Responses to positive affect and unique resting-state connectivity in individuals at clinical high-risk for psychosis

Katherine S.F. Damme a,b,*, Tina Gupta a,b, Claudia M. Haase a,b,c,d, Vijay A. Mittal a,b,c,d,e,f

a Department of Psychology, Northwestern University, Evanston, IL, USA
b Institute for Innovations in Developmental Sciences (DevSci), Northwestern University, Evanston and Chicago, IL, USA
c Human Development and Social Policy, Northwestern University, Evanston, IL, USA
d Institute for Policy Research (IPR), Northwestern University, Chicago, IL, USA
e Department of Psychiatry, Northwestern University, Chicago, IL, USA
f Medical Social Sciences, Northwestern University, Chicago, IL, USA

ARTICLE INFO

Keywords:
Positive affect
Emotion regulation
Clinical risk for psychosis
Resting-state connectivity
Nucleus accumbens
Anterior cingulate cortex

ABSTRACT

Individuals at clinical high-risk for psychosis (CHR) report dampened positive affect, while this deficit appears to be an important clinical marker, our current understanding of underlying causes is limited. Dysfunctional regulatory strategies (i.e., abnormal use of dampening, self-focused, or emotion-focused strategies) may account for dampening affect but has not yet been examined. Participants (57 CHR and 56 healthy controls) completed the Response to Positive Affect Scale, clinical interviews, and resting-state scan examining nucleus accumbens (NAcc) connectivity. Individuals at CHR for psychosis showed greater dampening (but no differences in self/ emotion-focus) in self-reported response to positive affect compared to healthy controls. In individuals at CHR, higher levels of dampening and lower levels of self-focus were associated with higher positive and lower negative symptoms. Dampering responses were related to decreased dorsal and rostral anterior cingulate cortex-NAcc resting-state connectivity in the CHR group but increased dorsal and rostral anterior cingulate cortex-NAcc resting-state connectivity in the healthy control group. Self-focused responses were related to increased dorso-lateral prefrontal cortex-NAcc resting-state connectivity in the CHR group but decreased resting-state connectivity in the healthy control group. Self-reported dampening of positive affect was elevated in individuals at CHR for psychosis. Dampering and self-focused responses were associated with distinct resting-state connectivity compared to peers, suggesting unique mechanisms underlying these emotion regulation strategies. Responses to positive affect may be a useful target for cognitive treatment, but individuals at CHR show distinct neuro-correlates and may require a tailored approach.

1. Introduction

Emotional functioning in schizophrenia is defined by high negative affect and low positive affect (Barch, 2008; Herbener et al., 2008; Kring and Ellis, 2013). These alterations are present prior to psychosis onset—among individuals at clinical high risk for psychosis (CHR; Fusar-Poli et al., 2014; Kelleher et al., 2012; Tully and Niendam, 2014). Interventions targeted at improving affect in psychosis have demonstrated insight into the regulation of positive emotions may yield critical treatment targets to improve symptoms and quality of life for CHR individuals (Addington et al., 2011; Grezellschak et al., 2015; Morrison et al., 2004; Morrison and Barratt, 2010; Phillips et al., 2007).

As a result, emotion regulation is an important contributor to both affective and psychotic symptoms and treatment target. However, to date, the treatment focus has been on negative emotions. Less is known about how CHR individuals regulate positive emotions (Barch, 2008). Indeed, insight into the regulation of positive emotions may yield critical treatment targets to improve symptoms and quality of life for CHR individuals.

As previously mentioned, research in psychosis spectrum populations has consistently found alterations in emotional function – lower positive affect and higher negative affect (Berenbaum and Oltmanns, 1992; Cowan et al., 2020; Herbener et al., 2008; Kring and Ellis, 2013;...
CHR individuals, in particular, experience lower trait levels of positive and higher trait levels of negative affect (Cowan et al., 2020; van der Steen et al., 2017; Yee et al., 2019). These traits may impact one’s concept of self, as CHR individuals have more negative and fewer positive core beliefs about themselves (Cowan et al., 2019; Damme et al., 2019). These affective tendencies also appear as lower levels of positive affect in response to emotionally valenced pictures (Gruber et al., 2018) and facial expression with CHR individuals having lower levels of positive and higher levels of negative facial expressions of emotions (Gupta et al., 2020, 2019). While findings regarding alterations in negative emotions vary somewhat depending on the approach, there is consistent evidence of reduced positive emotionality among CHR individuals which impacts many areas of function.

Despite these insights, it is not yet clear whether CHR individuals only show deficits in the generation of positive emotions (Gruber et al., 2018) or if these deficits may also extend to the regulation of positive emotions (Gilbert et al., 2017, 2019; Moskowitz et al., 2017). Although a paucity of work examines positive affect directly, psychosis is associated with deficits in responsibility to rewarding stimuli (Barch et al., 2017; Hanssen et al., 2020), which may provide insight into positive affect. In psychosis, deficits in reward responsivity relate to the level of risk for psychosis (Hanssen et al., 2020), deficits in motivation/pleasure, and impact cognition and learning (Barch et al., 2017). These reward deficits are frequently attributed to hypoactivation in the nucleus accumbens (NAcc) failing to appropriately mark the anticipation or receipt of reward (Radua et al., 2015; Zhang et al., 2016). However, network approaches suggest that connectivity to the NAcc may better account for deficits in rewarding experience for patients with psychosis (Chase et al., 2018). Although this was attributed to poor cognitive coordination (Chase et al., 2018), the role of emotion regulation in decreased positive affect has not been explored.

