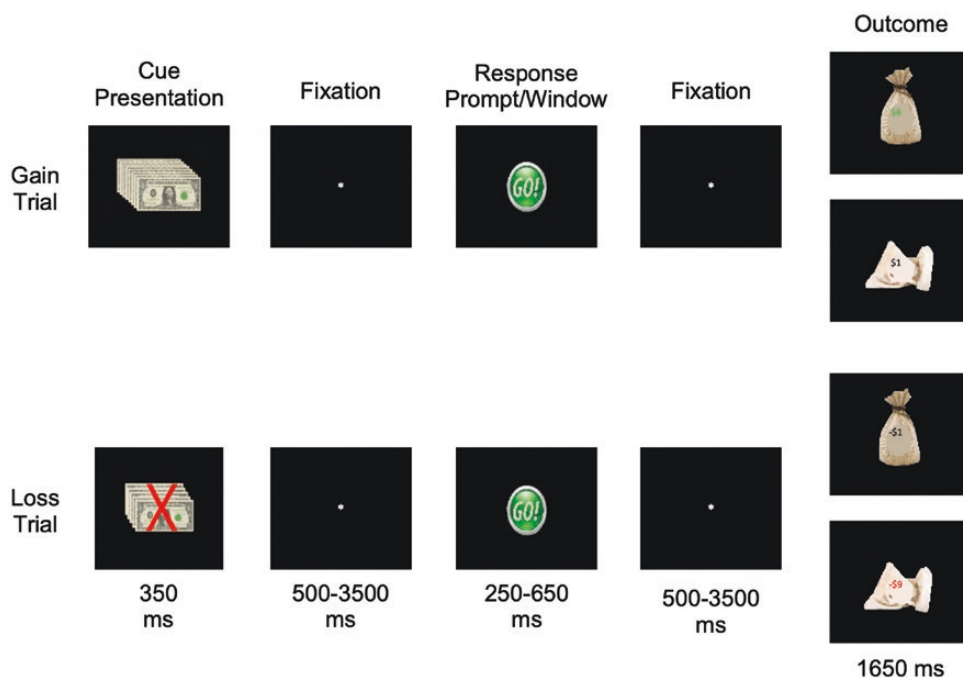


Fig. 1. Schematic depiction of the MID task. Participants were presented with a cue indicating whether they would receive money (gain), lose money (loss), or experience a neutral outcome (not shown). Responding within an acceptable time window allowed participants to win money on gain trials and avoid losing money on loss trials, but this window was adjusted to ensure 1/3 of responses were too slow, resulting in prediction errors. MID, monetary incentive delay.

an acceptable time window on loss trials, they would lose a nominal amount (\$1); otherwise, they would lose the cued amount (either \$5 or \$9). Importantly, the response window was adjusted to ensure a success rate of approximately 66%, thus eliciting surprising outcomes (ie, PEs) on about 34% of trials. Outcomes were displayed for 1650 ms. The task included 56 gain trials, 56 loss trials, and 28 neutral trials, together taking approximately 19 min.

MRI Data Acquisition and Analysis

We acquired whole-brain functional EPI images (for measurement of T2*-weighted blood-oxygen-level-dependent [BOLD] effects) in tandem with task performance using 3-T Siemens scanners (Erlangen, Germany). Twenty-eight participants were scanned with a Trio magnetom (32-channel head coil) and 17 were scanned with a PRISMA Fit (64-channel head coil) following a scanner upgrade at our research center. All other aspects of the scanning protocol, including the imaging sequence, stimulus software and presentation, and data processing pipeline remained consistent. We acquired functional images using the following parameters: 81 2-mm axial slices; 128×128 matrix; FOV = 22×22 cm; TR = 2 s. In the MID task, 480 images were acquired spanning 4 runs. For anatomical reference, we acquired a whole-brain T1-weighted structural image (MPRAGE; 1-mm³ isotropic voxels; TR = 2.2 seconds; TE = 4ms; FA = 20°).

