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Psychotic-like Experiences in Adolescents Enriched for High-Risk for Developing Severe Mental Illness: Change over Two-Years and Association with Neural Reward Processing and Affective Symptoms

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Abstract

Psychotic-like experiences (PLEs)--subclinical experiences or symptoms that resemble psychosis, such as hallucinations and delusional thoughts--often emerge during adolescence and are predictive of serious psychopathology. Understanding PLEs during adolescence is crucial due to co-occurring developmental changes in neural reward systems that heighten the risk for psychotic-related and affective psychopathology, especially in those with a family history of severe mental illness (SMI). We examined associations among PLEs, clinical symptoms, and neural reward function during this critical developmental period. Over two-years, 117 adolescents (aged 13–19 years at baseline) at high-risk (n=74) or low-risk (n=43) for SMI based on family history of affective or psychotic disorder completed symptom questionnaires annually and fMRI scanning at study entry during a guessing reward task. We assessed changes in PLEs over two-years and evaluated whether clinical symptoms (anxiety, depression, anhedonia) and response to rewards of

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Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by XD and TG. The first draft of the manuscript was written by XD and TG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare they that they have no conflict of interests.

Ethical Standards

All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All procedures were performed in compliance with the University of Pittsburgh Human Research Protection Office. Informed consent was obtained from all participants and assent was obtained for participants<18 years of age prior to inclusion in the study.

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the dorsal medial prefrontal cortex (dmPFC) and ventral striatum (VS) predicted PLEs two-years later. PLEs total scores and distress increased over time, with the high-risk group showing a greater rise in PLEs than the low-risk group. Heightened right VS neural activation and higher anxiety at baseline (but not left VS or dmPFC neural activation, depression, or anhedonia) predicted more PLEs at 24-months. Heightened vigilance and sensitivity to external stimuli may be important precursors to the development of PLEs for adolescents.

Keywords

Psychotic-like Experiences; Adolescence; Anxiety; Neural Reward Circuitry; Ventral Striatum

Introduction

Psychotic disorders such as schizophrenia occur in about 1–2% of the population [1] and have debilitating outcomes, including functional impairment, disability, and even suicide [2–4]. The progression of psychosis can be conceptualized as a continuum, beginning with subclinical experiences (i.e., distressing or impairing experiences that do not meet diagnostic criteria for psychosis) and potentially culminating in prodromal syndromes [5] such as clinical high-risk (CHR) syndromes or full-blown psychosis. Subclinical experiences are characterized by frequent, highly distressing, and/or impairing attenuated psychotic symptoms [6]. These subclinical experiences, also called psychotic-like experiences (PLEs), are a type of transient, subthreshold positive symptoms, including visual and auditory perception and unusual thoughts [7]. Although psychotic disorder diagnoses are relatively rare in the general population, subthreshold psychotic experiences are more prevalent (10–30% in the general population) [8,9], occurring in individuals with non-psychotic illnesses and, most commonly, among those at risk (e.g., familial risk) for developing severe mental illness (SMI) [5,10–12]. Previous studies have shown that, compared to the general population, having a first-degree relative with a psychotic disorder increases the risk of developing psychosis from 1% to 10% [13], highlighting the significance of familiality in the risk for the SMI onset.

While PLEs are often temporary, for some, PLEs can be persistent and distressing, and these trajectories of PLEs can lead to problematic outcomes, including the onset of psychosis [14]. PLEs are also more common in adolescents, with a prevalence of 7.5% compared with 5% in adults [5], and the risk of conversion to psychosis is 3.5 times higher in those with PLEs compared to those without [15]. Furthermore, there is increasing work showing that PLEs may be a marker of psychiatric liability more broadly, as PLEs are related to the emergence of other types of psychopathologies, such as depressive disorders [7,16,17].

The aberrant salience model is one conceptual framework explaining the development of positive symptoms (e.g., hallucinations, delusions) of psychosis and pre-psychotic phases [18,19]. Aberrant salience attribution suggests that positive symptoms (i.e., delusions or hallucinations) emerge due to misattributing the significance of a stimulus that would otherwise be considered irrelevant (such as believing a pattern of fallen leaves is sending a special message) [18,20,21]. Aberrant salience could also extend to events that are

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positive—events that are considered rewarding—although this area of literature is less developed. Disrupted reward systems, specifically attenuated responses to rewarding stimuli, are suggested to explain the emergence of negative symptoms (e.g., reductions in emotion, motivations, and behavior) [22,23]. However, the nature of general reward processing mechanisms (e.g., sensitivity to events/stimuli generally)--which are relevant to, but not exclusively tied to salience-based theories--may provide clues about broader associations between PLEs and reward sensitivity. While the salience model has been influential in explaining how adolescents with PLEs may inappropriately assign significance to neutral stimuli, focusing solely on salience attribution may miss broader patterns of dysfunction in the processing of valenced, or salient, stimuli. A key issue is how reward is processed, with investigations of neural reward systems perhaps capturing meaningful individual differences that may be relevant even before psychopathology emerges. Aberrant reward sensitivity may signal early vulnerability, even in the absence of salience misattribution.

