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Research paper

Anhedonia in adolescents at transdiagnostic familial risk for severe mental illness: Clustering by symptoms and mechanisms of association with behavior

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ABSTRACT

Background: Anhedonia is a transdiagnostic symptom of severe mental illness (SMI) and emerges during adolescence. Possible subphenotypes and neural mechanisms of anhedonia in adolescents at risk for SMI are understudied.

Methods: Adolescents at familial risk for SMI ($N = 81$) completed anhedonia (e.g., consummatory, anticipatory, social), demographic, and clinical measures and one year prior, a subsample ($N = 46$) completed fMRI scanning during a monetary reward task. Profiles were identified using *k*-means clustering of anhedonia type and differences in demographics, suicidal ideation, impulsivity, and emotional processes were examined. Moderation analyses were conducted to investigate whether levels of brain activation of reward regions moderated the relationships between anhedonia type and behaviors.

Results: Two-clusters emerged: *a high anhedonia profile (high-anhedonia)*, characterized by high levels of all types of anhedonia, ($N = 32$) and a *low anhedonia profile (low-anhedonia)*, characterized by low levels of anhedonia types ($N = 49$). Adolescents in the high-anhedonia profile reported more suicidal ideation and negative affect, and less positive affect and desire for emotional closeness than low-anhedonia profile. Furthermore, more suicidal ideation, less positive affect, and less desire for emotional closeness differentiated the familial high-risk, high-anhedonia profile adolescents from the familial high-risk, low-anhedonia profile adolescents. Across anhedonia profiles, moderation analyses revealed that adolescents with high dmPFC neural activation in response to reward had positive relationships between social, anticipatory, and consummatory anhedonia and suicidal ideation.

Limitations: Small subsample with fMRI data.

Conclusion: Profiles of anhedonia emerge transdiagnostically and vary on clinical features. Anhedonia severity and activation in frontostriatal reward areas have value for clinically important outcomes such as suicidal ideation.

1. Introduction

Anhedonia (i.e., diminished interest and pleasure) is a risk marker for mental illness onset and occurs in several psychiatric disorders including schizophrenia, depression, and bipolar disorder (Pizzagalli, 2022), disorders that are under the broad category of severe mental illness (SMI). Inconsistent findings remain regarding effective ways to treat anhedonia across disorders. The current conceptualization of

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anhedonia is predominantly derived from the schizophrenia literature (Berenbaum and Oltmanns, 2012; Gard et al., 2006; Gooding and Pflum, 2022; Kring, 1999; Strauss and Gold, 2012) and studies examining anhedonia in affective disorders have been scarce until recently. Additionally, anhedonia is not only a serious symptom of affective and schizophrenia-spectrum disorders, but it tends to occur early in the course of those disorders, likely starting during adolescence (Häfner, 2000; Myles-Worsley et al., 2007). Understanding risk for developing SMI in adolescents can provide developmental and mechanistic insights regarding the emergence of anhedonia during adolescence. Furthermore, although anhedonia is often examined as a single construct (i.e., general anhedonia), it is thought to comprise several processes based on the temporal association with reward (e.g., anticipatory vs consummatory anhedonia) or the class of reward (e.g., physical vs social anhedonia).

Anhedonia is a broad term that occurs in different phases or contexts of experience: social anhedonia (difficulty experiencing pleasure from social contacts, stimuli, interactions etc), consummatory anhedonia (difficulty enjoying pleasant events or experiences), and anticipatory anhedonia (difficulty looking forward to future rewards). In adults with schizophrenia, consummatory anhedonia tends to be intact and anticipatory anhedonia is diminished while in adults with Major Depressive Disorder (MDD), individuals experience both reduced consummatory and anticipatory anhedonia (Barch et al., 2016). Social anhedonia is observed across forms of SMI disorders (Barkus and Badcock, 2019; Gooding and Pflum, 2022). Although anhedonia is a criterion for a diagnosis of MDD (American Psychiatric Association, 2013), and anhedonia and depressed mood are both central features of depression (Fried et al., 2016), they appear to be distinct. For example, risk markers for anhedonia and depressed mood differ, with evidence suggesting anhedonia can differentiate between those with versus without suicidal ideation even when controlling for depressed mood (see meta-analysis, Ducasse et al., 2018).

Although the literature on anhedonia in adults with SMI is relatively well established, the literature on anhedonia during adolescence is more limited. What is known is that anhedonia can emerge as early as age 3 (Prabhakar et al., 2022) and is prevalent in adolescents both with (Lewinsohn et al., 2000) and without depression (Stringaris et al., 2015). Additionally, anhedonia increases in stability across adolescence (Bennik et al., 2014; Conway et al., 2017) and in some cases, slightly increases in severity (Conway et al., 2017). Social anhedonia, in particular, may peak around age 15 (Dodell-Feder and Germine, 2018). Anhedonia's emergence during adolescence is problematic, given that early adolescent positive affect is associated with positive outcomes in adulthood such as fewer conflicts in relationships, higher self-worth, lower feelings of loneliness, and lower severity of clinical symptoms such as depression and anxiety (Coffey and Warren, 2020; Gooding et al., 2021; Kansky et al., 2016).

Additionally, social anhedonia during adolescence and emerging adulthood is a risk marker for psychopathology later in life. For instance, adolescents and young adults with social anhedonia are at heightened risk for developing schizophrenia-spectrum disorders (Gooding, 2023; Gooding et al., 2005; Kwapil, 1998; Yang et al., 2022). While at times combined in the literature, anticipatory and consummatory anhedonia represent distinct phases, which is important to consider in the context of risk for psychopathology as there may be unique mechanisms at play contributing to outcomes (Barch et al., 2016). Furthermore, anhedonia assessed using clinician-rated interviews (e.g., DSM criterion) not only predicts MDD in adulthood (Pine et al., 1999; Wilcox and Anthony, 2004) but also predicts greater illness severity, episode duration, and number of MDD episodes later in life (Gabbay et al., 2015). While the published research examining adolescent anhedonia as a predictor of bipolar disorder is limited, anhedonia is present in adolescents with bipolar disorder (Dimick et al., 2021).

Adolescent anhedonia has several associations with emotional processes and problematic behaviors. Broadly, anhedonia has been defined as reduced positive affect (Pizzagalli, 2022). However, there is evidence that treatments for positive affect (i.e., positive affect training) can target negative affect as well (Craske et al., 2016, 2019) suggesting that anhedonia types (e.g., social, anticipatory, consummatory anhedonia) might differ in levels of negative affect. Additionally, social anhedonia is related to low positive emotionality in community samples of adolescents (Goldstein et al., 2021). Consummatory anhedonia is associated with suicidality in adolescents (Yang et al., 2022) including adolescents with depression (Auerbach et al., 2015). It has been posited that perhaps intense, prolonged feelings of anhedonia are intolerable, which can lead to suicidal ideation (Nock et al., 2005). In a recent meta-analysis (Gillissie et al., 2023) of associations between anhedonia and suicidality in adolescents and adults, individuals with suicidality reported high levels of general, anticipatory, and consummatory anhedonia, but there were moderate to large effects for the association between anticipatory anhedonia and suicidality in particular. This could suggest that difficulties envisioning or having motivation to experience positive future events could be a risk marker for suicide in adolescents even more than disruptions of in-the-moment experiences of pleasure. Furthermore, social anhedonia has also been found to relate to suicidal ideation (Yang et al., 2020). While not studied to date in adolescents, there is evidence of associations between social anhedonia and impulsivity in adults with MDD and schizophrenia (Amr and Volpe, 2013).