Single-Subject Analyses. All MRI data were preprocessed using the AFNI software package,⁶³ including coregistration of the EPI and anatomical images, warping the images to Talairach space, and smoothing them with an 8-mm FWHM kernel. Images were warped to Talairach space using the 452 International Consortium for Brain Mapping template, upsampling the images to 1.5-mm isotropic voxels. Emulating prior work,⁶⁴ volumes with >0.5-mm displacement in any plane were excluded from analysis, participants with >20% displacement were excluded altogether. No participants were excluded on this basis.

To model BOLD MRI signals acquired during the MID task, we constructed parametric regressors based on the timestamps of outcome events. For the MID, expected value was estimated to be $(2/3) \times \text{the optimal outcome} + (1/3) \times \text{the suboptimal outcome}$. This was because the experiment was calibrated such that participants responded within the acceptable response windows on 2/3 of trials. Thus, for the lose-\$9 condition, the expected value was estimated to be -\$3.67, and, for the lose-\$5 condition, the expected value was estimated to be -\$2.33 (because participants lost only \$1 when they responded within the acceptable time window). For the win-\$8 condition, the expected value was estimated to be \$5.67, and, for the win-\$15 condition, the expected value was estimated to be \$10.33 (because participants gained only \$1 when they failed to respond within the acceptable time window). On neutral trials, the expected

value was zero, regardless of the response. Prediction errors were computed by subtracting the expected value from the actual outcome, and PE magnitudes were “married” to the timestamps of feedback events. To represent the magnitudes of unsigned PEs over time, in regressor functions for single-subject voxel-wise time series (general linear models/GLMs), feedback timestamps were married to amplitudes representing the *absolute value* of PEs.

We also constructed binary, or nonparametric, regressors based on the timestamps of outcome events. As participants received the cued outcome on two-thirds of trials, outcomes matching cued amounts were considered “expected”; outcomes *not* matching cued amounts were considered “unexpected”. For these GLMs, expected, unexpected, and neutral outcomes were represented as separate binary regressors. Regressor functions for single-subject voxel-wise time series included head-motion vectors (L-R, A-P, I-S, pitch, roll, yaw) as nuisance regressors.

Statistical Analyses

Whole-brain Analyses of Event-related Neural Activations and Contrasts (ROIs). Effects of expected value magnitude, reward PE valence and magnitude, and outcome valence and magnitude in ventral striatum, ventromedial prefrontal cortex, and dACC were reported previously.²⁸ Here, we report on whole-brain analyses of parameter estimates (beta coefficients) evoked by parametric unsigned PE regressors (a one-sample *t*-test and an independent-samples *t*-test, with diagnostic group as a factor, using the AFNI 3dttest++ function⁶³). We also report on supplemental whole-brain analyses of beta coefficients for unexpected (ie, [unexpected – neutral]) outcomes and [unexpected – expected] contrasts, for which we used a voxel-wise threshold of $P = .001$ and a cluster-size threshold of 385 voxels.

Analyses of Event-related Neural Activations and Contrasts in Regions-of-interest (ROIs). We report effects of unsigned PE magnitude in four ROIs: left and right amygdala and left and right AI (Figure S1). Variables represented the average of all voxels within an ROI. For the amygdala, we used the volume as specified by the AFNI Talairach Daemon (center-of-mass coordinates: 24, 5, –15 and –23, 5, –15). The anterior insula ROIs consisted of 10-mm radius spheres, centered on coordinates previously used by our group (center-of-mass coordinates: 32, 18, 2 and –33, 19, 3).¹⁶

To determine whether youth at CHR display altered PE signals in the amygdala and insula relative to HVs, and to compare the CHR and HV groups on demographic factors, we used *t*-tests or chi square analyses as appropriate. To examine whether PE signals were associated with the severity of affective symptoms and adversity, we performed Spearman correlations (given the appearance of two bivariate outliers) between measures

of anxiety, depression, and trauma exposure and each of the primary neuroimaging variables. We supplemented trauma-ROI analyses by performing Mann–Whitney *U* tests on subgroups of youth at CHR with high or low trauma exposure. As only 5 participants denied all queried trauma types, we used a median split for the total trauma variable (0–1 vs ≥ 2 exposure types) which allowed for more acceptable subgroup sizes (9 CHR individuals with ≥ 2 exposures and 14 with ≤ 1). For violent trauma, participants were classified according to the presence ($n = 7$) vs absence ($n = 16$) of exposure. In supplementary analyses, we considered effects of age, comorbid diagnosis, medication use, and scanner on BOLD signals of interest.

