Neuroleptic-free youth at ultrahigh risk for psychosis evidence diminished emotion reactivity that is predicted by depression and anxiety

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1. Introduction

Anhedonia has long been considered a core feature of schizophrenia (Bleuler, 1950; Kraepelin, 1919). However, modern empirical research calls into question whether the traditional definition of anhedonia as a diminished capacity to experience pleasure accurately characterizes the nature of emotional experience abnormalities in the chronic phase of illness (see Kring and Moran, 2008 and Strauss and Gold, 2012 for reviews). For example, recent meta-analyses of laboratory-based studies that present participants with evocative stimuli indicate that individuals diagnosed with schizophrenia report experiencing levels of positive emotion (i.e., valence) (Cohen and Minor, 2010) and arousal (Llerena et al., 2012) that are comparable to healthy controls when exposed to pleasant stimuli. Some ecological momentary assessment (EMA) studies also indicate that persons with schizophrenia report increases in positive emotion that are comparable to healthy controls when engaged in real-world activities (Gard et al., 2007; Oorschot et al., 2013; Kimhy et al., 2016). Such findings have led some to propose that anhedonia should be re-conceptualized in schizophrenia and no longer considered a diminished capacity for pleasure (Strauss and Gold, 2012).

However, not all aspects of emotional experience are fully intact in individuals with schizophrenia. Laboratory-based studies indicate that individuals with schizophrenia report experiencing greater intensity of negative emotion than controls in response to unpleasant, pleasant, and neutral stimuli (Cohen and Minor, 2010). EMA studies also indicate increased intensity, frequency, and duration of negative emotion reactivity (Myin-Germeys et al., 2000). These findings may suggest that negative, rather than positive emotion reactivity abnormalities are central to schizophrenia (Horan et al., 2006; Cohen et al., 2011; Strauss and Gold, 2012). Despite the well-replicated finding of increased negative emotion reactivity in schizophrenia and evidence that these abnormalities predict poor clinical outcome (e.g., community-based functional outcome, symptoms), few studies have examined factors underlying increased negative emotion reactivity in this critical population. Several recent studies point to a role for emotion regulation abnormalities (i.e., impairments in using strategies to decrease the intensity, duration, or frequency of negative emotion), such that individuals with schizophrenia fail to effectively implement strategies to control emotional response. The magnitude of self-reported and neurophysiological emotion regulation abnormalities also predicts abnormal negative emotion reactivity and a range of clinical outcomes (e.g., social functioning,
psychotherapy, negative symptoms) (Horan et al., 2013; Strauss et al., 2013a, 2013b, 2015; Morris et al., 2012; van der Meer et al., 2014).

Although the affective landscape associated with the chronic phase of schizophrenia is becoming increasingly well mapped, few studies have examined emotional reactivity or regulation in the prodromal phase of illness. This represents a significant gap in the literature given the critical etiological relevance of the period immediately preceding onset (Haroun et al., 2006) and the presumed role of anhedonia in the transition from ultrahigh risk (UHR) state to diagnosable psychotic disorder (Meelh, 2001). The prodromal phase also offers an opportunity to examine emotional reactivity and regulation independent of the effects of antipsychotic medications that often confound interpretation in studies of the chronic phase of schizophrenia.

To our knowledge, only one published study has examined emotionality or regulation in UHR youth. Yee et al. (2010) examined a small group of UHR (n = 13) participants, as well as groups of first-episode schizophrenia patients (n = 40), chronic schizophrenia patients (n = 37), and healthy controls (n = 74), who viewed emotion-eliciting static images (e.g., threat, mutilation, contamination, illness, population, erotica, families, food, nature) while self-reported valence and arousal were reported separately. Relevant to the present study, the UHR group self-reported attenuated positive emotion to the pleasant pictures compared to the chronic schizophrenia group, and self-reported attenuated positive emotion to the neutral images compared to both the chronic and first-episode schizophrenia groups. Participants in the UHR group also reported attenuated negative emotion to unpleasant images compared to the chronic schizophrenia group.