PLEs could be associated with altered sensitivity of neural reward regions such as the ventral striatum (VS), which plays a key role in detecting salient (salience reflects changes in motivation and attention to both positive and negative stimuli in the environment) and rewarding events (in response to positive stimuli, such as monetary incentives or hedonic gains) [24,25]. In contrast, the medial prefrontal cortex (mPFC) is involved in reward valuation and modulating VS responses to reward [26]. Adults with schizophrenia exhibit hypoactivation of striatal responses to the anticipation of rewards (e.g., looking forward to future activities) (see Radua et al., 2015 and Zeng et al., 2022 for meta-analyses [27,28]), which is postulated to reflect difficulties assigning significance to motivational cues, having less motivation, and feeling less motivated. However, there have been mixed findings for VS response to reward *outcomes* (e.g., the in-the-moment experiences of rewards) in people with schizophrenia, with some fMRI studies showing “intact” responses [29] and others reporting striatal hyperactivation but mPFC hypoactivation (Zeng et al., 2022 for meta-analysis [28]). Neural reward processing is less understood in studies of youth at risk for SMI, even though disrupted neural reward systems are implicated in risk for depression, bipolar disorder, and psychosis [30]. For example, adolescents with a family history of depression—a disorder related to and a risk factor for PLEs—have disruptions in neural reward systems, including a dampening of VS response and heightened mPFC in response to rewards; this finding has been interpreted as an overregulation of the VS by the mPFC [31,32].

Adolescents who are particularly vulnerable to SMI—due to having a first-degree relative with SMI and exhibiting PLEs—may face an even greater risk of adverse outcomes [33]. This proposition highlights the importance of studying at-risk adolescents to understand mechanisms of PLEs, such as disrupted neural reward systems and, potentially, mechanisms of SMI.

Additionally, PLEs during adolescence often co-occur with affective symptoms. Commonly, depression and anxiety are higher in those with PLEs [34], with evidence of a bidirectional relationship in community-based samples of adolescents [35,36]. Furthermore, young adults in the community with either a major depressive disorder or anxiety disorder are more likely to report PLEs compared to those without [37]. The persistence and impairment caused

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by anxious and depressive symptoms may exacerbate PLEs and lead to higher levels of distress, increasing the chances of psychopathology onset [38,39]. Furthermore, anhedonia, a transdiagnostic symptom that emerges during adolescence [40], is a negative symptom of schizophrenia [41], a predictor of later SMI [42–44], and is related to PLEs [45]. Anhedonia involves difficulties with the enjoyment of, anticipation of, motivation for, and decision-making around pleasant experiences [46,47]. Cross-sectional studies have shown evidence of associations between anhedonia and PLEs in the general population [48]. If anxiety, depression, or anhedonia in adolescence predicts later PLEs, perhaps interventions for these common comorbid symptoms would be one way to prevent the progression of PLEs early in life—and, in particular, among adolescents who are at familial risk for SMIs.

The Present Study

The current study used a high-risk design to investigate whether neural reward function and non-psychotic clinical symptoms (anxiety, depression, and anhedonia) predict changes in PLEs across two-years in adolescents at varying levels of familial risk for psychotic and affective disorders. We were interested in whether (1) PLEs increased across three annual timepoints (baseline, 12-months, and 24-months); (2) high- and low-risk groups differed in the change in PLEs over time; and (3) baseline clinical symptoms and activation of the VS and dmPFC predicted PLEs over two-years in the entire sample and in an exploratory fashion, as a function of risk status [49,50]. Given the presence of PLEs in psychosis-risk and community-based samples of adolescents [33,51] and the risk window for PLEs and SMI in late adolescence [52,53], we predicted that there would be more PLEs and higher levels of distress from PLEs over time in the entire sample of adolescents across two-years. We also predicted that higher baseline neural activation of the VS in response to rewards would predict more PLEs and PLE distress at 24-months. Furthermore, given research suggesting that anxiety, depression, and anhedonia co-occur with and exacerbate PLEs [48,54], we predicted that more severe baseline anxiety, depression, and anhedonia would predict more PLEs and PLE distress two-years later.