Results

Demographics and Clinical Presentation

Table 2 and table S1 display the demographic and clinical characteristics of the participants in the sample. The CHR and HV groups were comparable on demographic variables. As expected, youth at CHR presented with high rates of cooccurring DSM disorders, particularly depressive and anxiety disorders, and correspondingly high levels of affective symptom severity. The behavioral results of the MID were reported previously²⁸ and are not considered here. Briefly, participants in both groups made more in-time responses to cues predicting gains or losses than to cues predicting neutral outcomes, and higher rates of in-time responses to cues predicting gains than losses.

Whole-Brain Analyses of BOLD Responses to Prediction Errors

In the entire sample, unsigned PEs activated AI (bilaterally) and dorsomedial prefrontal cortex, and deactivated large parts of the striatum (bilaterally). Unsigned PEs evoked deactivations of the right temporoparietal junction in HVs, but activations in youth at CHR, and this difference was statistically significant (table 3; figure 2A–D).

Binary unexpected outcomes also activated the dorsomedial prefrontal cortex/dACC and bilateral AI and deactivated the temporoparietal junction (table S2A). Similarly, examination of [unexpected – expected] contrasts in parameter estimates revealed greater activation of left AI and dorsomedial prefrontal cortex, and greater deactivation of the bilateral striatum, by unexpected outcomes (figure S3A–C, table S2B). Between-group comparisons of signal responses to unexpected outcomes suggested that relative to HV, youth at CHR presented with significantly less deactivation evoked by unexpected outcomes in the precentral gyrus. Exploratory independent samples whole-brain *t*-tests revealed between-group differences in the bilateral associative striatum for unexpected outcomes, and in the

Table 2. Demographic and Clinical Characteristics of the Sample

| | CHR (<i>n</i> = 26) | HV (<i>n</i> = 19) | Test Statistic | <i>P</i> |
|------------------------------|--|---------------------|--|----------|
| | Mean or Frequency (<i>SD</i> or %) | | (<i>t</i> , χ^2 , or <i>z</i>) | |
| Age | 17.60 (3.2) | 18.03 (4.44) | 0.37 | .710 |
| Female | 16 (57.1) | 7 (36.8) | 2.68 | .10 |
| Family income | | | | |
| <20k | 5 (26.3) | 5 (26.3) | 0.11 | .746 |
| 20k–59.9k | 4 (21.1) | 5 (26.3) | | |
| 60k–99.9k | 3 (15.8) | 3 (15.8) | | |
| ≥100k | 7 (36.8) | 6 (31.6) | | |
| Race | | | 0.05 | .831 |
| Black or African American | 9 (34.6) | 6 (31.6) | | |
| White | 9 (34.6) | 11 (57.9) | | |
| Asian | 6 (23.1) | 0 (0) | | |
| ≥1 race | 2 (7.7) | 2 (10.5) | | |
| DSM diagnoses | | | – | |
| Mood disorder | 19 (73.1) | – | | |
| Anxiety disorder | 24 (92.3) | – | | |
| PTSD | 8 (32) | – | | |
| ADHD | 10 (40) | – | | |
| Substance use disorder | 2 (8) | – | | |
| Medication | | | | |
| Antipsychotic | 6 (24) | – | | |
| Antidepressant | 8 (32) | – | | |
| Stimulant | 8 (32) | – | | |
| BASC-2 scales | | | | |
| Depressive symptoms | 53.32 (15.21) | 43.78 (5.58) | –2.87 | .007 |
| Anxiety symptoms | 53.48 (13.71) | 44.67 (9.15) | –2.53 | .016 |
| Violent traumas | 0.52 (0.99) | 0.47 (0.77) | –0.17 | .86 |
| Total traumas | 1.6 (1.73) | 0.79 (0.79) | –1.90 | .063 |

bilateral posterior insula for [unexpected – expected] contrasts (not corrected for multiple comparisons across the whole brain; [figure S3D](#), [table S2A](#), [B](#)).