Emotional closeness (i.e., feeling close and connected to others) (Flores et al., 2018) is a fundamental aspect of social functioning and well-being that is important to consider in the context of anhedonia as well, particularly social anhedonia. A failure to feel or unrealized desire to feel close to others may be a sign of or contribute to the emergence of anhedonia during adolescence, a developmental period in which peer relationships are changing in intensity and quality. This is further bolstered by evidence suggesting that more social/interpersonal pleasure during adolescence is associated with more affiliation (Gooding et al., 2021). There is likely heterogeneity in the association of anhedonia with these behaviors, with certain profiles of anhedonia or certain types of anhedonia having potentially greater associations. For instance, people more inclined toward social anhedonia could experience low desire for emotional closeness.

Relatedly, research on underlying neural circuitry of anhedonia converges to suggest that anhedonia is associated with disruptions in neural reward circuitry (Der-Avakian et al., 2012) even in young people at genetic risk for mood disorders (Kujawa et al., 2017). Studies of neural activation during reward receipt find reduced neural activation of the ventral striatum (VS), the hub of reward receipt, and increased activation in the medial prefrontal cortex (dmPFC) in response to reward in adolescents with major depression (Forbes et al., 2006, 2009; Gabbay et al., 2013; Gong et al., 2020; Keren et al., 2018). Neural reward impairments are also observed in those at risk for SMI (Liu et al., 2016; Millman et al., 2019; Nusslock et al., 2014; Olino et al., 2014). This pattern of findings is also consistent with studies of adolescents at familial high-risk for depression (Monk et al., 2008; Olino et al., 2015). Additionally, in those at risk for depression, decreased VS neural activation is observed during reward anticipation (Olino et al., 2014) and predicts symptoms in late adolescence (Morgan et al., 2013). As such, frontostriatal function contributes to reward-related clinical outcomes in adolescence and, in the context of being a vulnerability factor of anhedonia, could amplify anhedonia effects. Collectively, these findings underscore the importance of reward-related mechanisms in anhedonia across psychiatric illnesses. Given that brain activation can be conceptualized as a trait-like characteristic (Hasler et al., 2004), there may be utility in examining whether levels of brain activation of reward circuitry moderate the relationships between anhedonia type and problematic experiences and behaviors such as suicidal ideation. This may provide information on the role of specific neural vulnerability underlying the association of anhedonia with behavior. For example, higher levels of certain types of anhedonia could be related to problem behaviors among those who exhibit, say, reduced VS response.

1.1. The present study

Using cluster analytic approaches – which have been increasingly applied to SMI and adolescent risk samples (Cowan et al., 2020; Dean et al., 2018; Fonseca-Pedrero et al., 2016; Gupta et al., 2021.; Hybels et al., 2009; Lee et al., 2017; Ryan et al., 2018; Strauss et al., 2013) – allows for the ability to identify and characterize profiles of anhedonic phenotypes and examine their relevance to heterogeneity in neural mechanisms and problem behaviors. As such, the current study examined anhedonia profiles in a sample of 81 adolescents at varying risk for developing SMI. Specifically, adolescents completed fMRI scanning during a monetary reward task and, one year later, consummatory, anticipatory, and social anhedonia measures as well as demographic and clinical measures were collected. Anhedonia profiles were identified using a data-driven approach (*k*-means clustering) across measures, capturing a range of anhedonia types (i.e., anticipatory, consummatory, social). Profile differences in demographics, suicidal ideation, impulsivity, and emotional processes were examined. Furthermore, for a subset of individuals with available neuroimaging data, the investigation aimed to determine whether varying levels of neural activation to reward (dmPFC and VS) collected at baseline moderated relationships between anhedonia type and problematic behaviors and experiences.

Given differences across disorders in features of anhedonia, it was hypothesized that profiles would emerge based on types of anhedonia and that these profiles would differ in problematic behaviors and experiences (e.g., adolescents with anticipatory anhedonia profile would have higher suicidal ideation than those in other profiles). In addition, in a subsample, we predicted that dmPFC and VS activation would moderate associations between severity of the type of anhedonia (e.g., anticipatory) and problematic experiences and behaviors (e.g., suicidal ideation).

2. Methods

2.1. Participants

A total of 81 adolescents participated in this longitudinal study. These individuals were recruited as part of a larger, longitudinal study at a large University in North America. Data from this larger, longitudinal study were published in a separate paper that examined the moderating effect of neural reward activation for associations between sexual orientation victimization and depression (Eckstrand et al., 2022). This prior paper included a subsample of sexual minority youth while the current study did not include this subsample given the aims of the current study. Participants were eligible to participate if they were between the ages of 13–22 and met criteria for inclusion in either a "high-risk" or "low-risk" group. The high-risk group included those at familial risk for depression, bipolar disorder, or schizophrenia/schizoaffective disorder, determined by having a parent or full biological sibling with a history of one of the following: DSM-IV Dysthymic Disorder or Major Depressive Disorder or Depressive Disorder; Bipolar I or II Disorder, Schizophrenia or Schizoaffective Disorder. The familial low-risk group included those who did not have a first-degree relative with a history of *any* mood or psychotic disorder. For both groups, study eligibility was contingent on: 1) not taking any psychotropic medication for at least 2 weeks prior to the date of enrollment (other than a stimulant medication that was allowed only up to 36 h prior to the MRI scan), 2) absence of any DSM-IV affective or psychotic disorder diagnosis (lifetime), 3) no daily nicotine use, 4) no history of head trauma, and 5) no MRI contraindications. Potentially affected family members who were under the age of 18 were administered the modules from the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) (Kaufman et al., 1997). Adolescents were given the KSADS to determine lifetime psychiatric disorders. Participants were re-administered the SCID or KSADs, based on original interview, later in the study in order to confirm entry risk group; the current risk categories used in this study reflect any updates at re-assessment.

Table 1
Demographic details.

	High-anhedonia	Low-anhedonia	Total
Demographics			
Number of participants	32	49	81
Age	16.13 (1.58)	16.24 (1.69)	16.20 (1.64)
Number of girls	34	17	51
Race and ethnicity			
Asian	0	2	2
Black	15	13	28
Native Hawaiian/Pacific Islander	1	0	1
White	11	29	40
More than one race	3	5	8
Other	2	0	2
Hispanic	3	2	5
Symptoms			
Anxiety symptoms	17.19 (10.17)	14.39 (9.16)	16.89 (11.48)
Depressive symptoms	14.39 (7.24)	6.98 (7.24)	9.89 (8.78)
Anhedonia measures			
Social[1]	47.90 (8.99)	60.93 (5.67)	28.77 (9.56)
Consummatory	29.75 (3.57)	21.92 (4.73)	25.01 (5.76)
Anticipatory[1]	41.09 (7.31)	52.02 (4.68)	47.70 (7.92)
Neural reward activation (BOLD)			
Dorsal medial prefrontal cortex	−0.09 (1.79)	−0.007 (1.74)	−0.06 (1.75)
Ventral striatum	0.35 (1.15)	0.49 (0.84)	0.41 (1.04)

Note. [1]Social and anticipatory anhedonia measures are not reverse scored in the Table to ease interpretation and comparison of findings with the literature, lower scores reflect more anhedonia. Anhedonia is measured using the Anticipatory and Consummatory Interpersonal Pleasure Scale, Adolescent Version (ACIPS-A) (Gooding et al., 2016). For the ACIPS-A, the items reflected in this Table includes the full, 17-items with one item imputed as a result of random missing data, with lower scores reflecting anhedonia. Anticipatory anhedonia was measured using the Temporal Experience of Pleasure Scale (TEPS), with lower scores reflecting anhedonia. Consummatory anhedonia was measured using the Snaith-Hamilton Pleasure Scale, with higher scores reflecting more anhedonia. Reverse scored TEPS (SD) (higher scores reflect more anhedonia): High-anhedonia = 28.91(7.31), Low-anhedonia = 17.98(4.68). Reverse scored ACIPS-A without imputed item (16-items) M(SD): High-Anhedonia = 36.09 (7.23), Low-Anhedonia: 23.98(7.70). Age is represented in years. Race and ethnicity are counts. Depressive symptoms are taken from the Center for Epidemiological Studies-Depression (Lewinsohn et al., 1997). Anxiety symptoms are taken from the Screen for Child Anxiety Related Disorders (Birmaher et al., 1999). Neural reward activation represents neural reward activation to reward receipt > neutral receipt during a monetary reward guessing task. Blood-oxygen-level-dependent (BOLD).