Emotion regulation refers to the intentional, goal-directed response that one has to influence the intensity, duration, and type of emotion that they experience (Gross, 2013). Previous studies have documented heightened levels of maladaptive emotion regulation strategies in CHR individuals (van der Steen et al., 2017) and with psychosis (Kimby et al., 2016; Moran et al., 2018). However, these studies focused on the regulation of negative emotions (van der Steen et al., 2017). Thus, we lack critical knowledge about the regulation of positive emotions in CHR individuals, including whether positive affect is related to maladaptive emotion regulation strategies (Kimby et al., 2016), reduced positive reactivity (Gruber et al., 2018), or differences in the underlying biology of emotional regulation networks (Duggirala et al., 2020; Tully and Niendam, 2014). In affective neuroscience, emotion regulation processes are thought to originate in dorsal cortical regions, including the dorsolateral prefrontal cortex (dIPFC), ventrolateral prefrontal cortex (vIPFC), dACC, and dorsomedial prefrontal cortex (dmPFC). These regions then signal emotion generation regions (Phillips et al., 2008; Phillips and Swartz, 2014; Strakowski et al., 2012) – such as NAcc in positive affect (Chase et al., 2018; Floresco, 2015; Radua et al., 2015; Zhang et al., 2016). Activity in the NAcc appears to be a core neurobiological correlate of positive affect in cognitive reward (Haber and Knutson, 2010), depression (Bewernick et al., 2010; Francis and Lobo, 2017; Pizzagalli et al., 2009; Warner-Schmidt et al., 2012), and bipolar literature (Damme et al., 2017; Whittaker et al., 2016). Increased activity and connectivity of the NAcc are associated with increased positive affect in studies of hypomania (Damme et al., 2017), mania (Whittaker et al., 2016), and decreased activity is related to depression (Bewernick et al., 2010). The NAcc is also associated with down-regulating dopamine production (Grace, 2016; Robison et al., 2020) by setting off cascading effects to depress affect, cognition, and motor activity. However, it is possible that other emotion-generating regions may have a critical role in positive affect deficits in CHR individuals; decreased connectivity between the NAcc and emotion generation areas (via the rostral anterior cingulate cortex (rACC); Phillips et al., 2008; Phillips and Swartz, 2014) may insufficiently amplify the sensations (e.g., insular cortex; Cauda et al., 2011; Craig, 2009) or intensity of emotion (amygdala; Bonnet et al., 2015). As a result, connectivity to the NAcc may provide critical insight into the mechanisms underlying reduced positive affect (Chase et al., 2018) and the mechanisms underlying this deficit; whether NAcc is being overly regulated by cortical input, failing to engage other emotional regions, or both.

The current paper examines emotion regulation of positive affect in CHR individuals. Based on prior research in negative affect (van der Steen et al., 2017) in CHR for psychosis and psychosis, we expect that CHR individuals will show more frequent maladaptive emotion regulation strategies, i.e., dampening of positive affect, and less frequent adaptive emotion regulation strategies, i.e., self-focused and emotion-focused responses to positive affect. Next, we will examine how these response tendencies related to relevant clinical measures including, attenuated positive symptoms, attenuated negative symptoms (i.e., avolition, flattened affective expression, and disturbances in self-perception). Based on the effectiveness of emotion regulation strategies in addressing psychosis symptoms (Addington et al., 2011; Grezziuchak et al., 2015; Morrison et al., 2004; Morrison and Barratt, 2010; Phillips et al., 2007), we expect that dampening will be related to more severe positive and negative symptoms. Self- and emotion-focused responses will be related to reduced negative symptoms but reflect distinct relationships to subscales (i.e., avolition, experience of self and emotion, and flattened affect). Self-focused responses to positive affect will be related to fewer experiences of abnormalities in self-perception, whereas emotion-focused responses to positive affect should be related to reduced avolition and flattened affect. Finally, we examined resting-state functional connectivity to the NAcc (Chase et al., 2018) and expect that an active dampening of positive emotion will relate to resting-state connectivity. It is unclear if CHR individuals exhibit distinct emotion regulation, emotion generation, or unique regions related to responses to positive emotion. As a result of these competing hypotheses, we have taken an exploratory whole-brain approach to examine these questions.

2. Methods

2.1. Participants

Adolescent Development and Preventive Treatment (ADAPT) Program recruited 113 participants (57 CHR and 56 healthy control) between the ages of 12–21 ($M = 18.51, SEM = 2.08$). All procedures were approved by a local Institutional Review Board. Participants that were 18 years old or older provided written consent to participate. For participants that were under the age of 18, parents provided written consent, and the participant provided written assent. Individuals were included in the study if they met the criteria for a clinical high-risk (CHR) syndrome based on the Structured Interview for Psychosis-Risk Syndromes (SIPS; Miller et al., 2003). Specifically, if participants received a score of 3 (moderate) to 5 (severe but not psychotic) on any of the positive symptom dimensions scales (e.g., unusual thought content), then they were considered CHR for psychosis. Additional inclusion criteria included if an individual met for schizotypal personality disorder or had a first-degree relative with a psychotic disorder accompanying a decline in functioning. Exclusion criteria for both were if they met for a psychotic disorder. For healthy control participants, exclusion criteria also included the presence of a psychotic disorder in a first-degree relative as this may reflect latent genetic risk. The neuroimaging protocol also included several exclusionary criteria: presence of a neurological disorder, head injury, lifetime substance dependence, or the presence of any other contraindication to a magnetic resonance imaging environment (assessed via self-report during a clinician-rated interview; Deighton et al., 2016; Stowkowy and Addington, 2013). For healthy control participants, exclusion criteria also included the presence of a psychotic disorder in a first-degree relative as this may reflect latent genetic risk. Additionally, participants were excluded for the
presence or lifetime history of an Axis I psychotic disorder. All participants are between ages 12–21 (M = 18.51, SEM = 2.08).