Similarly, we are aware of only one published study that investigated emotion regulation in UHR youth. Kimhy et al. (2016) assessed UHR, control, and chronic schizophrenia participants with self-report questionnaires and interviews that measured habitual emotion regulation strategy use, emotional awareness, functional outcome, and symptoms. Findings indicated that UHR and chronic schizophrenia patients reported less frequent use of reappraisal than controls, and less use of reappraisal predicted poor community-based functional outcome (Kimhy et al., 2016). Thus, two initial studies provide preliminary evidence for diminished emotional reactivity and abnormal emotion regulation processes in UHR youth that predict poor community-based functional outcome; however, there is need for additional studies that replicate and extend these findings using adequately sized samples of neuroleptic-free UHR youth and laboratory-based emotional reactivity and regulation paradigms.

The current study presented UHR and control groups with pleasant, unpleasant, and neutral stimuli and asked them to make separate reports of positive and negative emotion in the context of emotional reactivity or regulation instructions. Three hypotheses were evaluated: 1) Based on initial evidence suggesting potential attenuation of emotional experience (Yee et al., 2010), we predicted that the UHR group would report less positive emotion to pleasant stimuli (i.e., a true anhedonia) and less negative emotion to unpleasant stimuli compared to controls. 2) Based on evidence for an emotion regulation abnormality in chronic schizophrenia (Horan et al., 2013; Strauss et al., 2013a, 2013b, 2015; Morris et al., 2012; van der Meer et al., 2014) and UHR youth (Kimhy et al., 2016), we hypothesized that UHR youth would fail to decrease negative emotion effectively using a distancing reappraisal strategy. 3) Based on evidence linking emotional reactivity and regulation abnormalities to poor community-based functional outcome in schizophrenia and UHR youth (Kimhy et al., 2016; Yee et al., 2010), we also predicted that emotional reactivity and regulation would be associated with poorer real-world social function in the UHR group.

2. Method

2.1. Participants

Participants in this IRB approved study included 61 adolescents/young adults (29 UHR and 32 controls) between the ages of 12-21 years (M = 18.76, SD = 2.14). Control participants were recruited via email, newspaper advertisements, and Craigslist. Recruitment of UHR participants utilized these sources as well, but also included an in-depth effort that targeted clinical (psychologist and psychiatrist), college counseling, psychiatric hospital and community-mental health center referrals (this involved recruitment presentations from ADAPT lab personnel, phone calls, as well as regular mailers). In addition, recruitment utilized a bus advertisement campaign spanning the Boulder, Aurora, and Denver Metropolitan areas, as well as presentations for community mental health events. Exclusion criteria for both groups included history of head injury, neurological disorder, DSM-IV-TR Axis I psychotic disorder or substance dependence, and being prescribed antipsychotic medication. The study also screened for recent cannabis use (in an effort to devise a representative sample, this was not treated as an exclusionary criteria). A urine sample was screened for the presence of tetrahydrocannabinol (THC cutoff 50 ng/mL) utilizing Instant Technologies iCup (Norfork, VA). The rapid drug screen has detection times up to one month and is commonly used in drug research (McRae-Clark et al., 2013). We also administered a self-report instrument, the Alcohol/Drug Use Scale (AUS/DUS) (Drake et al., 1996). Urine Panel data was unavailable for 6 controls and 4 UHR participants while self-report data was available for each participant. Results from the urine panel indicated that 4 controls (–13%), 13 (–45%) of UHR screened positive. Self-report results indicated at least some use in the past month or more frequent for 11 controls (–34%) and 17 UHR (–58%) participants. We did not include participants who endorsed using cannabis on the day of testing. Other comorbid Axis I disorders were not exclusion criteria for UHR participants. Rates of the most elevated current comorbid Axis I conditions in the UHR participants included anxiety disorders 10 (34.3%) and mood disorders 8 (27.6%). Comorbid Axis I disorders are typical of UHR individuals and the present rates are comparable to other studies (Fusar-Poli et al., 2014). The presence of any psychotic disorder in a first-degree relative or any Axis I disorder in the participant was exclusionary criteria for controls.