2.2. Ethical considerations

Institutional Review Board approval was obtained prior to the study. Written consent/assent was received from subjects and parents/guardians prior to procedures.

2.3. Anhedonia measures

In pursuit of a comprehensive approach in the characterization of anhedonia, multiple anhedonia measures were selected. Below, Cronbach alphas computed using the current sample are reported for each measure. The Anticipatory and Consummatory Interpersonal Pleasure Scale - Adolescent Version (ACIPS-A), $\alpha = 0.86$, is a 17-item measure used to assess social anhedonia (Gooding et al., 2016). Due to a technical error, one item was omitted from the survey ("I enjoy joking and talking with a friend or coworker"). Imputing the missing value to create a 17-item scale did not change the direction or magnitude of findings, and consequently the 16-item version was used in analyses. Please note that Table 1 includes means and standard deviations of the ACIPS-A both

with and without the imputed item. The Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006), α = 0.83, anticipatory anhedonia 10-item subscale was used, in which individuals were asked to provide ratings on a 6-point Likert scale. The Snaith-Hamilton Pleasure Scale (SHAPS) was used to measure consummatory anhedonia (Snaith et al., 1995), α = 0.82. This measure is a 14-item scale and the dimensional scoring (1–4 scale) was used rather than the binary score for each item so the total had greater range. Please note anhedonia scales were reversed scored in order to ease interpretation of findings so that higher scores reflected more anhedonia.

2.4. Depression and anxiety

To assess depressive symptoms, the Center for Epidemiological Studies-Depression (CES—D) was administered (Lewinsohn et al., 1997), α = 0.89. Scores range from 0 to 60 with higher scores meaning more depressive symptoms with a clinical cutoff of 16. Additionally, the Screen for Child Anxiety Related Disorders (SCARED) (Birmaher et al., 1999), α = 0.92, was used to assess for anxiety. Items range from 0 (not true or hardly true) to 2 (very true or often true) scale with higher scores indicating greater anxiety (with clinical significant levels reflected by total scores above or equal to the clinical cutoff of 25).

2.5. Suicidal ideation, impulsivity, and emotional processes

The Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), α = 0.83, is a 20-item measure that includes a positive affect domain with 10 items and a negative affect domain with 10 items as well. Scores fall on a 1 (very slightly or not at all) to 5 (extremely) scale. Higher scores on the positive affect subscale indicate more positive affect while higher scores on the negative affect subscale indicate more negative affect. The Suicidal Ideation Questionnaire (Reynolds, 1987), α = 0.83, is a 30-item measure that assesses suicidal ideation with higher scores indicating more suicidal ideation with responses falling on a 0 (almost every day) to 6 (I never had this thought) scale. The brief version of the Desire for Emotional Closeness Questionnaire (Flores and Berenbaum, 2012, 2014), α = 0.96, is a 20-item self-report measure that assesses emotional closeness. A 10-item subscale of this scale measures an individual's desire for feelings close to others, with higher scores indicating a stronger desire. Scores fall on a 5-point rating scale ranging from 1 (not at all) to 5 (extremely). The Barratt Impulsiveness Scale (Patton et al., 1995), α = 0.86, is a 30-item scale that measures impulsivity with higher scores indicating more impulsivity. Please see Supplemental Table 1 for correlations between behavioral measures.

2.6. Reward fMRI task

Neural reward systems were examined using an event-related card-guessing monetary reward task that included three outcome contexts (win, loss, and neutral outcome) and four anticipation contexts (possible win, possible loss, possible win or loss, and neutral) with a monetary value associated with each trial outcome ($1 per win; $0.50 deduction per loss; $0 for neutral) (Eckstrand et al., 2022). Trials were fixed in a pseudorandomized fashion where all participants received the same number and order of win, loss, or neutral trials. Each trial began with a visually presented "decision" card containing a question mark symbol where participants had 4 s to guess, through button press, whether the value of a presented card was higher or lower than 5. The anticipation phase began with a card presenting the trial type (possible win, possible loss, mixed, or neutral). After a jittered 2–6 s anticipation period, the "actual" numerical value of the card (1–9, generated randomly from the high or low range) was presented (500 ms). The outcome cue was then shown (a green upward-facing arrow for win, a red downward-facing arrow for loss, or a yellow circle for neutral feedback; 500 ms) followed by an intertrial interval of 1.5 s. Participants completed one 8-min block of 48 trials. Participants were informed that their performance would result in a monetary reward after the scan: $1 per win and $0.50 deduction per loss. While participants believed monetary outcome was due to performance, a fixed amount was given to all participants. All participants were debriefed regarding the fixed amount outcome at the final neuroimaging assessment (of 3 total). Win trials were comprised of a possible win anticipation period followed by a win or no-win outcome. Loss trials were comprised of a possible loss anticipation period followed by a loss or no-loss outcome. Mixed trials were comprised of a possible win or possible loss followed by either a win or loss outcome. Neutral trials had no anticipation of a win or loss followed by a no monetary change outcome.

2.7. fMRI acquisition parameters

Functional neuroimaging data were collected using a 3.0 Tesla Siemens Prisma MRI scanner. Blood-oxygenation-level-dependent (BOLD) images were acquired with a multi-band gradient echo EPI sequence (18 slices, three-factor multiband; 2.3 mm isotropic voxels; TR = 1500 ms, TE = 30 ms; field of view = 220 × 220 mm; matrix 96 × 96; flip angle 55°, bandwidth 1860 Hz Px–1). Structural 3D axial MPRAGE images (TR = 1500 ms, TE = 3.19 ms; flip angle 8° FOV = 256 × 256 mm; 1 mm isotropic voxels; 176 continuous slices) and fieldmaps (2.3 mm isotropic voxels; TR = 500 ms, TE1 = 4.92 ms, TE2 = 7.38 ms; FOV = 220 × 220 mm; flip angle 45°, bandwidth 1302 Hz Px–1) were acquired in the same session.

2.8. fMRI processing

Preprocessing and fMRI image analyses were performed using Statistical Parametric Mapping software, version 12. For each participant, BOLD images were realigned to the mean volume in the time series and co-registered with the participant's structural image. Field maps were used to correct for image distortion. Structural images were normalized using a non-linear transformation to the standard MNI/ICBM 152 tissue probability maps and segmented into gray matter, white matter, cerebrospinal fluid (CSF), and other tissues (e.g., bone). BOLD images were transformed into the same space using the structural image and resampled at $2mm^3$ isotropic voxel size. BOLD images were normalized and spatially smoothed (FWHM 6 mm).