2.2. Clinical Assessments.

The Structured Clinical Interview for DSM-IV (SCID) for Axis I disorders was administered to rule out any psychosis diagnosis in the sample. Any history of mood and anxiety disorders was also assessed using this clinical interview (Gibbon et al., 1997). In addition to the SCID, as mentioned, the Structured Interview for Psychosis-Risk Syndromes (SIPS) was used to identify individuals with a psychosis risk syndrome (Miller et al., 2003). The SIPS scale is a clinician-rated, semi-structured interview in which symptoms are rated for severity on a scale from 0 (absent) to 6 (severe and psychotic); ratings of 3 or higher are considered at relevant to risk for psychosis or unusually elevated. Qualifying SIPS criteria for a prodromal syndrome, defined by moderate-to-severe but not psychotic levels of positive symptoms (rated from 3 to 5 on a six-point scale; n = 51) or a decline in global functioning with the presence of schizotypal personality disorder or a family history of schizophrenia (n = 6; Miller et al., 2003). All clinical assessments were performed by clinical graduate trainees under the supervision of VAM. All interviewers received extensive training on the noted clinical interviews and were reliable, kappa ≥ 0.80. This measure was also used to investigate the total number of positive and negative symptoms that were endorsed and the severity of particular symptom dimensions of interest (i.e., avolition, disturbances in the experience of emotions and self, flattened emotional expression). Avolition items include prompts such as “Do you find that you have trouble getting motivated to do things?” and “Do you find that people have to push you to get things done?”. Disturbances in the experience of emotions and self-included prompts such as “Do you ever feel a loss of sense of self or feel disconnected from yourself or your life?” and “Do you find yourself having a harder time distinguishing between different emotions/feelings”.

Flattening emotional expression included items such as “Has anyone pointed out to you that you are less emotional or connected to people than you used to be?”. Post-hoc analyses were conducted to examine whether other positive and negative items (e.g., Hallucination, Poverty of Thought) related to self-reported response to positive affect; no other relevant psychosis symptoms were identified (r ≤ 0.25; p ≥ 0.05).

2.3. Responses to positive affect

Response to Positive Affect Scale (RPA; Feldman et al., 2008) is a 17-item questionnaire in which participants rate the frequency with which they have a specific reaction to positive affect on a 4-point Likert-type scale (i.e., 1- almost never to 4 almost always). The reactions fall into three types of classifications: dampening, self-focused, and emotion-focused, which have good reliability (alpha: 0.73-0.79; 3). In dampening reaction items, participants rate the frequency at which they focus on cognitions that may reduce positive affect, e.g., “When you are happy, how often do you... think that I don’t deserve this.” In self-focused reaction items, participants rate the frequency at which they focus on their role in the positive affect, e.g., “When you are happy, how often do you... think about how proud you are of yourself.” In emotion-focused reaction items, participants rate the frequency at which they focus on the experience of the positive affect, e.g., “When you are happy, how often do you... savor the moment.” Response to positive affect subscales were intercorrelated for internal structure, details in a supplemental table.

2.4. MRI acquisition and processing

Images were acquired in a 3T Siemens Tim Trio MRI scanner (Siemens AG, Munich, Germany with a standard 12-channel head coil, which included a resting-state functional image and structural image for registration. The resting-state sequence was acquired with a T2*-weighted echo-planar functional protocol (33 slices; field of view = 240 mm; 3.8 × 3.8 × 3.5 mm voxels; TR = 2.00 s; TE = 29 ms; Flip Angle = 75°). While participants closed their eyes during the 5 min 34 s scan. The structural image was an MPRAGE (sagittal acquisition, 120 interleaved slices; 256 mm field of view; isotropic voxels 1 mm3, GRAPPA parallel imaging factor of 2, Time to repetition (TR) = 2.53 s; Time to Echo (TE) = 1.64 ms, 3.5 ms, 5.36 ms, 7.22 ms, 9.08 ms; flip angle = 7°).

Data were preprocessed in FSL (v5; Jenkinson et al., 2012), which included brain extraction, high-pass filtering (100 s), and spatial smoothing (6-mm Full Width Half Max). Head motion was corrected with FSL MClFlirt and was then aligned to the subject’s T1 image using FSL’s border-based registration (BBR), and finally registered to FSL’s MNI Average 125T1 2-mm3 brain template using 12 degrees of freedom and nonlinear transformation with FSL’s FNIRT. To ensure that there were no significant differences in brain registration or warping due to neurodevelopmental differences related to age, Jacobian determinants images were compared across age, which did not significantly relate to subject neurodevelopmental stage (age quartile), F(3,107) = 2.51, p = .06, and did not differ by diagnostic risk group, F(1,99) = 0.99, p = .32.

To account for motion, temporal derivative regressors were calculated using the artifact detection software (ART; Adolphs, 2002; Gallace and Goldman, 1998), resulting in three translation and three rotation parameters. Additional image-specific confound regressors were based on brain activation and framewise movement. Brain activation outliers were calculated using the mean global brain activity, the z-normalized mean signal across all voxels as a function of time. Outliers were defined as any frames where the mean signal exceeded 3 SDs. Framewise measures of motion (a composite measure of total motion, or maximum voxel displacement, across translation and rotation) were used to identify any motion outliers; motion outliers were defined as frames where the absolute value of motion exceeded 1 mm. Two individuals were excluded from the resting-state functional analyses on the basis of motion. The temporal derivative of composite motion outliers (as described above) were calculated in the ART toolbox and was included as a nuisance regressor. The resultant motion regressors were entered into the model as a temporal derivative nuisance covariate at the subject level. Post-hoc analyses were conducted to examine differences in head motion by group, and groups did not differ in terms of head motion, t (109) = 0.22, p = .83. All data were visually inspected for artifacts before and after preprocessing.