Methods

Participants

A total of 117 adolescents with complete PLEs data (13–19 years; $M = 15.12$, $SD = 1.58$) participated in this study (Table 1). Participants were recruited from both the community and clinical settings. Recruitment strategies included advertisements, flyers, and Pitt+Me, a research participant registry through the University of Pittsburgh. The current sample is a subsample of a larger prospective study on the development of anhedonia. Participants were free of lifetime affective or schizophrenia spectrum disorders at entry but varied in familial history relevant to anhedonia. Participants were classified as either “high-risk” based on having a first-degree relative with a history of Depressive Disorder, Bipolar I or II Disorder, or Schizophrenia/Schizoaffective Disorder or “low-risk”, i.e., having no first-degree relative with the noted disorders, respectively. Participants were enrolled with the intention of including 66% of participants from high-risk families: as such, we refer to our sample as being enriched for high risk for developing SMI. Exclusion criteria included serious medical conditions, history of concussion with loss of consciousness,

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lifetime serious neurological disorder, substance dependence, daily use of nicotine, and MRI contraindications. Participants could not take stimulant medication for the 36 hours preceding the scan.

The Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) [55] was administered to all adolescents and siblings under 18, and the Structured Clinical Interview for DSM Disorders (SCID) [56] was administered to first-degree relatives age 18+ to determine eligibility. Later in the study, the participants were re-administered the SCID or KSADS to confirm study eligibility and risk group; risk classifications used in analyses reflect any updates at re-assessment.

Psychotic-like Experiences

The Prodromal Questionnaire, Brief Version (PQ-B) [57] assessed total scores and distress levels of PLEs. Higher scores indicate more PLEs and distress.117 participants had PQ-B data at study entry, 92 participants had data at 12-month follow-up, and 70 participants had data at 24-month follow-up. We examined differences in risk status and symptoms between the participants who completed all visits and participants who did not complete 12-month and/or 24-month follow-up visits to better understand the nature of the sample. Our findings revealed that participants who did not complete all visits had greater depression severity at study entry, $t(109)=-2.04$, $p=0.045$, $d=-0.41$ (completed: M[SD]=9.89 [6.98]; did not complete all visits: 13.33[9.98]) and anhedonia at study entry, $t(107)=-2.52$, $p=0.01$, $d=-0.49$ (completed: M[SD]=24.21[5.96]; did not complete all visits: 27.00[5.42]). There were no differences in risk status ($p=0.23$), anxiety at study entry ($p=0.51$), or PLEs at study entry ($p=0.12$)

Depression, Anxiety, Anhedonia

The Center for Epidemiologic Studies Depression Scale (CES-D) [58] was used to identify and assess depressive symptoms. The Screen for Child Anxiety Related Disorders (SCARED) [59] was used to assess anxiety symptoms. Total sum scores were used for the CES-D and SCARED, where higher scores reflect more severity. The Snaith-Hamilton Pleasure Scale (SHAPS) [60] was used to assess anhedonia. Dimensional scoring (1–4 Likert scale) was used for this 14-item measure.

Other

The State and Local Youth Risk Behavior Survey (YRBS) [61] was administered to collect data on cannabis use frequency, given that there have been reported associations between cannabis use and PLEs [62].

Function in Neural Reward Circuitry: Guessing Reward Task.

Participants completed an fMRI scan during a monetary reward task involving card guessing [63]. The task consisted of 3 outcome contexts (win, loss, and neutral outcome) and 4 anticipation contexts (possible win, possible loss, mixed win or loss, and neutral) with monetary values associated with each outcome ($1 per win; deduction of $0.50 for loss; $0 for neutral). Participants were unaware that the task and the outcomes were fixed such that all participants received the same number and order of win, loss, or neutral trials. After

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using a button press to guess whether a card number would be greater or less than 5 (4 seconds), participants were informed of the possible trial outcomes using an anticipation cue (2–6 seconds, jittered; *reward anticipation*). Then, participants were shown the "actual" card number (selected randomly; 500 ms), followed by a symbol (500 ms) indicating whether they won money, lost money, or had no change in earnings (*reward outcome*). Between each pair of trials, there was a jittered 0.5–1.5 second inter-trial interval. The paradigm was administered in an 8-minute block, with 48 trials and 12 trials per trial type.