For first-level neuroimaging analyses, completed in SPM12, a fixed effect general linear model (GLM) was performed for each participant. The 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 was applied to regressors to eliminate collinearity between regressors. Volumes with high motion and artifacts were identified using the Artifact Detection Toolkit (image intensity >3SD from the mean intensity or where movement 0.5 mm in translation or 0.01° in rotation from the previous image) (64) and were entered as covariates in the subject-level GLM to reduce motion-related noise. Lastly, the six motion realignment parameters were entered as covariates to control for head movement. A 128 s high-pass filter and autoregressive modeling were implemented during fitting. Participants with mean movement of >3°/mm were excluded from analyses.

First-level contrast images for the win > neutral outcome condition, reflecting neural reward activation, were entered into second-level SPM analyses. Age was entered as a covariate, given that neural reward systems develop across the age range included in the study. Reward activation defined by the mean within-cluster BOLD signal was extracted from the second-level design for VS and dmPFC (Forbes et al., 2010). VS was defined using Neurosynth's meta-analytic "reward" mask (Yarkoni et al., 2011), thresholded at 75 % to isolate reward-related VS-activation (Baranger et al., 2021); dmPFC was defined using WFU PickAtlas.

ROI analyses are often used to explore functional specificity in an anatomical region after voxelwise analyses have already been

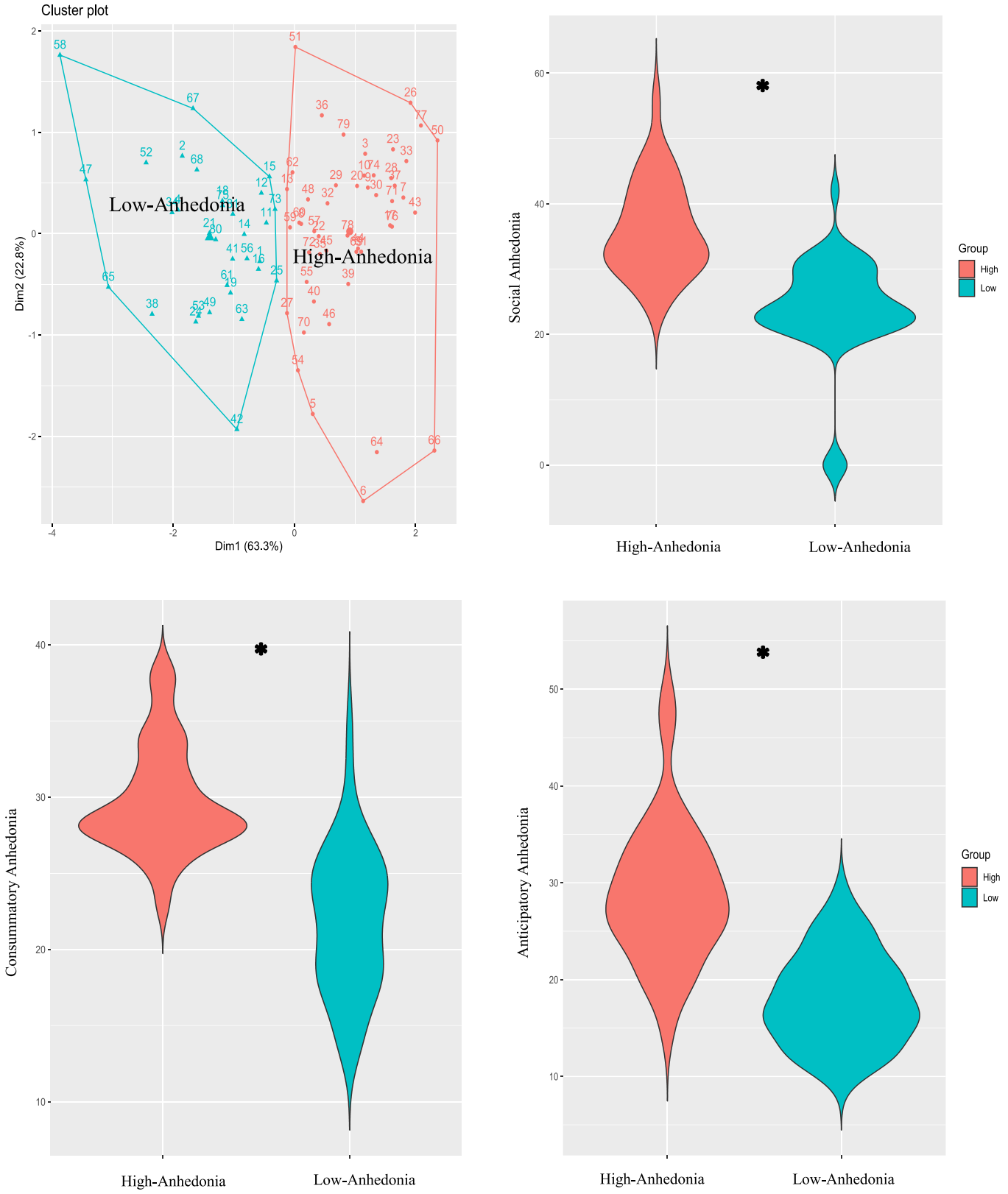


Fig. 1. Anhedonia-based Profiles. *Note.* The cluster plot shows the *k*-means clustering results. Social anhedonia was measured using the Anticipatory and Consummatory Interpersonal Pleasure Scale, Adolescent Version (Gooding et al., 2016). Consummatory anhedonia was measured by the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995). Anticipatory anhedonia was measured by the Temporal Experience of Pleasure Scale (Gard et al., 2006). Anhedonia measures are reverse scored so that higher scores reflect more anhedonia. *$p < 0.05$.

performed (Poldrack, 2007). In this case, our prior research (Eckstrand et al., 2022) showed in voxelwise analyses that the VS, dmPFC/anterior cingulate cortex, and right orbitofrontal cortex were significantly activated in the reward > neutral outcome for this monetary reward task in this sample. Here, we extended this to examine the specific relationship of activity in VS and dmPFC, given they have also been heavily implicated in anhedonia in addition to monetary reward, in anhedonia profiles.

2.9. Statistical approach

To identify the optimal number of profiles, anhedonia measures were first z-scored and then submitted into a cluster analysis using R Studio Pro with the *k*-means function using the "cluster" package (Maechler, 2019). Inspection of silhouette and elbow plots as well as gap statistics were used in order to decide the optimal number of clusters. Once cluster group number was assigned and cluster group membership was identified, subsequent analyses were conducted in SPSS 28 (SPSS Inc., Chicago IL USA). Independent *t*-tests and chi-square tests were used to assess differences in demographics and the distribution of variables such as gender and risk categories. Then, independent t-tests were applied to characterize profiles by examining differences in anhedonia types. Independent t-tests were used to assess for profile differences in demographics, suicidal ideation, impulsivity, and emotional processes. Profile differences were examined in BOLD signal response to reward outcome > neutral in the dmPFC and VS collected 1 year prior in a subset of participants with available and usable imaging data ($N = 46$). To examine whether the interaction of neural activation to reward and anhedonia type (anticipatory, consummatory, and social anhedonia) predicted problematic behaviors and experiences, we used regression analyses. Post hoc analyses using the PROCESS moderation program in SPSS (Hayes, 2012) with brain activation as the moderator were used to confirm findings and findings were unpacked using the Johnson-Neyman (JN) technique. To reduce Type 1 error, models were restricted to behavior variables for which there were profile differences. Corrections for multiple comparisons were applied within each set of tests using a Benjamini Hochberg correction with a false discovery rate of 0.05. A note is made regarding corrections for multiple comparisons throughout for each set of tests.