ROI Analyses of BOLD Responses to Prediction Errors

None of the between-group comparisons of unsigned PE responses in a priori amygdala or AI ROIs were statistically significant (despite modest effect sizes; [table S3](#)), and none of the symptom variables were significantly related to unsigned responses in either structure. However, greater unsigned signal activations in the right amygdala were associated with a more severe history of exposure to violent traumas ($\rho = .436$, $P = .038$) and greater unsigned signal activations in the left amygdala were associated with more severe history of total trauma exposure ($\rho = .433$, $P = .039$) among youth at CHR. The results of Mann–Whitney *U* tests supported the correlational results in that CHR youth with ≥2 trauma exposures of any kind presented with significantly stronger left unsigned amygdala activation than those with ≤1 exposure, with a large effect ($z = -2.394$,

Table 3. Results of Whole-Brain *t*-Tests on Parametric Regressors Representing Unsigned Prediction Errors Across the Full Sample and Between Groups

| R/L | Brain Area | Peak x | Peak y | Peak z | #Voxels |
|---|---|------------|------------|------------|-------------|
| Full sample | | | | | |
| L | Dorsal Anterior Cingulate Cortex | 0 | 36 | 45 | 100 |
| R | Anterior Insula | 48 | 24 | –4 | 2134 |
| R | Dorsomedial Pre- frontal Cortex | 0 | 24 | 69 | 1297 |
| L | Anterior Insula | –53 | 23 | 4 | 1378 |
| L | Ventral Striatum | –23 | 11 | –1 | 2365 |
| R | Ventral Striatum | 20 | 9 | –4 | 1427 |
| R | Anterior Tem- poral Cortex | 54 | 8 | –34 | 964 |
| L | Dorsal Caudate | –20 | 8 | 28 | 160 |
| R | Dorsal Caudate | 17 | –23 | 30 | 421 |
| L | Primary Motor Cortex | –27 | –27 | 58 | 279 |
| L | Primary Sensory Cortex | –17 | –32 | 69 | 189 |
| R | Superior Tem- poral Sulcus | 59 | –41 | –5 | 222 |
| R | Temporoparietal Junction | 38 | –36 | 22 | 191 |
| Clinical High risk vs Healthy Volunteer | | | | | |
| R | Temporoparietal Junction | 38 | –36 | 22 | 191 |

Note: Bold font indicates regional activation, standard font indicates regional deactivation.

$P = .016$, $\eta^2 = .261$). Similarly, those exposed to violent trauma showed greater right unsigned amygdala activation, with a large effect size approaching statistical significance ($z = -1.871$, $P = .065$, $\eta^2 = .159$; [figure 3](#)). No significant relations between trauma exposure and unsigned PE signal in the AI were observed.

None of the between-group comparisons of parameter estimates from analyses with binary regressors in a priori ROIs were significant ([table S4](#)), and no correlations were observed between these regressors and affective symptoms or trauma histories in youth at CHR.

Effects of Age, Comorbidity, Medication, and Scanner on BOLD Signals of Interest

Results of supplementary analyses considering the effects of age, comorbidity, medication, and scanner are presented in the [Supplementary Results](#) and [tables S4–S12](#). Participants with CHR and cooccurring PTSD showed reduced AI activation responses to PE relative to those without PTSD, and participants taking antidepressants showed a negative AI response to PE whereas those not taking antidepressants showed a positive one. Youth at CHR scanned following the scanner upgrade presented with greater differentiation of unexpected and expected outcomes in the right AI relative to those scanned before the

upgrade but did not differ in the severity of affective symptoms or trauma exposure. There were no other associations between PE-evoked BOLD activity in ROIs and age, psychiatric comorbidity, medication use, or scanner.