fMRI Acquisition, Preprocessing, and Analyses: We collected brain imaging data using a 3.0 Tesla Siemens Prisma MRI scanner. To measure brain activity, we used blood-oxygen-level dependent (BOLD) imaging. These images were collected using a fast, multi-slice technique called multi-band gradient echo EPI sequence that covered 18 slices of the brain at once, had high resolution (2.3 mm isotropic voxels), were taken every 1.5 seconds (TR=1500 ms), with a signaling time (TE) of 30 ms. The field of view was 220 × 220 mm with a 96 × 96 image matrix, flip angle of 58°, and bandwidth of 1736 Hz Px–1. In the same session, we also collected structural images of the brain using a 3D MPRAGE sequence. The resolution of the structural scan was 1 mm isotropic voxels and included 176 continuous slices, TR=1500ms, TE of 3.19 ms, a flip angle of 8°, and field of view of 256 × 256 mm. Additionally, fieldmaps were collected and used to correct for any distortions in functional images. These had the same 2.3 mm resolution as BOLD scans, with a TR of 550 ms, two echo times, TE1=4.92 ms, TE2=7.38 ms; field of view of 220 × 220 mm, flip angle of 50°, and bandwidth 380 Hz Px–1).

Preprocessing and fMRI image analyses were performed using Statistical Parametric Mapping software, version 12. For each participant, BOLD images were realigned to correct for any movement between volumes and matched with participant's anatomical brain scan. Field maps were used to correct for distortions in the images caused by the magnetic field. Structural images of the brain were transformed using a non-linear transformation to fit the MNI/ICBM 152 standard brain template and separated into different types of tissues: gray matter, white matter, cerebrospinal fluid (CSF), and other tissues (e.g., bone). BOLD images were transformed into the same standard space using the structural image and resized at $2mm^3$ isotropic voxels using a 6 mm filter to help identify consistent activity patterns across the brain.

For first-level neuroimaging analyses completed in SPM12, a fixed effects general linear model (GLM) included choice, anticipation, and outcome phases of each trial, with 5 contrasts: win>neutral outcome, win>neutral anticipation, win>loss outcome, win>loss anticipation, win>non-win outcome. Gram-Schmidt orthogonalization, which is a mathematical technique to ensure that predictors do not overlap with each other, was applied to regressors to eliminate collinearity, ensuring more reliable results. The Artifact Detection Toolkit was also used to identify any scans with excessive head movement or unusual signal intensity (more than 3 standard deviations from the mean, or movement greater than 0.5 mm or 0.01 degrees) [64] and were included as regressors in the GLM to correct for excessive noise due to motion or artifact. Lastly, the six motion realignment parameters were entered as covariates. A 128 s high-pass filter was used to slow signal drifts and autoregressive modeling (AR1) were implemented during fitting.

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Participants were excluded from analyses if they demonstrated any of the following: VS coverage of <50% (n=8), responded to <75% of trials (n=4), mean movement ≥3 mm/degrees in any direction (n=6), or technical problems (e.g., task files corrupt) (n=8) were excluded from analyses. A total of 81 participants had VS neural activation data, and a total of 82 participants had dmPFC neural activation data. Participants' first-level contrast images for win > neutral outcome condition (representing neural reward activation) were entered into a second-level GLM. Reward activation in the VS and dmPFC was operationalized as the extracted mean principal eigenvariate of suprathreshold clusters across the entire region of interest. The VS was defined using Neurosynth's meta-analytic "reward" mask [65], thresholded at 75% to constrain activity [66]. The dmPFC was defined from the Neurosynth "reward" mask and structurally constrained to the Automated Anatomical Labeling parcellation region "medial superior frontal gyrus" (region F1M) using the Wake Forest University Pickatlas toolbox. Extracted eigenvalues were utilized in subsequent analyses. The dmPFC is a midline structure that lies along the sagittal plane (x=0) and is typically analyzed using a single bilateral mask, as it spans both hemispheres without clear lateralization [67,68]. The ventral striatum was masked separately for the left and right sides due to its hemispheric asymmetries in function and lateral location [69–71].

Statistical Approach

Repeated measures Analysis of Variance (ANOVA) with time as the repeated measure examined changes in PLEs (total scores and distress scores) across two-years and between risk groups (i.e., group x time interaction). Pairwise sample t-tests examined differences in PLEs between different timepoints (baseline to 12-months, 12- to 24-months). A total of four hypothesis-testing regression models were conducted to examine: (1) whether neural activation (right VS, left VS, and dmPFC) predicted PLE total scores, (2) whether neutral activation (right VS, left VS, and dmPFC) predicted PLE distress scores, (3) whether symptoms (depression, anxiety, anhedonia) predicted PLE total scores, and (4) whether symptoms (depression, anxiety, anhedonia) predicted PLE distress scores. Exploratory analyses were conducted to assess

whether risk group x neural activation (right VS, left VS, dmPFC) and risk group x symptom (anxiety, depression, anhedonia) interactions predict PLEs two-years later (no findings with risk group – see supplement for tables). Covarying for age did not change the direction or magnitude of the results. Given the low number of participants with cannabis use, this variable was not included as a covariate. We controlled for multiple comparisons using the Benjamini-Hochberg procedure with a false discovery rate (FDR) threshold of 0.10.