2.2. Measures

2.2.1. UHR categorization

The Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 1999) was administered to detect the presence of a prodromal syndrome in three possible ways: 1) the presence of attenuated positive symptoms and/or 2) decline in global functioning accompanying the presence of schizotypal personality disorder and age > 19 and/or 3) a family history of schizophrenia with decline in functioning (Miller et al., 1999). In the present study 89.7% met for category 1 alone, 3.4% met for category 3 alone, and 6.9% met for both categories 1 and 3 (no participants met for category 2). The SIPS contains an instrument, the Scale of Prodromal Symptoms (SOPS), which rates the severity of relevant symptoms along a 7-point scale ranging from absent to severe and psychotic. Ratings in the range of 3 to 5 are required for designation as “prodromal”. This measure gauges several distinct categories of prodromal symptom domains including positive (unusual thoughts, suspiciousness, grandiosity, perceptual abnormalities, disorganized communication) and negative dimensions (social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness, occupational functioning). The Structured Clinical Interview for the Diagnostic and Statistical Manual was administered to determine the presence of psychosis and substance dependence exclusionary criteria (SCID-I) (First et al., 1995). Clinical interviews were conducted in person by advanced doctoral students, trained over a two-month period. All interviewers had inter-rater reliabilities that exceeded the minimum study criterion of Kappa ≥80. The clinical interviews were completed on both UHR and Control groups (see Table 1).

2.2.2. Global social functioning

Social functioning was assessed with the Global Functioning Scale: Social (GFS-S) (Auther et al., 2006). This inventory provides ratings of...
functioning on a 10-point Likert scale where a score of 10 reflects “Superior Social/Interpersonal Functioning” and 1 indicates “Extreme Social Isolation”. The scale was designed for adolescents and has been found to be valid and reliable in assessing at-risk populations (Auther et al., 2006).

2.2.3. Depression and anxiety

The Beck Depression Inventory II (BDI-II: Beck et al., 1996) and Beck Anxiety Inventory (BAI: Beck et al., 1988), both 21-item self-report questionnaires, were administered to assess depression and anxiety, respectively.

2.2.4. Emotional reactivity and regulation task

The emotional reactivity and regulation task was modeled after previous research (Kross et al., 2009). During the task, participants viewed a series of well-validated pleasant (n = 36), unpleasant (n = 36), and neutral (n = 36) static photographs from the International Affective Picture System (IAPS) (Lang et al., 2005). An example trial diagram is presented in Fig. 1. On each trial, participants were provided with a 2-second instruction cue instructing them to perform either an emotional reactivity or regulation task, after which a single standardized IAPS image (pleasant, unpleasant, or neutral) was presented for 8 s in a randomized order. The stimulus was followed by a jittered blank screen with prompts to complete two self-reports of emotional experience corresponding to how positive and how negative they felt. The unipolar ratings of positive and negative emotion made in response each image were completed using a 1 (not at all) to 5 (extremely) scale. After the two ratings, there was a 4-second inter-trial interval prior to the next trial. The task was completed in a quiet, individual testing room at a distance of approximately 24″ away from a computer monitor. Ratings were made manually using a keyboard. The 108 experimental block trials were completed after task orientation and a block of x practice trials. The entire task (instruction, practice, and experimental trials) took approximately 30 min, after which participants were debriefed and compensated for their participation.

2.3. Data analysis

Group differences in demographic and clinical variables were evaluated using one-way ANOVAs and chi-square analyses. To test hypotheses 1 and 2, two separate 2 (Group: UHR, Control) × 3 (Valence: Positive, Negative, Neutral) × 2 (Cue: Immerse, Distance) repeated-measures ANOVAs were conducted for self-reported positive emotion and negative emotion. A Greenhouse-Geisser correction was used when assumptions for sphericity were not met. Significant interactions were followed-up by one-way ANOVAs and within-group paired-samples t-tests. To test hypothesis 3, correlations were examined between clinical variables (i.e., social functional outcome, depression, anxiety) and self-reported positive emotion to pleasant stimuli and negative emotion to unpleasant stimuli (collapsed across immediate/distance conditions).

