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Weighing the predictive role of neural factors for adolescent anhedonia in the presence of demographic and clinical factors

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ABSTRACT

Anhedonia, a transdiagnostic symptom of psychopathology associated with pernicious clinical course, has putative mechanisms in neural reward systems and emerges during adolescence. However, the relative contributions of neural, demographic, and clinical factors to its development are unclear. 73 adolescents (13–19 years) at varying familial risk for developing anhedonia reported demographic and clinical characteristics at study entry, reported anhedonia up to three times annually, and underwent fMRI during a monetary reward paradigm. Least absolute shrinkage and selection operator (LASSO) regression, which allows for a large number of intercorrelated predictors for feature selection, revealed that among demographic, clinical, and neural factors, 10 features predicted peak anhedonia over two years: impulsivity; activation in dorsal caudate, sub-gyral temporal lobe, and cuneus; and negative FC between the ventral striatum and six regions implicated in motor and/or decision-making aspects of reward. Neural factors explained an additional 40 % of variance above impulsivity. Findings indicate that in adolescents at risk for severe mental illness, disrupted motor and decision-making reward pathways could contribute to the development of anhedonia. Additionally, anhedonia should be defined in multiple domains, beyond mere phenomenology.

1. Introduction

Anhedonia, defined as a diminished ability to experience or anticipate pleasure, is a meaningful transdiagnostic symptom of severe mental illness (SMI)—namely, affective and schizophrenia-spectrum disorders [1,2] —and typically emerges during adolescence [3]. Anhedonia is shaped by a variety of domains, including neural mechanisms underpinning reward response and dysfunction [4,5], which are undergoing development during adolescence, clinical features involving mood and behavioral components [1,2], and demographic characteristics impacting developmental trajectories, such as age and gender [6–8]. Importantly, anhedonia is a risk factor for psychiatric illnesses [9] and can influence the developmental trajectory of adolescents' mental health, contributing to problematic course and outcomes, including higher depression severity, longer time to remission, recurrence rates, and substance use [10–12]. Anhedonia can also interrupt key developmental processes involving the self, social functioning, academic/vocational goals, and self-regulation, negatively impacting learning and potentially contributing to isolation and suicidal thinking [13,14]. Given multimodal influences on anhedonia's development, identifying factors across modalities that predict anhedonia can generate a more comprehensive understanding of anhedonia and inform identification and intervention efforts.

Developmental psychopathology provides a valuable approach to investigating the emergence of symptoms (e.g. anhedonia) through longitudinal, prospective, transdiagnostic designs with high-risk samples. This approach allows for investigation of the emergence of anhedonia during a vulnerable developmental window but before the onset of serious psychopathology—when mechanisms are uncorrupted by psychopathology-related alterations to cognition, behavior, and physiology [3]. Including a sample varying in robust risk factors, such as family history [15], increases the chance of observing psychopathology

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[16]. Thus, determining the mechanisms of anhedonia requires studying it over time in populations likely to experience it. An optimal understanding of the development of anhedonia, a transdiagnostic symptom, would further require including adolescents with family history of affective or schizophrenia-spectrum disorders.

Clinical neuroscience models propose anhedonia is associated with neural reward systems, which develop considerably during adolescence [4,5]. Primary reward regions consist of the ventral striatum (VS), the hub of the reward system that is involved in reward motivation and response to pleasurable stimuli [17], and the medial prefrontal cortex (mPFC), which is involved in reward-based decision-making, reward valuation, and regulation of reward response [18,19]. Young people with anhedonia and depression typically exhibit dampened VS and dorsal striatum activity and elevated mPFC response to reward, and greater functional connectivity (FC) between VS and mPFC [20,21]. The anterior cingulate cortex (ACC) is also involved in evaluating rewards and regulating reward response and exhibits altered connectivity with the striatum in adolescents experiencing anhedonia [22,23]. Secondary reward systems include the supplementary motor area (SMA), which is involved in reward-focused behavior, evaluation, and learning [24], and whose functional connectivity with the striatum is associated with anhedonia severity in adolescents [23]. Additionally, the thalamus, a major recipient of dopaminergic projections, contributes to evaluating emotional stimuli, relaying reward information, and computing reward consequences of behaviors [25–27].