Results

Change in Psychotic-Like Experiences Across Two-Years

PLEs total scores and distress levels increased with time across the entire sample (total: $F(2,128) = 6.06$, $p = 0.009$, $\eta_p^2 = 0.09$; distress: $F(2,104) = 9.97$, $p < 0.001$, $\eta_p^2 = 0.16$). Pairwise sample t-tests revealed there was no difference from baseline to 12-months in total scores, $t(91) = 0.29$, $p = 0.77$, or distress, $t(83) = 0.78$, $p = 0.44$, but PLEs increased from

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12-months to 24-months in both total number and distress (total: $t(64) = -3.22$, $p = 0.002$; distress, $t(53) = -3.62$, $p < 0.001$). See Fig.1a, 1b.

When examining a risk group x time interaction in predicting changes in PLEs, there was a significant interaction: the high-risk group showed an increase with time in the number of PLEs compared with the low-risk group, $F(2,126) = 3.79$, $p = 0.04$, $\eta_p^2 = 0.06$. There were no significant risk group x time interactions with distress from PLEs, $p = 0.19$.

Baseline Neural Reward Activation Predicting Psychotic-Like Experiences Two-Years Later

In the whole sample, higher right VS activation at baseline predicted more PLEs at 24-months (Table 2). PLEs were unrelated to left VS or dmPFC activation and there were no findings with distress levels.

Baseline Symptoms Predicting Psychotic-Like Experiences Two-Years Later

In the whole sample, higher anxiety severity at baseline (but not depression or anhedonia) predicted more PLEs two-years later (Table 3). There were no findings with distress levels.

Discussion

Our findings revealed that the number of PLEs and distress levels increased across two-years in a unique adolescent sample enriched for high risk for developing SMI. This approach allowed us to identify patterns of PLEs before they potentially worsen, which could enhance how PLEs are conceptualized and inform prevention and intervention strategies. As expected, the familial high-risk group exhibited a steeper increase in PLEs across the two-years compared to the low-risk group. Furthermore, anxiety and neural activation of the right VS emerged as predictors of more PLEs two-years later. Together, these data highlight the significance of two factors—one clinical, one neural—as potential early markers for PLEs progression, especially in adolescents who are already at heightened risk.

Our analyses revealed that the number of PLEs and distress from PLEs increased over two-years in the whole group. Distress from PLEs has been shown to distinguish clinically relevant PLEs and is an important target for intervention and prevention to reduce adverse outcomes, including the emergence of psychopathology [72–74]. Our results also showed that most adolescents reported approximately 2 total PLEs, which is low, but the number of PLEs reported increased across two years in the whole sample and for youth at high-risk for developing SMI. Furthermore, PLE distress levels increased across time in the whole sample, reaching clinically meaningful levels from 12-months to 24-months, after a relatively stable phase from baseline to 12-months. A low number of PLEs endorsed by our sample is somewhat expected given the nature of our sample. Notably, this was not a CHR study: participants were recruited as a part of a larger study of the development of anhedonia and related psychopathology. As such, the study employed a longitudinal design and included a sample of participants who had familial transdiagnostic risk for psychopathology (affective disorder or schizophrenia in first-degree relatives) *and* who had no personal history of such psychopathology at baseline. The larger study was intentionally designed to examine the onset and change in anhedonia and related psychopathology by focusing on adolescents at risk for such psychopathology, without a personal history of

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it, and at a developmental period of vulnerability to it [75]. While many studies have focused on examining PLEs in the general population [12,76,77] or adolescents at risk for psychosis [78,79], our findings provide support that PLEs may be meaningful in adolescents enriched for high risk for developing SMI, although more research is needed to examine PLEs outcomes in other, related samples of youth. Interestingly, we did not observe group differences in PLEs at baseline but did at follow up. This pattern reflects the importance of taking a developmental perspective and utilizing high-risk designs in examining symptoms even before they emerge to track changes, examine associated clinical and neural correlates, and better characterize who is most vulnerable.