3. Results

3.1. Anhedonia cluster groups

Silhouette plots, elbow plots, and gap statistics revealed that a 2-cluster solution was optimal (Fig. 1). Discriminant function analysis was applied to assess the probability that cluster membership was assigned correctly and groups were stable. Discriminant function analysis of the two-cluster solution revealed 94 % of the clusters were classified correctly. In order to further investigate how these profiles were characterized, profile differences on the anhedonia measures included in the cluster analysis (anticipatory, consummatory, and social) were examined. There were profile differences in consummatory anhedonia, $t(79) = 7.99$, $p < 0.001$, $d = 1.82$; anticipatory anhedonia, $t(79) = 8.21$, $p < 0.001$, $d = 1.87$, and social anhedonia, $t(79) = 7.09$, $p < 0.001$, $d = 1.61$ in that one group had higher anhedonia severity (termed *high-anhedonia*, $N = 32$) and another group had lower anhedonia severity (termed *low-anhedonia*, $N = 49$).

3.2. Demographic and clinical characteristics of the anhedonia profiles

There were no profile differences in age, $t(79) = -0.32$, $p = 0.75$ or gender, X^2 (2) = 5.38, $p = 0.07$, but there were differences in parental education, $t(46) = -2.29$, $p = 0.03$ (parents of the low-anhedonia profile had completed more schooling than parents of those in the high-anhedonia profile), $d = 0.68$. Furthermore, a chi-square test revealed

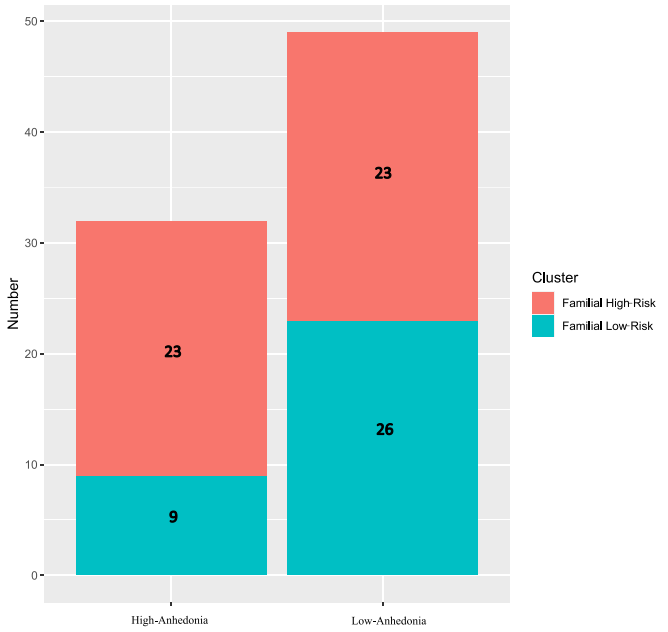


Fig. 2. Distribution of risk categories within each transdiagnostic anhedonia profile. *Note.* $N = 81$. Individuals included are adolescents at familial low-and high-risk for SMI (high includes high-risk for depression, bipolar disorder, schizophrenia/schizoaffective).

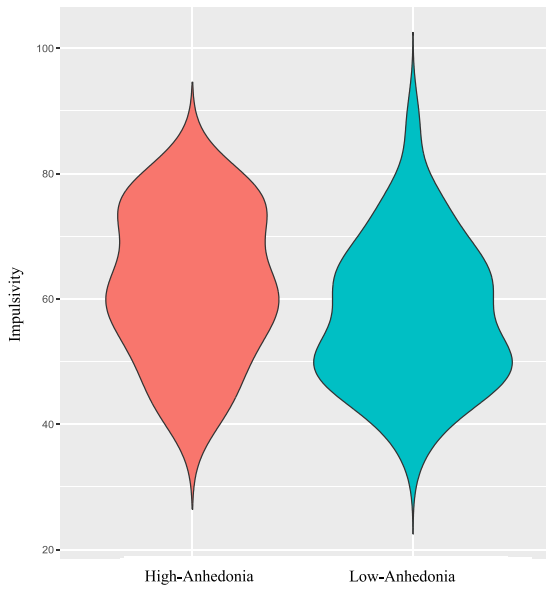
that there was a higher proportion (53.1 %) of adolescents at low familial risk in the low-anhedonia profile as compared to the high-anhedonia profile (28.1 %) (Fig. 2). X^2 (1) = 4.91, $p = 0.03$ (Fig. 2). There was an even number of familial high-risk individuals ($N = 23$ in each profile). There were no profile differences in the distribution of race; X^2 (5) = 10.64, $p = 0.059$. Furthermore, there were no profile differences on anxiety scores, $t(79) = 0.19$, $p = 0.43$ but there were in depression scores, $t(77) = 4.00$, $p < 0.001$, $d = 0.92$, with individuals in the high-anhedonia profile reporting a greater severity of depressive symptoms compared to the low-anhedonia profile (although the means for both profiles were below the clinical cutoff). See Table 1 for sample details and Fig. 2 for distribution of high/low-risk categories. See supplement for breakdown of first-degree relative diagnoses. Additionally, given the wide age range of the sample, age by profile predicting anhedonia type was examined and there were no relationships ($p > 0.18$).

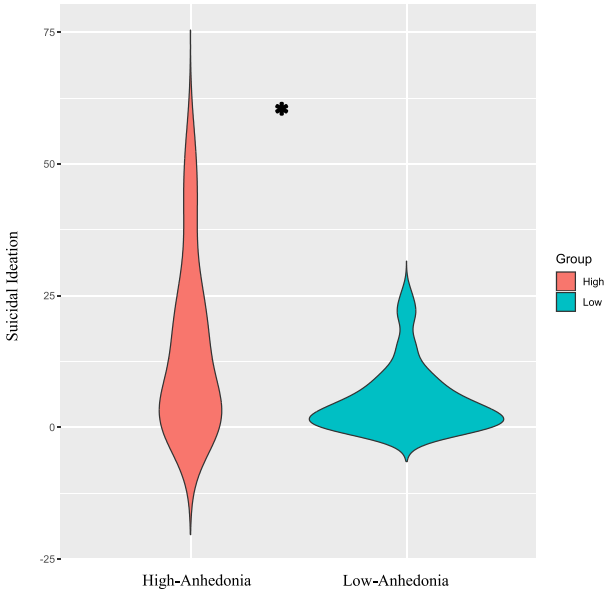
3.3. Profile differences in suicidal ideation, impulsivity, emotional processes, and neural reward activation

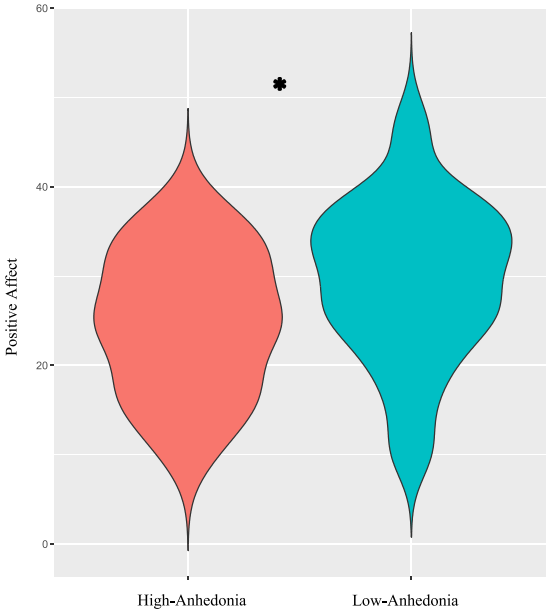
There were profile differences in that the high-anhedonia profile reported more suicidal ideation, $t(77) = -3.72$, $p < 0.001$, $d = 0.85$, less positive affect, $t(78) = -2.41$, $p = 0.02$, $d = 0.55$, more negative affect, $t(79) = 2.35$, $p = 0.02$, $d = 0.59$, and less desire for emotional closeness, $t(75) = -4.84$, $p < 0.001$, $d = 1.12$. There were no profile differences in impulsivity, $t(63) = 1.65$, $p = 0.10$, and VS, $t(44) = 0.43$, $p = 0.44$, and dmPFC, $t(44) = 0.16$, $p = 0.44$ neural activation in response to rewards. All findings survived correction for multiple comparison. See Fig. 3.