Table 1

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Ultra high-risk</th>
<th>Healthy youth control</th>
<th>All</th>
<th>Test-statistic, p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (N and %)</td>
<td>18 (62.1%)</td>
<td>13 (40.6%)</td>
<td>31 (50.8%)</td>
<td>$\chi^2 = 2.80, p = 0.13$</td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.00 (1.65)</td>
<td>18.50 (2.54)</td>
<td>18.74 (2.16)</td>
<td>F = 0.81, p = 0.36</td>
</tr>
<tr>
<td>Parental education (years)</td>
<td>15.79 (2.14)</td>
<td>15.92 (2.71)</td>
<td>15.86 (2.44)</td>
<td>F = 0.04, p = 0.84</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIPS positive</td>
<td>11.93 (5.41)</td>
<td>0.50 (1.01)</td>
<td>5.93 (6.87)</td>
<td>F = 138.0, p &lt; 0.001</td>
</tr>
<tr>
<td>SIPS negative</td>
<td>7.48 (5.79)</td>
<td>0.31 (1.28)</td>
<td>3.72 (5.44)</td>
<td>F = 467.7, p &lt; 0.001</td>
</tr>
<tr>
<td>SIPS disorganized</td>
<td>4.62 (3.60)</td>
<td>0.19 (0.47)</td>
<td>2.30 (3.34)</td>
<td>F = 467.7, p &lt; 0.001</td>
</tr>
<tr>
<td>Functional outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFS-S</td>
<td>7.17 (1.34)</td>
<td>8.75 (0.62)</td>
<td>8.00 (1.29)</td>
<td>F = 36.0, p &lt; 0.001</td>
</tr>
</tbody>
</table>

Note: Functioning was assessed with the Global Functioning Scale; Social (GFS-S). Mean values are displayed with standard deviation in parentheses where applicable.

3. Results

3.1. Group demographics

There were no significant group differences in age, parental education, or sex. The UHR group was rated as having significantly poorer global social functioning than controls (Table 1).

3.2. Group differences in emotional reactivity and regulation

3.2.1. Positive emotion

For positive emotion, the main effects of Valence and Cue were significant; however, the main effect of Group was nonsignificant. The two-way interactions of Cue × Valence and Valence × Group were significant; however, the Cue × Group interaction was nonsignificant. The three-way Valence × Cue × Group interaction was nonsignificant (Table 2). The significant Valence × Group interaction was followed-up by a series of post hoc one-way ANOVAs and within-group paired-samples t-tests that evaluated intensity of positive emotion per valence category collapsing cue condition. Groups did not significantly differ on self-reported positive emotion to neutral or unpleasant stimuli, but there was a nonsignificant trend for pleasant stimuli. Both groups experienced the expected pattern of pleasant > neutral > unpleasant (Table 2). Thus, the significant Valence × Group interaction generally reflects the trend toward reduced hedonic response to pleasant stimuli in UHR youth.
3.2.2. Negative emotion

For negative emotion, the main effects of Cue and Valence were significant; however, the main effect of Group was nonsignificant. The two-way Valence × Group and Cue × Valence interactions were significant; however, the Cue × Group interaction was nonsignificant. The three-way Valence × Cue × Group interaction was nonsignificant (see Table 2). The significant Valence × Group interaction was followed-up by post hoc one-way ANOVAs and within-group paired-samples t-tests that evaluated intensity of negative emotion across each valence condition, collapsing across cue condition. Groups did not differ in self-reported negative emotion to neutral or pleasant stimuli; however, there was a trend toward UHR experiencing less negative emotion to unpleasant stimuli than HC. Both groups evidenced the expected pattern of unpleasant > neutral > pleasant (Table 2). Thus, the significant Valence × Group interaction generally reflects the trend toward reduced negative emotion to unpleasant stimuli.