Heightened activation of the right VS during reward response was associated with more PLEs two-years later. These findings coincide with previous research in children with anxiety disorders and behavioral inhibition, which also show hypersensitivity of the VS in the anticipation of rewards [80–82]. The lateralized association with right, but not left, VS activity and the number of PLEs–though not hypothesized–may point to lateralization in automatic emotional reactivity and salience detection, particularly in response to aversive or threatening stimuli [70,83,84]. Prior literature has linked right-lateralized striatal activity to negative affect, distress, and withdrawal motivation in the face of threat in individuals with heightened negative affect or at risk for affective and psychotic disorders [30,85–87]. Elevations in the right VS in response to positive rewards may also reflect adolescents' attribution of rewarding stimuli as being more meaningful and salient, consistent with the right hemisphere's role in processing personally relevant stimuli [88,89]. As such, some adolescents who are vulnerable to developing SMI and who experience PLEs may be more sensitive to rewards—which is developmentally informative since reward systems and VS response reach a sensitivity peak during adolescence [90–93]—a possibility that should be investigated with additional longitudinal research.

Additionally, more severe anxiety predicted an increase in the PLEs (not distress) over the two-year period, consistent with research suggesting that anxiety is a precursor in the development of SMI [94–96] and is common among adolescents at risk for psychopathology [97]. The experience of anxiety, with its accompanying vigilance for threat and concern about personal safety [98,99], could lead adolescents to notice or report more PLEs. There are likely bidirectional associations at play, where more PLEs might lead to anxiety, and/or anxiety might enhance PLEs and increase vigilance for PLEs.

There are important limitations to discussion. It is important to note that study visits overlapped with the COVID-19 pandemic where participants were unable to complete in-person study procedures. Future work is needed to replicate these findings given these prior circumstances. Additionally, our analyses showed that participants who did not complete all study visits had greater depression and anhedonia severity compared to the participants who did complete all procedures. It is possible that depression and anhedonia, including challenges with motivation, could have interfered with completion of study procedures for some individuals. Because of this, it is possible that our final sample may underrepresent youth with more severe symptoms. This potential bias should be considered when generalizing findings. Additional research is needed with larger sample sizes and longer follow-up duration. Associations may vary across populations of adolescents, which will be

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important to examine in the future. Additionally, our sample was relatively healthy. Studies could benefit from extending this work to clinical samples. Including measures of pubertal status or hormonal levels in future research with younger, less mature adolescents could help clarify the role of biological maturation in the development of PLEs. Furthermore, as our study focused primarily on clinical measures, we did not include environmental or life influences as potential confounding variables. Future studies could benefit from incorporating questionnaires on family dynamics, peer influence, or life stressors to better understand how these environmental factors may contribute to the development of PLEs and neural reward processing. A further consideration is the use of the PQ-B, a self-report screening tool that, while widely used in research, is not a diagnostic instrument. Although the goal of our study was to examine psychosis-risk symptoms in a nonclinical sample, it is important to note that the PQ-B does have high false positive rates in work with CHR youth. Given its relatively high false positive rate, future studies could consider incorporating clinical interviews to more accurately identify risk syndromes such as CHR.

This study shows that PLEs are elevated across two-years in a unique adolescent sample enriched for high risk for developing SMI. Anxiety and heightened striatal response to rewards were each associated with PLEs two-years later—a potentially important finding that may contribute to conceptual models of PLEs development and early intervention approaches. Heightened vigilance and sensitivity to external stimuli may be important precursors to developing PLEs for some youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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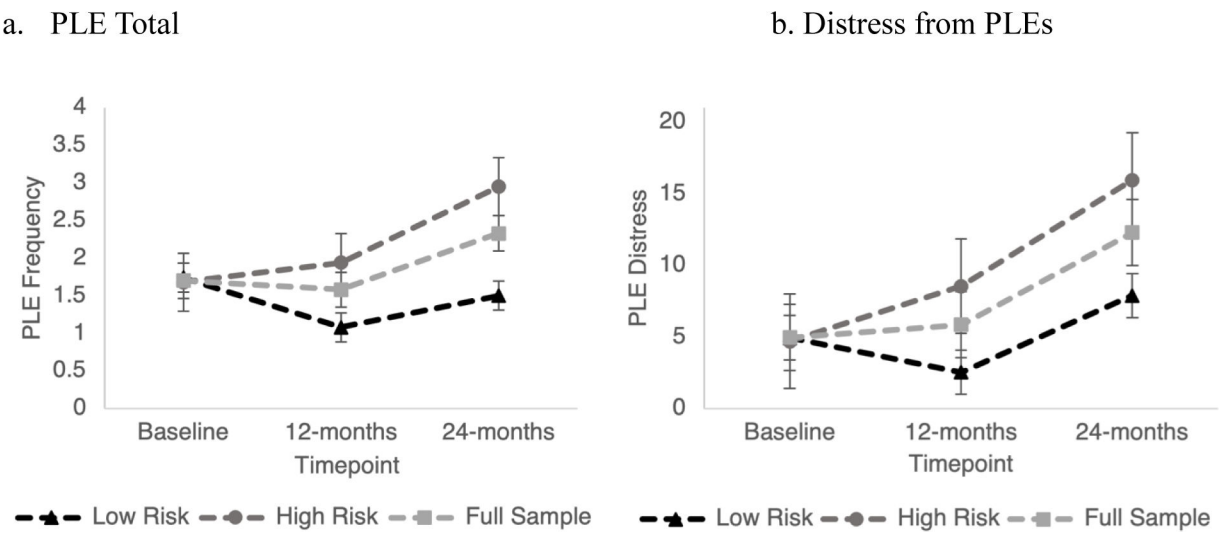