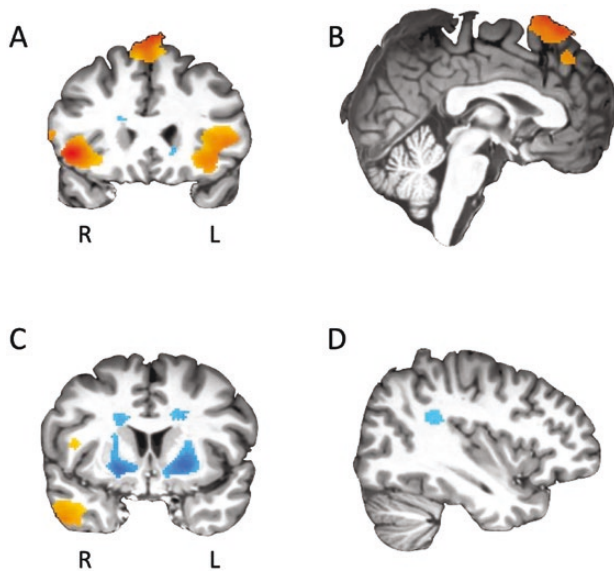


Fig. 2. A–C. Clusters showing significant BOLD signal modulations by the magnitudes of unsigned prediction errors. A. Activations in dorsomedial prefrontal cortex and left and right anterior insula visible in brain image cut at $y = 24$. B. Activation in dorsomedial prefrontal cortex visible in brain image cut at $x = 0$. C. Deactivations in dorsal and ventral striatum visible in brain image cut at $y = 10$. D. Clusters showing significant between-group differences in BOLD signal modulations by the magnitudes of unsigned prediction errors. Between-group difference in temporo-parietal junction visible in brain image cut at $x = 39$. BOLD, blood-oxygen level dependent.

Discussion

This study aimed to assess the intersection between adversity exposure, affective distress, and neural salience signals evoked by PEs among individuals at CHR for psychosis. We observed that relative to HV, individuals at CHR exhibited aberrant activation responses to surprising outcomes in the temporoparietal junction and reduced deactivation responses to such outcomes in the precentral gyrus, posterior insula, and associative striatum. Further, amygdala responses to unsigned PEs were associated with histories of adversity: CHR youth with greater violent trauma exposure presented with stronger activation responses to unsigned PEs in the right amygdala, and those with greater total trauma exposure presented with stronger activation responses to unsigned PEs in the left amygdala. Contrary to our hypotheses, we observed no significant between-group differences in neural responses to surprising outcomes in the amygdala or anterior insula, and no significant correlations between these signals and affective symptoms. These findings add to the growing understanding of salience network function in people at CHR and to knowledge of this network's association with clinical presentation and adversity exposure among those at risk.

An increasing number of studies suggests mild impairments of the salience and reward networks in youth at CHR,^{28,39,65} but the extent to which unvalenced signals participate in these abnormalities has been understudied. Here, we found that unsigned PEs were encoded in several salience network structures, consistent with a recent study in which unsigned errors were represented in the dACC and supported learning among individuals at CHR.³³ We extend these findings by showing that youth at CHR present with aberrant activation responses to