3.3. Correlations between emotional reactivity and clinical outcomes

For hypothesis 3, we examined associations between emotion response domains that were found to be impaired in the UHR group (i.e., positive emotion response to positive images and negative emotion response to negative images) and global social functioning. As seen in Fig. 2, there was a moderate positive relationship between positive emotional reactivity and social functioning in the UHR group ($r = 0.49, p < 0.01$), indicating that attenuated positive emotional reactivity was linked to poorer real-world social functioning (note: on the social functional scale higher scores represent superior functioning). Similar scores on the immersion and distancing conditions in the UHR group may reflect reduced emotional reactivity during both conditions, causing the distancing condition to have restricted range available to decrease emotional experience.

To explore potential processes contributing to emotional experience abnormalities in UHR youth, we also conducted correlations between self-report on the task and measures of depression and anxiety. In UHR, greater severity of depression on the BDI ($r = -0.39, p < 0.04$) and anxiety on the BAI ($r = -0.42, p < 0.03$) were associated with lower self-reported positive emotion to pleasant stimuli. BDI and BAI scores were not significantly correlated with self-reported negative emotion to unpleasant stimuli.

4. Discussion

The current study examined emotional reactivity and regulation in UHR youth. Several important findings emerged. First, the UHR group generally evidenced diminished emotional reactivity to both pleasant and unpleasant stimuli. This was supported by significant Group × Valence interactions for self-reports of both positive and negative emotion. However, it should be noted that the post hoc ANOVAs were only at a trend level for both reports of positive emotion to pleasant stimuli and reports of negative emotion to unpleasant stimuli, due to relatively small sample sizes. These findings are generally consistent with the results of Yee et al. (2010), which used an analogous laboratory-based paradigm. Second, emotion regulation abnormalities in response to instructed cue to regulate were not observed in UHR youth, potentially because of low emotional reactivity to unpleasant and pleasant stimuli. These findings are contrary to Kimhy et al. (2016), who found abnormalities in the use of reappraisal to regulate emotion using a trait self-report emotion questionnaire. Conflicting findings between our study and Kimhy et al. (2016) may reflect differences in methodology (i.e., self-reports to laboratory-based stimuli vs. trait questionnaires), potentially suggesting a dissociation between the capacity to implement strategies when directly instructed to do so in a controlled setting versus the likelihood of selecting and effectively implementing a strategy during real-world contexts that are less structured. Future studies using ecological momentary assessment may be able to disentangle these possibilities. Third, we observed a significant association between poorer community-based social outcome and diminished emotional reactivity to both pleasant and unpleasant stimuli. These findings may suggest a role for emotional experience abnormalities in daily social functioning, which is strongly associated with overall quality of life (Addington and Addington, 2008) and more severe occupational and social dysfunction later in life (Addington and Addington, 2005). Emotional reactivity abnormalities that occur in adolescence may therefore set the stage for more a severe course of illness in the future.

These three major findings are also important because they suggest areas of divergence from the chronic phase of schizophrenia. In the chronic phase, reactivity to pleasant and unpleasant stimuli is intact (diminished in UHR), emotion regulation is impaired (spared in UHR), and poor social outcome is associated with greater reactivity to unpleasant stimuli (associated with less reactivity in UHR) (Strauss and Herbener, 2011; Cohen and Minor, 2010; Kring and Moran, 2008; Strauss et al., 2013a, 2013b, 2015; Horan et al., 2013). There are several possible accounts for these diverging results across phases of illness. First, emotional experience abnormalities present during the UHR period may represent a more pernicious course of the illness. Adolescence has been described as a period of rapid emotional changes (Lerner and Steinberg, 2004) and so may represent a time of emotional vulnerability for the UHR group during which potential group differences with...
healthy control groups may be amplified. Another explanation is that although the UHR group represents a help seeking population with considerable clinical issues (Addington et al., 2011), only a small percentage will develop psychosis. Perhaps the remaining majority of UHR individuals who will not convert include a large proportion of individuals who will eventually be diagnosed with disorders characterized by low emotional responsiveness (e.g., schizotypal personality disorder/elevated-schizotopy, depression) (Cohen et al., 2012). Future studies are needed to determine if those who convert actually show higher emotional responsiveness at baseline than those UHR individuals who do not transition to psychosis. It is of course also possible that subtle methodological differences between the present investigation and previous studies in adult patients with schizophrenia may account for potential differences. However, the consistency in results observed between our study and the UHR study by Yee et al. (2010), which also used static evocative stimuli, provides some assurance that the current results are reliable and perhaps reflect true course related differences, rather than methodological factors.