Fig. 1. Psychotic-like experiences, at annual time points across 24-months

Note. Psychotic-like experiences (PLE) total scores & distress (baseline, 12-months, and 24-months): Prodromal Questionnaires, Brief Version [57]; higher scores indicate more severity. When examining a risk group x time interaction in predicting changes in PLEs, the high-risk group showed a steeper increase compared to the low-risk group. High-risk and low-risk groups are defined by the participants' familial history of depressive disorders, bipolar disorders, or schizophrenia-spectrum disorders. While both groups had no personal history of any of these disorders at study entry, high-risk participants had a first-degree family history of these forms of psychopathology, while low-risk participants had none.

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Table 1.

Sample characteristics

Variables	Low-Risk	High-Risk	Total	*Statistic*
N (counts)	43	74	117	
[a] **Age (years), *M*(SD)**	15.19 (1.72)	15.08 (1.51)	15.12 (1.58)	$t(115)= 0.35$
Girls (counts)	25	41	66	$X^2(1) = 0.08$
[b] **Race (counts)**				$X^2(5) = 2.96$
Asian	1	0	1	
Black	14	29	43	
Native Hawaiian/Pacific Islander	0	1	1	
Native American/Alaska Native	0	0	0	
White	24	36	60	
More than one race	3	6	9	
Other	1	2	3	
[c] **Parental Education (counts)**				$X^2(5) = 12.87^*$
Some primary school	0	5	5	
High school or GED	10	11	21	
Technical School	0	8	8	
Some College	7	21	28	
College Degree	15	15	30	
Master or Doctoral level	8	11	19	
[d] **PLE Total, *M*(SD)**				
Baseline	1.74 (2.86)	1.68 (2.55)	1.70 (2.66)	$t(115) = 0.13$
12-month	1.08 (2.19)	1.94 (3.07)	1.58 (2.75)	$t(90) = -1.50$
24-month	1.50 (2.73)	2.95 (3.93)	2.33 (3.52)	$t(68) = -1.73$
[e] **PLE Distress, *M*(SD)**				
Baseline	4.95 (10.07)	4.70 (10.31)	4.79 (10.18)	$t(114) = 0.13$
12-month	2.54 (7.42)	8.54 (17.19)	5.86 (14.00)	$t(83) = -1.98$
24-month	7.89 (11.28)	15.94 (18.34)	12.29 (15.84)	$t(58) = -1.99$
Depression, *M*(SD)	10.18 (7.77)	12.06 (8.93)	11.38 (8.54)	$t(109) = -1.12$
Anxiety, *M*(SD)	18.28 (12.41)	20.83 (13.20)	19.86 (12.91)	$t(111) = -1.02$
Anhedonia, *M*(SD)	24.28 (6.67)	26.04 (5.32)	25.41 (5.87)	$t(107) = -1.51$
Cannabis, Past 30 days (counts)	6	17	23	$X^2(1) = 1.17$

Note. Psychotic-Like Experiences (PLE) total and distress scores were collected using the Prodromal Questionnaires, Brief Version where higher scores indicate more PLEs/higher distress levels. High-risk and low-risk groups are defined by the participants' familial risk for depressive disorders, bipolar disorders, or schizophrenia spectrum disorders. High-risk participants have a first-degree family history of the mental disorders mentioned above, and the low-risk participants do not. *M*=mean, SD=standard deviation.

[a] Age range of the sample is 13–19 years.

[b] Participants were asked to self-report their race, and we thus use this term in reporting demographic characteristics. The use of the race descriptor is consistent with the definition proposed by Ford and Kelly (2005), in which race has facets including personal identity, group identity, and biological characteristics.

[c] There were 6 participants without parental education data.