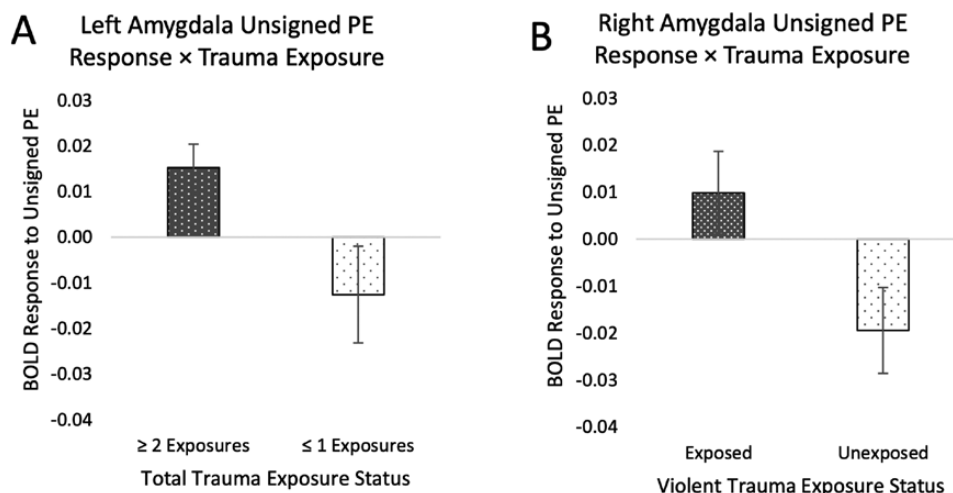


Fig. 3. Bar graphs depicting relations of PE signals with trauma exposure in youth at CHR for psychosis. Error bars represent standard errors. A. Greater left amygdala activation to unsigned PE among participants with lifetime exposure to two or more trauma types. B. Greater right amygdala activation to unsigned PE among CHR participants with lifetime exposure to violent trauma. BOLD, blood-oxygen level dependent; CHR, clinical high-risk; PE, prediction error.

parametric unsigned PEs in the temporoparietal junction and reduced signal suppression in response to binary unexpected outcomes in the precentral gyrus, posterior insula, and associative striatum. Of note, the temporoparietal junction is considered a node of the salience network given consistent evidence that it responds to a range of novel stimuli (ie, auditory, visual, tactile),⁵ covaries in resting activity with other salience network structures,⁶⁶ and includes subregions that encode a variety of PEs, particularly unsigned PEs.^{14,53} The normative response of the temporoparietal junction to PE in this study was deactivation (as opposed to activation), consistent with findings from prior studies suggesting that greater suppression of this area in response to increasing attentional demands (cognitive load and surprise) supports filtering of cognitive and perceptual information in healthy individuals.⁶⁷ Thus, our observation of aberrant PE-evoked activation of the temporoparietal junction in CHR youth may reflect impaired filtering of internal or external information, consistent with the hypothesis that enhance salience signaling may be involved in the initial formation of psychotic symptoms.⁸

Despite our findings of altered encoding of surprising outcomes in several salience/reward network structures in youth at CHR, we observed no significant between-group differences in PE signaling in the AI or amygdala, our *a priori* ROIs. These findings are consistent with prior studies reporting a similar degree of unsigned PE encoding in the amygdala across HV and individuals with early-stage or chronic psychosis.^{33,68} Animal research suggests that unsigned PEs originate in the amygdala and propagate to other salience network structures, where they modulate the degree of relevance signaled by signed error representations.¹² Given these basic findings alongside evidence of widespread functional dysconnectivity in psychosis,⁶⁹ it is possible that unsigned PEs are more or less properly generated within the amygdala in psychosis but transport abnormally to other nodes of the salience or reward networks, such as the insula and striatum.⁶⁸ Additional work is needed to address this speculation, such as studies integrating structural or functional connectivity analyses with event-related salience paradigms. It should also be noted that despite nonsignificant CHR-HV differences in our ROI responses to PE, effect size estimates were modest in magnitude, suggesting that certain unobserved subgroups of individuals at CHR (eg, those with later transition to psychosis) may present with altered unsigned PE signaling in the amygdala or AI despite the appearance of overall similarity to HV at baseline. Larger samples and longitudinal research will be essential for investigating this possibility.

A novel contribution of this research was its focus on the relation of adversity exposure to PE signaling in youth at CHR for psychosis. Exposure to serious stressors in childhood can dramatically alter neurodevelopment, and the amygdala in particular can be sensitized to

unexpected events.⁵² Given more recent evidence that stress exposure alters neurobehavioral measures of salience processing,^{48,49,51} the study of unsigned PE signals in young people at CHR represents a valuable opportunity to shed light on the potential pathways through which preventable contributors to psychopathology may give rise to symptoms. Our finding that participants with greater trauma histories presented with stronger encoding of unsigned PEs in the amygdala extends prior work by suggesting that early life stress may sensitize the amygdala to surprise, irrespective of its valence. Given that unsigned signals are particularly valuable when uncertainty is high, we speculate that trauma may sensitize the amygdala to surprise by increasing the sensitivity, vigilance, or amount of attention paid to subtle, unanticipated outcomes, potentially bringing about (eg) fear, rumination, suspiciousness, or referential thinking. Although replication of these findings is needed, our finding of an association between trauma histories and the magnitude of unsigned PE signaling in the amygdala in CHR youth supports the idea that adverse life experiences may influence later psychopathology in part through their effects on the salience network.