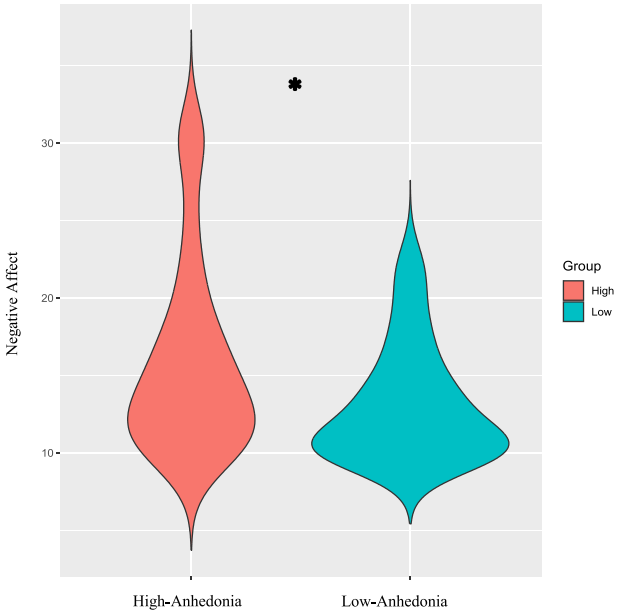
3.4. Levels of brain activation and relationships between anhedonia type and behaviors

As shown in Figs. 4A, 4B, 4C, post hoc analyses with mean-centered variables (with brain activation as the moderator) revealed brain-behavior patterns. In particular, regions of significance analyses indicated that at high levels of dmPFC neural activation in response to rewards, there was a positive relationship between suicidal ideation and









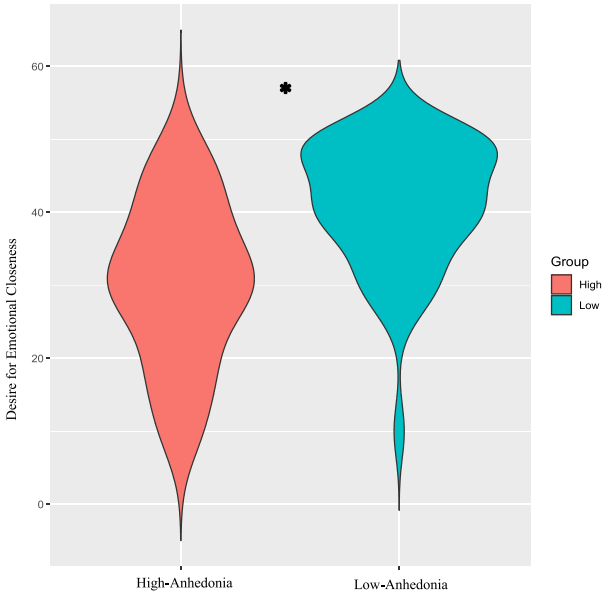


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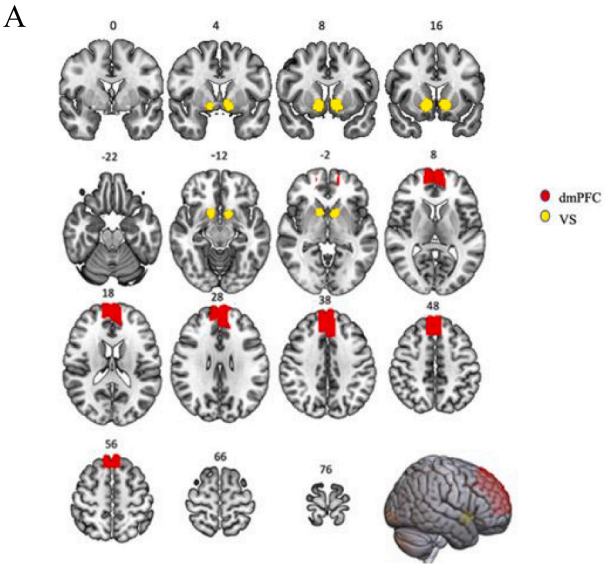
Fig. 3. Summary of findings comparing anhedonia profiles on impulsivity, suicidal ideation, positive and negative affect, and desire for emotional closeness. *Note.* Suicidal ideation is a sum score from the Suicidal Ideation Questionnaire (Reynolds, 1987). Impulsivity is taken from the Barratt Impulsivity Scale (Patton et al., 1995). Positive and negative affect are scores derived from the Positive and Negative Affect Schedule (Watson et al., 1988). Desire for Emotional Closeness is from the Emotional Closeness Questionnaire, Desire for Emotional Closeness subscale (Flores and Berenbaum, 2012). *$p < 0.05$.



Note. Brain regions depicted are from neurosynth

	Predicting	R^2	*F*	*p*	*ME*	*Interaction*	*ß*	*p*
Social Anh*dmPFC	SI	0.38	8.37	< 0.001	dmPFC, p = 0.007	S	0.30	0.002
	PA	0.28	1.20	0.32	--	--	–	–
	NA	0.27	3.66	0.01	EC, $p < 0.001$	NS	–	–
	Close	0.63	9.18	< 0.001	Social Anh, $p < 0.001$	--	–	–
Ant Anh*dmPFC	SI	0.35	7.25	< 0.001	Ant, $p = 0.046$ dmPFC, $p = 0.009$	S	0.24	0.002
	PA	0.15	2.40	0.08	--	--	–	–
	NA	0.12	1.84	0.15	--	--	–	–
	Close	0.59	7.40	0.004	Ant, $p < 0.001$	NS	–	–
Consum Anh*dmPFC	SI	0.17	2.86	0.048	dmPFC, $p = 0.04$	S	0.30	0.016
	PA	0.02	0.24	0.87	--	--	--	--
	NA	0.40	6.71	< 0.001	Consum, $p = 0.006$ Gender, $p = 0.008$	NS	--	--
	Close	0.53	5.40	.003	Consum, $p < 0.001$	NS	--	--

Note. $N = 46$. dmPFC = dorsal medial prefrontal cortex, neural activation in response to rewards. ME = main effects. PA = positive affect. NA = negative affect. EC = emotional closeness. SI = suicidal ideation. *ß* = unstandardized beta. Social Anh = social anhedonia. Ant = anticipatory anhedonia. Consum = consummatory anhedonia. NS = nonsignificant. S = significant. Analyses survived correction for multiple comparisons

Fig. 4A. Interaction between dorsal medial prefrontal cortex neural activation and anhedonia type predicting emotional processes and problematic behaviors. *Note.* Brain regions depicted are from neurosynth. *Note.* $N = 46$. dmPFC = dorsal medial prefrontal cortex, neural activation in response to rewards. ME = main effects. PA = positive affect. NA = negative affect. EC = emotional closeness. SI = suicidal ideation. *ß* = unstandardized beta. Social Anh = social anhedonia. Ant = anticipatory anhedonia. Consum = consummatory anhedonia. NS = nonsignificant. S = significant. Analyses survived correction for multiple comparisons.

social anhedonia (> −0.15 [arbitrary BOLD units], $ß = 0.24$, $p = 0.05$, 53 % of the sample), consummatory anhedonia, (> 0.51, $ß = 0.50$, $p = 0.05$, 36 % of the sample), and anticipatory anhedonia (> 0.08, $ß = 0.29$, $p = 0.05$, 48.89 % of the sample). Findings survived correction for multiple comparisons.