Resting-state functional connectivity analyses were performed in the CONN toolbox regions of interest (ROI)-to-voxel analyses v.20.b (Whitfield-Gabrieli and Nieto-Castanon, 2012) and SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/SPM12/). Anatomical images were segmented into gray matter, white matter, and CSF with SPM12 to create masks for signal extraction. The Conn toolbox extracts five temporal components from the segmented CSF and white matter, which were entered as confound regressors in the subject-level GLM. Additional denoising regressors corresponding to gray matter, white matter, cerebrospinal fluid (CSF), and mean global signal were included to remove related variance. Quality assurance parameters were produced by CONN were inspected for all subjects to ensure that the global signal was sufficiently reduced, the distribution of the resting-state connectivity was normal, and the spatial distribution of the BOLD signal. In the CONN toolbox ROI-to-voxel analyses, the time course of each voxel in the ROI were averaged to create an ROI level time course. Then, each ROI time course is correlated with Fischer’s transformed bivariate coefficient representing the resting-state functional connectivity between the ROI and each voxel in the brain. Clusters-level inferences were conducted using Gaussian Random Field theory (Worsley et al., 1996), beginning with a parametric map of F-values and thresholding this map at an apriori-defined threshold height of p < .001 applied to the voxel level. Each cluster was then characterized by its size and compared to a null distribution of the probability of clusters of that size occurring in a random field. Results depict only those values that cluster size achieves a threshold of p < .05 false discovery rate corrected (FDR; Chumbley et al., 2010; Chumbley and Friston, 2009).
ROIs were defined by segmenting the MNI 152 2 mm$^3$ template using an automatic parcellation method available in FreeSurfer (Fischl, 2012), which uses cortical surface landmarks to delineate cortical areas defined in the Desikan atlas (Desikan et al., 2006).

2.5. Analytical strategy

Group demographics (age, sex, and race) were compared across the CHR and Control groups using t-tests and chi-squares, respectively. Any significant demographic differences would be accounted for in later models. First, we examined whether groups differed in terms of the frequency of particular self-reported responses to positive affect (emotion-focus, self-focus, dampening) with t-tests. Next, we examined the extent to which these cognitive responses to positive affect reflected positive symptoms, and negative symptoms, in separate general linear models of only individuals at clinical high risk for psychosis in separate models for positive and negative symptoms. Simple relationships were conducted in follow-up analyses revealed similar patterns of results, see Supplemental Materials. In an exploratory set of analyses, we then examined theoretically relevant subscales for each symptom dimension to protect power and reduce the total number of comparisons. Follow-up analyses confirmed that no other subscales were relevant beyond the theoretically identified symptoms. Finally, in exploratory analyses, we looked for regions whose resting-state connectivity to the ventral striatum related to self-reported response to positive affect in resting-state data controlling for the other self-reported response to positive affect subscales. Multiple comparisons were corrected by aim and subscale (aim 1–p < .05, aim 2–p < .016, and aim 3–random field theory parametric correction with a voxel-level threshold of p < .001 uncorrected and a cluster-level threshold set to p < .05 FDR corrected for cluster size (Worsley et al., 1999). All analyses were run with and without individuals taking antipsychotics (n = 8) or anti-depressants (n = 8), which did not impact the magnitude or direction of the effect sizes reported below (See Supplemental Table 3 for more information). Although two subjects were excluded from the imaging analyses based on the quality of their resting-state functional images, all of the following results include all subjects for whom data was available to preserve power and transparency (113 for self-report and symptoms, 111 for resting-state connectivity analyses).

3. Results

3.1. Participants

Our sample included 113 participants (52% female), Table 1. There were no significant differences in the distribution of biological sex by group, χ$^2$(112.1) = 3.51, p = .06. There was also not a significant difference in age between the CHR and control groups, t(111) = 0.02, p = .98. As expected, the two groups did significantly differ on clinical measures of attenuated positive symptoms in that the CHR group had more severe positive, t(111) = 17.64, p < .001, d = 3.39, and negative symptoms, t(111) = 9.23, p < .001, d = 3.29. Groups did not significantly differ in terms of their own years of education, t(111) = 0.39, p = .70, parental education (mother: t(111) = 0.28, p = .78; father: t(111) = 0.31, p = .76). Socioeconomic status did not significantly vary by group, χ$^2$(107.6) = 3.59, p = .73, or race, χ$^2$(106.7) = 9.24, p = .23, Supplemental Table 1.

3.2. Group differences in self-reported frequency responses to positive affect

3.2.1. Dampening response to positive affect

The CHR group had significantly higher in their use of dampening responses to positive affect, t(111) = 5.55, p < .001, compared to healthy peers, Table 2 and Fig. 1A.

| Variables of Interest | CHR Mean (SD) | Control Mean (SD) | Group Differences |
|-----------------------|---------------|-------------------|-------------------|
| Emotion-Focused       | 13.32         | 13.21             | t(111) = 0.17, p = .86 |
| Frequency             | (3.27)        | (2.92)            |                  |
| Self-Focused Frequency| 9.11(2.78)    | 9.60(2.77)        | t(111) = 0.94, p = .35 |
| Dampening Frequency   | 16.13         | 11.66             | t(111) = 5.55, p < .001 |
| Positive Total Symptoms| 11.65       | 0.40(1.03)        | t(111) = 17.64, p < .001 |
| Negative Total Symptoms| 9.39 (7.39) | 0.25 (0.54)       | t(111) = 9.23, p < .001 |

3.2.3. Emotion-focused response to positive affect

In a general linear regression, positive symptoms were related to dampening, self-focused, and emotion-focused responses to positive affect simultaneously, Table 3 and Supplemental Fig. 1. Responses to positive affect significantly contributed to the models of positive symptoms, r$^2$-change = 0.30, F(3,108) = 15.49, p < .001.