Anhedonia is related to clinical characteristics, including many that involve difficulties with affect or behavior regulation. Anhedonia is a cardinal symptom of depression, is correlated with depression severity [10], and involves similar disruptions in neural reward systems [28]. Additionally, depression can exacerbate or mutually reinforce anhedonia given negative cognitive biases [29] and difficulties modulating behavior based on prior reward [30]. Anhedonia is related to anxiety, as it is postulated as a mechanism for anxiety's progression into depression [31]. Anxiety is thought to generate anhedonia through overshadowing pleasant aspects of ambiguous situations via aversive cognitive processes and through behavioral avoidance that leads to less frequent experiences of reward and devaluation of rewarding stimuli through reduced reinforcement [31]. Anhedonia could have associations with hypomania, as the two states are inversely related through their opposite motivations for, expectations about, and responses to reward [32]. As another potential link to hypomania, anhedonia is prevalent during depressive episodes in adolescents with bipolar disorder [33]. Anhedonia is linked to sleep disturbances: sleep deprivation disrupts adolescents' neural response to reward [34]. The two are thought to have a bidirectional association, as both reflect mood and physiologic dysregulation [35]. Anhedonia is a strong predictor of suicidality [36–38], including among adolescents [39]. Conceptual models propose that this occurs even in the absence of depressed mood [40], and is due to the intolerable nature of the anhedonic state [41]. Furthermore, anhedonia is related to psychosis-risk symptoms in adolescents [42], possibly because adolescents with such symptoms have limited cognitive resources and motivation to engage in enjoyable activities due to preoccupation with unusual thoughts and perceptual experiences [43]. Finally, anhedonia may have an underappreciated association with impulsivity, as both involve disruptions of reward-driven behavior and extreme levels of impulsivity often accompany difficulties with emotion regulation [44].

Within a somewhat underdeveloped literature, anhedonia appears to vary with demographic variables, such as age, gender, and race/ethnicity. Studies with adolescents have reported both decreases [6] and increases with age [45]. Reports of gender effects in anhedonia are inconsistent although some evidence indicates boys experience more anhedonia [7,8], with increases in mid-adolescence [46]. Sex differences in anhedonia may be a result of developmental factors such as puberty which can include increases in pubertal hormones and differences in problematic social responses by peers to physical changes [47,48]. Furthermore, evidence of racial and ethnic differences indicates White people experience lower anhedonia than Asian, Black or Hispanic people [49], which could reflect inequity in access to healthcare [50].

Common conceptualizations of anhedonia, with their focus on phenomenology, self-report measurement, and experiential deficits, give inadequate attention to anhedonia's multimodal nature. Understanding how different domains (i.e., neural, clinical, and demographic) influence anhedonia—and its development—is necessary to pinpoint how they are differentially related. Prior studies have rarely investigated all three domains to examine their relative impact in contributing to anhedonia and its development.

The current study examined the development of anhedonia across adolescence using a prospective, transdiagnostic, high-risk design focused on the relative contributions of demographic, clinical, and neural characteristics. We applied a machine-learning approach to feature selection that allows the inclusion of numerous predictors relative to the number of cases, accommodates multicollinearity, and builds on investigations of behavior problems in high-risk youth [51]. We elected to focus on the reward outcome phase of a guessing reward task given anhedonia's standard and traditional definition—diminished experiences of pleasure and responses to pleasurable stimuli [52]—which is closely tied to consummatory response to reward. We have examined this task in several previous papers in our lab [37] and have found activation in reward regions implicated in reward receipt (e.g., VS) during this phase of the task [53]. As anhedonia fluctuates with time and with other symptoms, we focused on peak severity over up to two years (baseline, 12 months, 24 months) to capture variability in person-specific intensity during the period of emergence. We predicted that factors from all three domains (clinical, neural, and demographic) would be related to anhedonia. Furthermore, with the hypothesis that reward systems have unique importance for the development of anhedonia, we predicted that neural factors would have predictive value in the presence of demographic and clinical factors.