B

	Predicting	R^2	*F*	*p*	*ME*	*Interaction*	*ß*	*p*
Social Anh*VS	SI	0.38	2.30	0.09	--	--	--	--
	PA	0.03	0.47	0.71	--	--	--	--
	NA	0.49	4.47	0.008	Social Anh, p = 0.009	NS	--	--
	Close	0.64	9.56	0.001	Social Anh, p < 0.001	NS	--	--
Ant Anh*VS	SI	0.40	2.67	0.06	--	--	--	--
	PA	0.11	1.74	0.17	--	--	--	--
	NA	0.17	2.93	0.04	Ant, p = 0.01	NS	--	--
	Close	0.34	7.01	< 0.001	Ant, p = 0.002	NS	--	--
Consum Anh*VS	SI	0.05	0.66	0.58	--	--	--	--
	PA	0.06	0.94	0.43	--	--	--	--
	NA	0.15	2.39	0.08	--	--	--	--
	Close	0.55	5.98	0.002	Consum, p < 0.001	NS	--	--

Note. N = 46. VS = ventral striatum; ME = main effects; PA = positive affect; NA = negative affect; Close = emotional closeness; SI = suicidal ideation; $ß$ = unstandardized beta; Social Anh = social anhedonia; Ant Anh = anticipatory anhedonia; Consum Anh = consummatory anhedonia; NS = nonsignificant; S = significant, analyses survived correction for multiple comparisons

Fig. 4B. Interaction between ventral striatum neural activation and anhedonia type predicting emotional processes and problematic behaviors. *Note.* N = 46. VS = ventral striatum; ME = main effects; PA = positive affect; NA = negative affect; Close = emotional closeness; SI = suicidal ideation; $ß$ = unstandardized beta; Social Anh = social anhedonia; Ant Anh = anticipatory anhedonia; Consum Anh = consummatory anhedonia; NS = nonsignificant; S = significant, analyses survived correction for multiple comparisons.

3.5. Exploratory analyses comparing familial high-risk individuals in the low-anhedonia profile versus the high-anhedonia profile

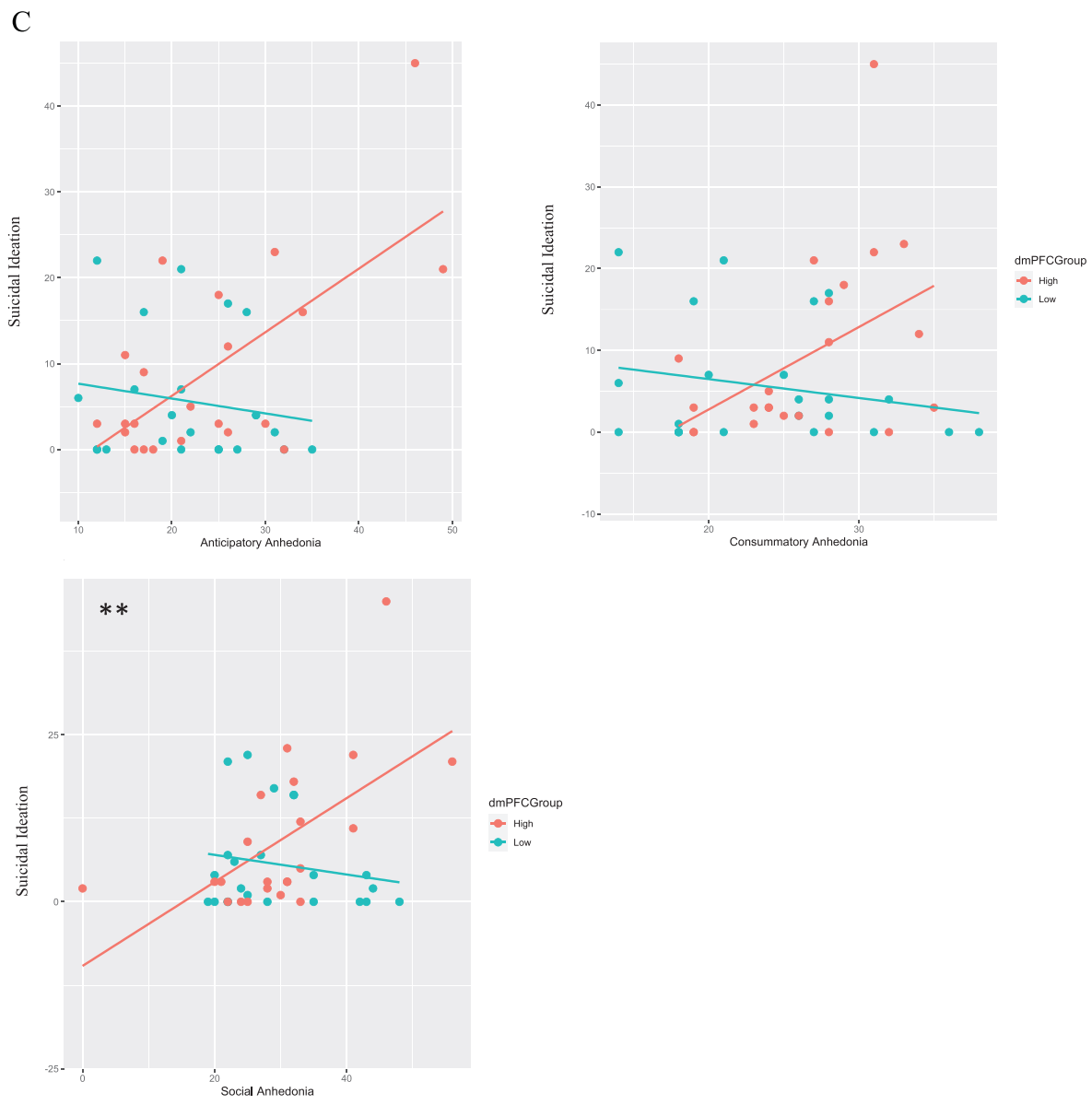
Given there were 23 individuals at familial high-risk in the high-anhedonia profile (72 %) and 23 individuals at familial low-risk in the low-anhedonia profile (47 %), exploratory analyses were conducted comparing these groups on sample demographics and symptoms, and problematic experiences and behaviors. Overall, the familial high-risk, high-anhedonia profile adolescents experienced more suicidal ideation, d = 0.73, lower positive affect, d = 0.64, and less desire for emotional closeness, d = 1.00, than the high-risk, low-anhedonia profile adolescents, p = [0.002–0.02]. Furthermore, the familial high-risk, high-anhedonia profile of adolescents had a greater proportion of boys, p = 0.03. There were no other differences, ps = 0.13–0.84.

4. Discussion

The current study found there are anhedonia profiles in adolescents at familial risk for SMI. While these profiles did not vary in the context of anhedonia type as predicted, these data suggest that individuals at high familial risk for SMI can experience varying levels of anhedonia. Additionally, neural reward brain activation moderated the relationship between anhedonia type and suicidal ideation which highlights unique variation in possible underlying brain vulnerability and mechanisms in those at familial risk.