3.3. Neglected Symptom Total

In a general linear regression, negative symptoms were related to dampening, self-focused, and emotion-focused responses to positive affect simultaneously, Table 2 and Supplemental Fig. 1. Responses to positive affect significantly contributed to the models of negative symptoms, r$^2$-change = 0.24, F(3,108) = 11.44, p < .001.

3.4. Prodromal emotional and self symptoms exploratory analyses

3.4.1. Avolition

In a general linear regression, avolition rating was related to dampening, self-focused, and emotion-focused responses to positive affect simultaneously. Responses to positive affect significantly contributed to the models of avolition, r$^2$-change = 0.21, F(3,108) = 9.74, p < .001.
3.4.2. Disturbance in experience of emotion and self

In a general linear regression, the experience of emotion was related to dampening, self-focused, and emotion-focused responses to positive affect simultaneously. Responses to positive affect significantly contributed to the models of experience of emotion and self, \( r^2 \)-change = 0.27, \( F(3,108) = 13.45, p < .001 \).

3.4.3. Flattened emotional expression

In a general linear regression, flattened emotional expression rating was related to dampening, self-focused, and emotion-focused responses to positive affect simultaneously. Responses to positive affect significantly contributed to the models of flattened affective expression, \( r^2 \)-change = 0.16, \( F(3,108) = 11.44, p < .001 \).

3.5. Group differences in resting-state connectivity related to self-reported response to positive affect

3.5.1. Dampening response

There was a significant group (CHR, Control) by dampening response to positive affect interaction in three clusters: dorsal anterior cingulate cortex (dACC), rostral anterior cingulate cortex (rACC), and thalamus, Table 4. Increased dampening of positive affect was related to decreased NAcc-dACC resting-state connectivity (Cluster size: 259, p-FDR = 0.0006) in the CHR group (Left NAcc: \( r = -0.13, \) Right NAcc: \( r = -0.47 \)), but increased resting-state connectivity in control subjects was positively related to Dampening (Left NAcc: \( r = 0.27, \) Right NAcc: \( r = 0.46 \)), Fig. 2. Increased cognitive dampening of positive affect was related to decreased NAcc-rACC resting-state connectivity (Cluster size: 96, p-FDR = 0.003) in the CHR group (Right NAcc: \( r = -0.43, \) Left NAcc: \( r = -0.55 \), but increased resting-state connectivity in control subjects was positively related to Dampening (Left NAcc: \( r = 0.37, \) Right NAcc: \( r = 0.44 \)), Fig. 3. Increased cognitive dampening of positive affect was related to increased NAcc-Thalamic resting-state connectivity (Cluster size: 99, p-FDR = 0.003) in the CHR group (Left NAcc: \( r = 0.20, \) Right NAcc: \( r = 0.49 \), but decreased resting-state connectivity in control subjects was positively related to Dampening (Left NAcc: \( r^2 = -0.14, \) Right NAcc: \( r^2 = -0.31 \)), Fig. 4.

3.5.2. Self-focused response

Self-focused response was related to distinct striatal resting-state connectivity in the CHR group compared to the control group in the dorsal lateral prefrontal cortex (Cluster size: 104, p-FDR = 0.04), Table 2. Increased self-focused response to positive affect was not related to resting-state connectivity in the CHR group (Left NAcc: \( r = -0.14, \) Right NAcc: \( r = 0.18 \), but was related to decreased resting-state connectivity in the healthy controls (Left NAcc: \( r = -0.09, \) Right NAcc: \( r = -0.40 \), Fig. 5, see Supplemental Table 2.

3.5.2.1. Emotion-focused response. Emotion-focused response was not related to distinct striatal resting-state connectivity in the CHR group compared to the control group.

4. Discussion

The present study is the first, to our knowledge, to provide evidence for altered regulation of positive emotions in the CHR group. First, the CHR group showed specific alterations in self-reported response to positive affect; higher levels of dampening responses to positive affect but no differences in self or emotion-focused responses to positive affect compared to healthy peers. In terms of clinical correlates, higher self-reported levels of dampening and lower levels of self-focus in response to positive affect were related to higher levels of positive and negative symptoms individuals at CHR. In the continued exploration of theoretically-relevant symptoms, higher levels of self-reported dampening and lower levels of self-focus in response to positive affect related to higher levels of avolition, disturbances in emotions and self, and flattened emotional expression in individuals at CHR. In terms of NAcc resting-state functional connectivity, the self-reported frequency of dampening and self-focused responses to positive emotion showed distinct patterns of resting-state connectivity across the CHR groups and peers. Healthy peers show decreased depression-like resting-state connectivity patterns related to adaptive responses and increased

Table 3

| Attenuated Psychosis Symptoms (SIPRS) | Dampening | Self-Focused | Emotion Focused |
|--------------------------------------|-----------|--------------|-----------------|
| Positive Symptoms                    | \( B = 0.54, t = 6.64, p < .001 \) | \( B = -0.24, t = 2.31, p = .02 \) | \( B = 0.15, t = 1.44, p = .15 \) |
| Negative Symptoms                    | \( B = 0.42, t = 4.99, p < .001 \) | \( B = -0.34, t = 2.31, p = .002 \) | \( B = 0.06, t = 0.55, p = .58 \) |
| Avolition                            | \( B = 0.37, t = 4.33, p < .001 \) | \( B = -0.35, t = 3.15, p = .02 \) | \( B = 0.05, t = 0.47, p = .64 \) |
| Disturbances in Experience of Emotions and Self | \( B = 0.45, t = 5.49, p < .001 \) | \( B = -0.34, t = 3.20, p = .002 \) | \( B = 0.05, t = 0.44, p = .003 \) |
| Flattened Expression of Emotion      | \( B = 0.33, t = 3.64, p < .001 \) | \( B = -0.29, t = 2.52, p = .013 \) | \( B = 0.05, t = 0.39, p = .70 \) |