The current results are also generally consistent with an emerging “paradox” regarding hedonic functioning among schizophrenia-spectrum disorders. Specifically, schizotypal and UHR groups report diminished experience of positive emotion to pleasant stimuli (i.e., a true hedonic deficit), whereas chronic schizophrenia patients do not (Cohen et al., 2012; Yee et al., 2010; Kring and Moran, 2008). At first glance, this pattern of results appears to defy logic—those in the healthier range of the schizophrenia-spectrum are more impaired. However, our correlational findings may provide some clarity on this issue. We found that hedonic deficits on the laboratory-based task were associated with greater severity of depression and anxiety. Given prior studies indicating that the prevalence of depression and anxiety tends to be higher in UHR and schizotypy than chronic schizophrenia (Lewandowski et al., 2006; Fusar-Poli et al., 2014; Braga et al., 2005), the inherent paradox may reflect developmental shifts in comorbid psychopathology. The majority of youth categorized as UHR do not go on to develop a psychotic disorder—they most often develop a mood or anxiety disorder (Addington et al., 2011). Our results are cross-sectional and cannot speak to whether UHR with hedonic deficits are more likely to transition to a mood/anxiety than psychotic disorder; prospective longitudinal studies are needed to achieve this purpose.

Although this investigation includes several methodological strengths including an innovative emotional response task and a neuroleptic-free sample (Tremeau, 2006) there are several noteworthy limitations. First, while the present sample size is larger than the other available studies examining emotional responding in UHR youth (Yee et al., 2010), the sample size might be too small to reach statistical significance in the post-hoc one-way ANOVAs. Future studies should aim to include a larger sample size. Furthermore, there is currently no follow-up data from which to examine the prospective significance of the obtained results. It will be integral for future studies to include a longitudinal design. Second, consistent with other reports of this population (Buchy et al., 2015) we detected elevated recent cannabis use across the sample. While including these individuals supports the external validity of these findings, future collaborative studies with larger samples are necessary to evaluate critical questions about relationships between emotional experience and cannabis. Third, the current UHR sample had relatively high levels of functional outcome. It is unclear how well findings generalize to lower functioning samples. Finally, there are also several important future directions regarding the study of emotional experience in UHR youth. It will be important to determine the specificity of our findings for emotional experience, by also assessing factors important for later integration including motivation, decision making and goal-setting. In the same vein, future studies should incorporate neuroendocrine, multimodal imaging, and psychophysiology approaches to elucidate other neurobiological aspects of...
positive and negative valence systems (Cuthbert and Insel, 2013; Insel et al., 2010). Kimhy et al. (2012) have also demonstrated that low emotional awareness is associated with emotion regulation and reactivity deficits. Emotional awareness deficits could be one process impacting emotional experience in UHR samples, lowering self-reports of positive and negative emotion. Future studies should determine whether emotional awareness drives hedonic deficits in UHR samples to a greater extent than depression and anxiety.

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Conflicts of interest
V.A.M. is a consultant to Takeda Pharmaceuticals. No other authors have any disclosures.

Contributors
DRS. Gruber and Mittal conceptualized the study; and Drs. Gruber, Mittal and Strauss and Ms. Dombrecht conducted analyses, interpreted data and drafted the manuscript.

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