Results suggesting that there are two anhedonia profiles in the transdiagnostic, adolescent risk sample underscore the importance of considering a broad-spectrum diagnostic approach and the utility of cluster analytic approaches to discern anhedonia profiles. Importantly, the clusters did not include distinct anhedonia types. This may suggest that different types of anhedonia despite phase or context may have similar severity and outcomes. Furthermore, anhedonia in general, rather than specific types may pose risk for SMI. With this, as expected, the high-anhedonia profile appeared to be the more severely impacted. Importantly, there were 9 individuals from the low-risk group who were in the high-anhedonia profile while there were an even number of individuals at familial high-risk in each profile (N = 23 in each group). Furthermore, results from chi-square tests revealed there were more familial low-risk adolescents in the low anhedonia profile. These data suggest that there may be heterogeneity in anhedonia severity in the context of risk for psychopathology.

Differences on demographics and problematic behaviors and experiences provide clarification regarding profiles of anhedonia in this transdiagnostic sample, particularly for the high-anhedonia profile. This profile included more adolescent parents with less education and adolescents endorsed more problematic behaviors and experiences such as more suicidal ideation and negative affect, and less positive affect and desire for emotional closeness. Furthermore, the high-anhedonia profile had greater severity of depressive symptoms (although the score was below the clinical cutoff). In prior research, parental education, which is a proxy and factor for family socioeconomic status has been found to be associated with depressive symptoms among adolescents (Wickrama et al., 2009) but this is understudied in the context of anhedonia. Furthermore, these data add to the literature on anhedonia and suicidality in adolescents (e.g., Auerbach et al., 2015) by suggesting that adolescents with anhedonia regardless of familial risk status may be at heightened risk for suicidal behaviors. Importantly, as shown in Fig. 3, the high-anhedonia group had a wider distribution of suicidal ideation scores compared to the low-anhedonia group. This variability could suggest that there may be within-profile subgroups of adolescents endorsing varying levels of suicidal ideation that also have high anhedonia levels. While findings of less positive affect were expected,



Note. $N = 46$. Visualization of unpacked analyses showing high and low activation of the dorsal medial prefrontal cortex (dmPFC) (moderator, which was divided based on median split for illustration purposes here), **a small number of cases at *very low levels of dmPFC* activation had a negative relationship between social anhedonia and suicidal ideation.

Fig. 4C. Unpacking Interactions. *Note.* $N = 46$. Visualization of unpacked analyses showing high and low activation of the dorsal medial prefrontal cortex (dmPFC) (moderator, which was divided based on median split for illustration purposes here), **a small number of cases at *very low levels of dmPFC* activation had a negative relationship between social anhedonia and suicidal ideation.

findings that the high-anhedonia profile had more negative affect is more nuanced. This is the case given that anhedonia is often conceptualized as decreases in positive affect (Pizzagalli, 2022); however anhedonia treatments target negative affect as well (Craske et al., 2016, 2019). Additionally, findings of less desire for emotional closeness in the high-anhedonia profile may reflect the influence of anhedonia on adolescent social development. Between profile differences of adolescents at familial high-risk indicate that there could be a subgroup of adolescents at familial high-risk where this genetic vulnerability may heighten the likelihood of developing certain problematic outcomes (in this case, suicidal ideation, less positive affect, and less desire for emotional closeness). Since causality cannot be inferred from this study, more work is needed modeling behavioral and affective consequences of anhedonia development longitudinally in adolescents.

Given the impairments observed in the high-anhedonia profile, these findings may have implications for the development of treatments and interventions for anhedonia. As anhedonia can have consequences for long-term functioning, poor response to treatment (e.g., McMakin et al., 2012), and problematic clinical course (Shankman et al., 2014), it is critical to improve methods to identify anhedonia early and deliver interventions as soon as possible. However, there is a large gap in the literature in regard to treatments for anhedonia in adolescents. There may be promise in targeting anhedonia by using psychosocial, behavioral approaches such as behavioral activation therapy (Lewinsohn,

1974) or Positive Affect Treatment to provide reinforcement for social or active behaviors, reduce avoidance, and improve mood (e.g., Craske et al., 2016, 2019). Furthermore, there may be promise in the use of neuromodulation techniques, such as transcranial magnetic stimulation, that target the frontostriatal circuit mechanisms of anhedonia (Downar et al., 2014; Rodrigues et al., 2020). While used in clinical settings with adults, these interventions now have evidence of being safe and efficacious for adolescents (Croarkin and MacMaster, 2019) (and they are included in several ongoing investigations in our lab). Future research could continue to develop these techniques, especially given that brain-based approaches can have rapid effects and that during adolescence anhedonia and related syndromes can impact normative developmental outcomes and experiences.

Findings from moderation and JN analyses provide insights regarding the possible influences of anhedonia *types* and problematic behaviors and experiences in the context of neural activation vulnerability in risk samples. Specifically, anhedonia severity was related to suicidal ideation only for those with high dmPFC neural activation in response to reward. This result could suggest that in the context of higher dmPFC activation, those with more anhedonia severity, regardless of type, may also have higher intensity of suicidal ideation consistent with broader anhedonia and suicidal ideation associations in the literature (Auerbach et al., 2022; Bonanni et al., 2019; Sagud et al., 2021). Notably, adolescents with depression commonly exhibit higher dmPFC response than their typically developing peers, and this has been interpreted as excessive regulation of reward responding (given connectivity with the VS) or excessive self-focus (given the role of dmPFC in rumination and the default mode network) (e.g., Forbes et al., 2009; Forbes and Dahl, 2012; Keren et al., 2018). Perhaps adolescents who have stable patterns of such excessive regulation or self-focus are more prone to develop suicidal ideation when they experience anhedonia.

There are strengths to the study (e.g., high-risk design, multiple measures of anhedonia) but also limitations. Accordingly, there may be measurement-related confounds that could be convoluting findings. For example, consummatory anhedonia may be tapping into aspects of anticipatory anhedonia (e.g., responding to items about what one typically enjoys requires anticipating such experiences), and social anhedonia entails both consummatory and anticipatory anhedonia. Accordingly, future research is needed to continue to disentangle differences in anhedonia among adolescents, and in particular, studies that include transdiagnosic samples. Larger samples sizes are needed for the cluster and neuroimaging analyses. Furthermore, while this study included longitudinal data, more longitudinal studies are needed to help detect developmental trajectories of transdiagnostic anhedonia and examine questions more fully related to prediction and clinical outcomes. While we examined social, anticipatory, and consummatory anhedonia using scales well established in the field for assessing these constructs, it would be useful to integrate other measures as well to strengthen the construct validity of findings. Additionally, other latent class analysis approaches in future work are needed in confirming clusters.

5. Conclusion

Taken together, profiles of anhedonia emerge transdiagnostically in adolescents and may vary on clinical features and reward-circuit function. Additionally, these data are informative in regard to elucidating our understanding of underlying mechanisms of anhedonia, a topic that is understudied. These data also inform factors that may influence the development of anhedonia during adolescence and could further development of treatment strategies for those at risk for psychopathology.

CRediT authorship contribution statement

EEF attained funding and oversaw data collection. TG and EEF developed the study concept and design. TG and EEF interpreted findings in consultation with CJL, GLH, JS, NDR, MLP, LEF, and DAP. All co-authors contributed to the preparation of the final manuscript with revisions. All authors approved the final manuscript.

Role of funding source

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Declaration of competing interest

Over the past 3 years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Karla Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka, Sage Therapeutics, Sunovion, and Takeda; he has received honoraria from the Psychonomic Society and American Psychological Association (for editorial work) and from Alkermes; he has received research funding from the Brain and Behavior Research Foundation, Dana Foundation, Wellcome Leap, Millennium Pharmaceuticals, and NIMH; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.11.062.

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