Table 4

| Coordinates | Cluster Size | Region                  | p-FDR |
|-------------|--------------|-------------------------|-------|
| -54, +24, +30 | 104          | Dorsal Lateral Prefrontal | 0.04  |
| Dampening   | 259          | Anterior Cingulate Gyrus | 0.0006|
| -18, -28, +18 | 96          | Anterior Cingulate Gyrus | 0.003 |
| -14, -12, +8  | 99           | Thalamus                | 0.003 |
Fig. 2. Group Differences in Nucleus Accumbens – dorsal Anterior Cingulate Cortex Resting-State Connectivity by Dampening Response to Positive Affect CHR – Clinical high-risk for psychosis group; CON – healthy control peer group; NAcc- Nucleus Accumbens.

Fig. 3. Group Differences in Nucleus Accumbens – rostral Anterior Cingulate Cortex Resting-State Connectivity by Dampening Response to Positive Affect CHR – Clinical high-risk for psychosis group; CON – healthy control peer group; NAcc- Nucleus Accumbens.

Fig. 4. Group Differences in Nucleus Accumbens – Thalamus Resting-State Connectivity by Dampening Response to Positive Affect CHR – Clinical high-risk for psychosis group; CON – healthy control peer group; NAcc- Nucleus Accumbens.

Fig. 5. Group Differences in Nucleus Accumbens Resting-State Connectivity by Self-Focused Response to Positive Affect CHR – Clinical high-risk for psychosis group; CON – healthy control peer group; NAcc- Nucleus Accumbens.
NeuroImage: Clinical 33 (2022) 102946

Our findings show that the CHR group more frequently engaged in damping of positive affect, a maladaptive emotion regulation strategy (Burr et al., 2017). Not only do CHR individuals do not only generate lower levels of positive emotions (Gruber et al., 2018; Gupta et al., 2019), our findings show that once elicited, CHR individuals engage in damping of positive affect. At the same time, the CHR group did not show alterations in self-reported self-focused and emotion-focused responses to positive affect, two adaptive emotion regulation strategies (Feldman et al., 2008). This pattern is reminiscent of previous findings, showing that CHR individuals engaged in more maladaptive coping strategies but did not show alterations in adaptive coping strategies when it comes to family stress (Yee et al., 2020), and thus point towards another area of preserved function among CHR individuals. These findings highlight a specific treatment target (i.e., reducing positive affect dampening cognitions) and leveraging intact use of self-focused and emotion-focused responses to positive affect are important resources that could be nurtured and utilized in targeted interventions.

Given the important function that positive emotions serve, we expected responses to positive affect to be linked with clinical symptomatology. Our findings showed that higher self-reported levels of damping responses to positive affect were related to higher positive and negative symptoms in CHR individuals (Burr et al., 2017). In contrast, self-reported engagement in self-focused responses to positive affect related to lower positive and negative symptoms in CHR individuals. These findings are consistent with current psychosis literature that has found that emotional regulation strategies are related to symptom severity (Kimhy et al., 2012; Moran et al., 2018) and that treatment targeting emotion regulation strategies benefit both positive and negative symptoms (Addington et al., 2011; Grezellschak et al., 2015; Morrison et al., 2004; Morrison and Barratt, 2010; Phillips et al., 2007). In an exploration of theoretically-relevant symptoms, self-reported self-focused response to positive affect related to less avolition, disturbances in emotions and self, and flattened emotional expression; higher frequency of self-reported damping response to positive affect related to elevations in these symptoms. This provides a few critical insights: emotion regulation strategies are related to particular core symptoms of psychosis, and though they account for some variance in these symptoms (B’s = 0.29–0.45), emotion regulation strategies are not simply capturing these symptoms accounting for only part of the variance.

Maladaptive, self-reported damping responses to positive affect were associated with increased dACC-NAcc and rACC-NAcc resting-state connectivity in healthy controls. However, CHR individuals showed decreased dACC-NAcc and rACC-NAcc resting-state connectivity associated with damping. In neurobiological models of emotion regulation, the dACC-NAcc is related to maladaptive emotion regulation strategies (e.g., rumination; Cooney et al., 2010; Sheena et al., 2021) and a biomarker of treatment response in depression (Kimhy et al., 2012). The rACC is described as an integration hub between emotion generation regions and dorsal cortical regions (Phillips et al., 2008; Phillips and Swartz, 2014), potentially serving a gate-keeping role over generating positive emotions. In fact, connectivity between rACC-NAcc is associated with anhedonia (Wacker et al., 2009). Although this reasoning explains the healthy peer resting-state connectivity, CHR individuals showed a distinct pattern. This distinct pattern might be explained by previous findings of reduced emotional reactivity (Gruber et al., 2018), which may require less recruitment of dACC and rACC during damping to dampen positive affect if less positive affect is generated. In contrast, elevated damping of positive affect was also associated with increased thalamus-NAcc resting-state connectivity in CHR individuals but decreased resting-state connectivity in healthy controls. Although the thalamus was not predicted in our hypotheses based on emotion regulation models, thalamic activity has been associated with dampening cognitive strategies during a reward paradigm (Gilbert et al., 2019) and was altered in psychosis populations (Chase et al., 2018). Additionally, a review of emotion regulation task-based functional MRI across the psychosis spectrum has identified the thalamus as a region uniquely recruited in psychosis individuals suggesting that it reflects an integration of distinct attentional, emotional, and cognitive functions to manage emotional responses (Duggirala et al., 2020).