[d] Sample size of PLE total data at 12-months: low-risk $N = 39$, high-risk $N = 53$; 24-month low-risk $N = 30$, high-risk $N = 40$.

[e] The sample size of PLE distress data: Baseline low-risk $N = 42$, high-risk $N = 74$; 12-month low-risk $N = 37$, high-risk $N = 48$; 24-month low-risk $N = 27$, high-risk $N = 33$. Depression data was collected using the Center for Epidemiological Studies-Depression, anxiety scores were collected using the Screen for Child Anxiety Related Disorders; for both high scores indicate more severity. Anhedonia data was collected using the Snaith-Hamilton Pleasure Scale where higher scores indicate more severity. Cannabis use was collected using the The State and Local Youth Risk Behavior Survey.

* $p < .05$

** $p < .01$

*** $p < .005$.

See supplement for the range of measure scores.

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Table 2.

Neural reward activation predicting psychotic-like experiences (total scores and distress) 24-months later

Predictor(s)	R^2	F	*p*	*β*	*t*	*95% CI Lower, Upper*	*Adjusted p-value*
Model 1: ***Total PLEs at 24-months***	0.39	5.30	<0.001				
PLE total (baseline)				−0.11	−0.44	−0.63, 0.40	0.66
PLE total (12-months)				1.17	3.20	0.43, 1.91	0.015
Left ventral striatum				−1.13	−1.53	−2.63, 0.36	0.22
Right ventral striatum				2.32	2.61	0.52, 4.11	0.03
Dorsal medial prefrontal cortex				−0.36	−1.16	−0.98, 0.27	0.31
Model 2: ***Distress from PLEs at 24-months***	0.40	4.57	0.003				
PLE distress (baseline)				0.19	0.51	−0.83, 10.69	0.61
PLE distress (12-months)				0.75	3.11	0.26, 1.24	0.02
Left ventral striatum				−4.53	−1.22	−12.10, 3.04	0.29
Right ventral striatum				9.75	2.20	0.77, 18.83	0.085
Dorsal medial prefrontal cortex				−2.74	−1.95	−5.59, 0.11	0.10

Note. The findings shown are from the full sample. Psychotic-like experience (PLE) total scores & distress levels were collected from the Prodromal Questionnaires, Brief Version; higher scores indicate more severity. Neural activation was in response to reward outcomes during a guessing card task. Maps for baseline left ventral striatum, right ventral striatum, and dorsal medial prefrontal cortex regions of interest were retrieved from meta-analytic fMRI findings for those regions in neurosynth.com. 95% confidence intervals (CI: uncorrected) are reported: lower, upper. A Benjamini-Hochberg correction was applied to analyses (FDR=0.10) and *p*-values adjusted for this correction are reported in the table ("adjusted p-value").

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Table 3.

Anxiety, depression, and anhedonia predicting psychotic-like experiences (total scores and distress) 24-months later

Predictor(s)	R^2	F	*p*	*β*	*t*	*95% CI Lower, Upper*	*Adjusted p-value*
Model 1: ***Total PLEs at 24-months***	0.43	8.22	<0.001				
PLE total (baseline)				−0.22	−0.98	−0.67, 0.23	0.45
PLE total (12-months)				1.26	3.94	0.62, 1.90	0.005
Depression (baseline)				−0.03	−0.44	−0.19, 0.12	0.66
Anxiety (baseline)				0.09	2.37	0.01, 0.17	0.05
Anhedonia (baseline)				0.06	0.93	−0.07, 0.20	0.45
Model 2: ***Distress from PLEs at 24-months***	0.29	3.47	0.01				
PLE distress (baseline)				−0.07	−0.24	−0.67, 0.53	0.81
PLE distress (12-months)				0.68	2.72	0.17, 1.18	0.05
Depression (baseline)				0.16	−0.46	−0.69, 1.02	0.81
Anxiety (baseline)				0.32	0.39	−0.13, 0.77	0.40
Anhedonia (baseline)				0.24	1.43	−0.60, 1.09	0.81

Note. The findings shown are from the full sample. Psychotic-like experiences (PLE) total scores and distress levels were measured using Prodromal Questionnaires, Brief Version. Depression was measured using the Center for Epidemiological Studies-Depression, anxiety was measured using the Screen for Child Anxiety Related Disorders, and anhedonia was measured with the Snaith-Hamilton Pleasure Scale. Higher scores indicate more severity for all mentioned questionnaires. 95% confidence intervals (CI) are reported: lower, upper. A Benjamini-Hochberg correction was applied to analyses (FDR=0.10) and *p*-values adjusted for this correction are reported in the table ("adjusted p-value").