Our study's focus on the intersection between affective symptoms and PE signaling in youth at CHR was motivated in part by the observations that depressive and anxiety disorders are characterized by similar salience and reward circuit abnormalities as those seen in the CHR population^{70,71} and that most individuals at CHR present with cooccurring disorders of depression and/or anxiety.³⁵ In our sample, 73% of CHR participants were diagnosed with a depressive disorder, 92% with an anxiety disorder, and 32% with a trauma-related disorder. Given the complex admixture of psychiatric symptoms presenting in the help-seeking CHR population and the fact that most do not develop a formal psychotic disorder (but do experience persistent or incident symptoms of other kinds^{72,73}), dissociating the neural or environmental contributors to distinct dimensions of psychopathology in this group is needed to refine our understanding of global illness development and refine targets for treatment. Interestingly, affective symptomatology was unrelated to PE signaling in the salience network in the present study; however, supplementary analyses suggested that CHR youth with cooccurring PTSD may show altered neural responses to PE relative to those without cooccurring PTSD. Prior studies reporting associations between affective symptoms and neurobehavioral representations of salience or reward processing in CHR have typically focused on signed PEs,^{28,39} although one study of adults with schizophrenia found that behavioral responses to unsigned errors were associated with negative symptoms,⁶⁸ and another study of veterans with PTSD found that amygdala responses to unsigned PEs were associated with the severity of PTSD symptoms.⁵⁰ More studies are needed to investigate the relative contributions of affective and psychotic

dimensions of psychopathology to neural and behavioral aspects of salience signaling in the high-risk stages of psychosis.

Our results should be considered in light of several study limitations. First, despite their theoretical relevance to salience signaling in psychosis, our findings of altered responses to PE in the temporoparietal junction and precentral gyrus were not prespecified areas of interest, and findings of altered posterior insula and associative striatum signaling in CHR did not survive whole-brain correction; replication of these results will therefore be especially important. Second, several participants were taking medications that impact on the dopaminergic and/or serotonergic systems involved in salience-related neural functioning. Although a focus on help-seeking participants increases pretest risk enrichment in CHR research⁷⁴ and intensive treatment histories are the norm in this population,⁷⁵ studies of unmedicated participants and/or larger samples capable of parsing participants by medication status are needed to determine the possible effects of these medications on findings like ours. Third, although our imaging protocol (eg, sequences, task presentation, data processing pipeline) remained consistent across the study, not all participants were scanned on the same machine due to a scanner upgrade during the study period. Despite showing similar levels of symptomatology and trauma histories, youth at CHR scanned following the upgrade showed evidence of greater [unexpected – expected] BOLD contrasts in the right AI relative to those scanned before the upgrade, which should be considered in the context of our findings.

Fourth, our study lacked a clinical comparison group. Given that our analyses intentionally focused on putatively transdiagnostic phenomena (ie, salience, affective, and stress-related measures), a clinical comparison group presenting with affective illness but without identifiable psychosis risk would be key in teasing apart common and specific abnormalities of psychosis, depression, or anxiety. Future studies incorporating such comparators are vital to promoting a more comprehensive and developmental understanding of psychopathology.^{36,37}

In summary, our findings provide support for a role of salience network dysfunction in the CHR stage of psychosis and highlight the importance of considering unvalenced PE signals in neurobiological studies of this population. Encoding of these errors may be intact within the amygdala and AI but abnormal in other areas of the salience and reward networks, although more studies are needed to increase confidence in these findings. Severe stressors experienced prior to identification may potentiate changes in how a young person's brain responds to salient or unexpected outcomes. The nature of these changes is relevant to our understanding of psychotic disorders, but also depressive, anxiety, and stress-related disorders, highlighting the overlap of these syndromes and the need for more research aiming to elucidate their

differences and similarities at early clinical stages, when intervention is most promising.

Supplementary Data

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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