More adaptive responses (self-reported self-focus response) to positive affect were related to less DLPFC-NAcc resting-state connectivity, a traditional biomarker of depression symptoms (Du et al., 2018; Grace, 2016), in the healthy controls but not in CHR individuals. The healthy control group showed resting-state connectivity that was consistent with expectations that increased DLPFC-NAcc would relate to less adaptive self-reported responses to positive affect, as in major depression disorder reflecting less cognitive control over positive affect (Phillips et al., 2008). However, individuals at CHR were showing increased DLPFC-NAcc related to self-reported self-focused responses to positive affect. This distinct pattern was not expected, especially given high rates of comorbid depression diagnoses that had previously been reported in CHR individuals (Addington et al., 2011; Fusar-Poli et al., 2014; Kelz et al., 2012; Tully and Nyendam, 2014). However, there is some evidence that the DLPFC may be recruited for the active reappraisal of automatic emotions (Phillips et al., 2008). Indeed, in individuals with CHR for psychosis, this may engage in emotion regulation of the elevated negative affect (van der Steen et al., 2017). Additionally, active reappraisal may be occurring during a self-focused response in CHR individuals as they have a low positive and high negative self-concept (Cowan et al., 2019; Damme et al., 2019). Such a response would not be necessary for their healthy peers who traditionally have a high positive and low negative self-concept (Cowan et al., 2019; Damme et al., 2019) that is consistent with a self-response to positive affect.

The present study highlights the importance of examining positive affect in CHR individuals in a multi-level approach. Despite this contribution, there are a number of limitations that are important to consider. Although the current study sample is similar to or larger than previous studies (Damme et al., 2019; Gilbert et al., 2019; van der Steen et al., 2017); a larger sample size may be able to account for more of the heterogeneity within the CHR group; including comorbid diagnoses (Gruber et al., 2018; McAusland et al., 2017). A larger study sample size would also enable a more exploratory approach to the neural underpinnings of emotion regulation in CHR individuals. Similarly, the current study was not able to investigate the nature of the role of antipsychotics given the few subjects receiving those medications (n = 8); however, it is critical to note that these medications may impact striatal regions that are central to positive affect (Kapur and Marques, 2016; Nielsen et al., 2016). Additionally, the scale at the center of this paper, Responses to Positive Affect Scale, was developed to examine rumination in individuals with or at risk for depression but has not been adapted or evaluated for use in CHR individuals. This concern may be somewhat mitigated by the high reliability in the current sample (alpha: 0.73–0.84) which is consistent with previous findings in other samples (alpha: 0.73–0.79; Feldman et al., 2008), see Supplement Table 1. It is also notable that this same three-factor structure has been extended and validated in individuals with bipolar disorder (Krass et al., 2019). However, the possibility remains that alternative emotional strategies may be linked directly to this population that are not detected in the current questionnaire. The current study did not attempt to parse out attenuated psychotic symptoms from the emotion regulation strategies. It is notable, however, that the attenuated symptoms only accounted for a small but significant percentage of the variance in symptoms, which means that the subscales aren’t measuring symptoms alone. Nevertheless, future studies should consider developing a measure specific to CHR individuals. Finally, although there are distinct processes relevant to positive and negative emotions in CHR...
individuals (Gupta et al., 2019), there may be benefits to examining both positive and negative affect in a single sample. Future studies should examine how emotion regulation contributes to both positive and negative affect in CHR individuals.

In conclusion, the CHR group shows more frequent dampening of positive affect and distinct resting-state connectivity profiles underlying self-reported responses to positive affect, which are related to symptoms as predicted in our hypothesis. Healthy peers showed expected patterns of resting-state connectivity related to cognitive control strategies (DLPFC-NACC) and conflicting emotional patterns (ACC-NACC) based on depression literature (Du et al., 2018; Pizzagalli, 2011; Wacker et al., 2009). In contrast, the CHR group did not show depression-like resting-state connectivity. Although unexpected, this paper contributes to a larger literature that suggests psychosis and depression may show similar emotional and behavioral endophenotypes that result from distinct underlying neurobiological mechanisms (Barch, 2008; Barch et al., 2016; Gold, 2011). These findings emphasize the importance of examining the neural underpinnings of emotion regulation in CHR individuals.

Declaration of Competing Interest

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

Funding

This work was supported by the National Institutes of Mental Health (VAM Grant R01MH094650, R01MH112545–01, R01MH103231, R01MH118741, R21/R33MH103231; T32MH26368 to KSFD; R21MH115231 to C.M.H. and V.A.M).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.102946.

References

Addington, J., Epstein, I., Liu, L.U., French, P., Boydlund, K.M., Zipursky, R.B., 2011. A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. Schizophr Res 125 (1), 54–61. https://doi.org/10.1016/j.schres.2010.01.015.

Adolphs, R., 2002. Neural systems for recognizing emotion. Curr. Opin. Neurobiol. 12 (2), 169–177.

Barch, D.M., 2008. Emotion, Motivation, and Reward Processing in Schizophrenia Spectrum Disorders: What We Know and Where We Need to Go. Schizophrenia Bull 34, 816–818. https://doi.org/10.1093/scan/nsw092.

Barch, D.M., Carter, C.S., Gold, J.M., Strauss, G.P., 2020. Heterogeneity of affect during positive activity scheduling. Behaviour Research and Therapy 91, 91–101. https://doi.org/10.1016/j.brat.2017.01.010.

Cauda, P., Savanar, A.E., D’Amico, F., Sacco, K., Duca, S., Geminiani, G.C., 2011. Functional connectivity and coactivation of the nucleus accumbens: a combined functional connectivity and structure-based meta-analysis. J Cogn Neurosci 23, 2864–2877. https://doi.org/10.1162/jocn.2011.21511.

Chane, H.W., Loritemi, P., Wensing, A., Murch, S.B.H., Nick-Jockschat, T., 2018. Meta-analytic evidence for altered mesolimbic responses to reward in schizophrenia. Human Brain Mapping 39 (7), 2917–2928. https://doi.org/10.1002/hbm.24049.

Chumbley, J., Friston, K., 2009. False discovery rate revisited: FDR and topological inference using Gaussian random fields. Neurimage 44 (1), 62–70. https://doi.org/10.1016/j.neuroimage.2008.05.021.

Chumbley, J., Worsley, K., Flandin, G., Friston, K., 2010. Topological FDR for neuroimaging. Neuroimage 49 (4), 3057–3064. https://doi.org/10.1016/j.neuroimage.2009.10.099.

Cooney, R.E., Joormann, J., Eugene, F., Dennis, E.L., Gotlib, I.H., 2010. Neural correlates of rumination in depression. Cognitive, Affective, & Behavioral Neuroscience 10 (4), 464–478. https://doi.org/10.3758/CABN.10.4.464.

Cowan, H.R., McAdams, D.P., Mittal, V.A., 2019. Core beliefs in healthy youth and youth at ultra high-risk for psychosis: Dimensionality and links to depression, anxiety, and attenuated psychotic symptoms. Dev. Psychopathol. 31 (1), 379–392. https://doi.org/10.1017/S0033291718002525.

Damm, K.S., Young, C.B., Nunnloch, R., 2017. Elevated nucleus accumbens structural connectivity associated with proneness to hypomania: a reward bias by negative affective perspective. Soc Cogn Affect Neurosci 12, 928–936. https://doi.org/10.1093/scan/nmx017.

Damm, K.S.F., Pellietier-Baldelli, A., Cowan, H.R., Orr, J.M., Mittal, V.A., 2019. Distinct negative affect profiles of connectivity during self-reference task and rest in youth at clinical high risk for psychosis. Hum Brain Map 40 (11), 3254–3264. https://doi.org/10.1002/hbm.24595.

Deighton, S., Buchy, L., Cadenhead, K.S., Cannon, T.D., Cornblat, B.A., McClaskey, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Wollter, E.F., Woods, S.W., Bearden, C.E., Mathalon, D., Addington, J., 2016. Traumatic brain injury in individuals at clinical high risk for psychosis. Schizophrenia Research 174 (1–3), 77–81. https://doi.org/10.1016/j.schres.2016.04.041.

Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neurimage 31 (3), 968–985. https://doi.org/10.1016/j.neuroimage.2006.01.021.

Du, L., Liu, H., Wu, D., Chao, F., Zhang, L., Wang, K., Huang, C., Gao, Y., Tang, Y., 2018. Stimulated left DLPFC/nucleus accumbens functional connectivity predicts the anti-depressant and anti-anxiety effects of TMS for depression. Transl Psychiatry 7, 1–10. https://doi.org/10.1038/s41398-017-0005-6.

Duggirala, S.X., Schwartz, M., Pinheiro, A.P., Kotz, S.A., 2020. Interaction of emotion and cognitive control along the psychosis continuum: A critical review. International Journal of Psychophysiology 147, 156–175. https://doi.org/10.1016/j.ijpsycho.2019.11.004.

Feldman, G.C., Joormann, J., Johnson, S.L., 2008. Responses to Positive Affect: A Self-Report Measure of Rumination and Dampening. Cogn Ther Res 32 (4), 507–525. https://doi.org/10.1007/s10608-006-9083-0.

Fischl, B., 2012. FreeSurfer. FreeSurfer. Neurimage, 20 YEARS OF IMRI 62 (2), 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021.

Floresco, S.B., 2015. The nucleus accumbens: an interface between cognition, emotion, and action. Annu Rev Psychol 66 (1), 25–52. https://doi.org/10.1146/annurev-psych-010213-115159.

Francis, T.C., Lobo, M.K., 2017. Emerging Role for Nucleus Accumbens Medium Spiny Neuron Subtypes in Depression. Biological Psychiatry, Stress and Neuroplasticity 81, 645–653. https://doi.org/10.1016/j.biopsych.2015.09.007.

Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A.R., McGuire, P.K., 2014. Comorbid Depression and Anti-Anxiety Effects of rTMS for Depression. Deep Brain Stimulation 67 (2), 110–116. https://doi.org/10.1016/j.dbrest.2013.09.013.

Bonferroni, L., Comte, A., Tajti, M., Miotto, J.L., Moulin, T., Medeiros de Bustos, E., 2015. The role of the amygdala in the perception of positive emotions: an ‘intensity detector’. Front Behav Neurosci 9, 178. https://doi.org/10.3389/fnbeh.2015.00178.

Burr, L.A., Javidi, M., Jell, G., Werner-Seidler, A., Dunn, B.D., 2017. Turning lemonade into lemons: Dampening appraisals reduce positive affect and increase negative affect during positive activity scheduling. Behaviour Research and Therapy 91, 91–101. https://doi.org/10.1016/j.brat.2017.01.010.

Gabhainn, S., Savanar, A.E., D’Amico, F., Sacco, K., Duca, S., Geminiani, G.C., 2011. Functional connectivity and coactivation of the nucleus accumbens: a combined functional connectivity and structure-based meta-analysis. J Cogn Neurosci 23, 2864–2877. https://doi.org/10.1162/jocn.2011.21511.

Gilbert, K.E., 2019. Positive Affect and Neural Reward Responding in Healthy Children: Implications for Affective Instability. Journal of Clinical Child & Adolescent Psychology 48, 120–130. https://doi.org/10.1007/s10862-018-0461-0.