2. Methods

2.1. Participants

73 healthy adolescents aged 13–19 years-old, at high (n = 48) or low (n = 25) familial risk for affective or psychotic disorders were recruited for a larger, longitudinal study investigating the development of anhedonia in adolescents (see Table 1 for sample characteristics). Participants were excluded if they had a current or past diagnosis of depressive or psychotic disorders or if they were taking psychotropic medications, aside from stimulant medications, within two weeks of their study screening visit. Low-risk participants had no history of affective of psychotic disorders in their first-degree relatives, while high-risk participants had a parent or sibling with a history of severe mental illness (see Table 1 for more information). Recruitment methods included social media advertisements, flyers around Pittsburgh, and an online research registry affiliated with the [masked for review]. Informed consent was obtained from all participants. Written assent was obtained for participants< 18 years of age. All procedures were performed in compliance with [masked for review] Human Research Protection Office (#STUDY20050116, initial approval date: 6/16/20).

2.2. Clinical interview

Parents or siblings aged≥ 18 were administered mood and schizophrenia-spectrum disorders sections of the Structured Clinical Interview for DSM-IV (SCID-IV) [54] to assess lifetime psychopathology. Participants and siblings< 18 were administered the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) [55] to assess DSM-IV diagnoses. SCID-IV or KSADS was later reconducted for parents and adolescents, respectively, to confirm diagnoses and risk status; risk groups in analyses reflect findings at re-interview. Clinical interviews

Table 1
Sample Characteristics.

Variable			*N*	%/*M* (*SD*)	Range
Demographic Characteristics					
Gender	Boys		34	46.6 %	-
	Girls		39	53.4 %	-
Race	White		38	52.1 %	-
	Non-White		35	47.9 %	-
	Black		24	32.9 %	-
	Asian		1	1.4 %	-
	Hawaiian/Pacific Islander		1	1.4 %	-
	Other[1]		9	12.3 %	-
	Hispanic		3	4.1 %	-
Risk	Low-Risk		25	34.2 %	-
Group	High-Risk[2]	Total High-Risk	48	65.8 %	-
		Major Depressive Disorder or Dysthymic Disorder	28	58.3 %	-
		Bipolar Disorder	17	35.4 %	-
		Schizophrenia or Schizoaffective Disorder	3	6.3 %	-
Age			73	15.3 (1.6)	13–19
Visits Completed			73	2.5(0.7)	1–3
Clinical Characteristics					
Peak Anhedonia[3]			73	28.0 (5.1)	16–41
Depression			73	10.9 (7.5)	0–34
Anxiety			73	21.2 (12.7)	0–55
Sleep Disturbance			73	18.4 (6.7)	8–38
Psychosis-Risk Symptoms			73	1.8(2.5)	0–13
Impulsivity			73	63.3 (12.4)	40–103
Hypomanic Symptoms			73	10.8 (1.8)	10–22
Suicidal Ideation			73	1.0(0.1)	1–2
Psychiatric Diagnoses at Study Entry					
No Diagnosis			66	90.4 %	-
Anxiety Disorder			5	6.8 %	-
Post-traumatic Stress Disorder			1	1.4 %	-
Conduct Disorder			1	1.4 %	-

Note. Demographics, risk status, depression, anxiety, sleep disturbances, psychosis-risk symptoms, impulsivity, hypomanic symptoms, and suicidal ideation values were collected at baseline.[1]Includes participants reporting more than one race. [2]Participants in the high-risk group had a 1st-degree relative with a history of depression, bipolar disorder, or schizophrenia spectrum disorder, while those in the low-risk group had no such history. Percentage of participants in the high-risk group with 1st-degree relatives from each diagnosis are listed in the table above as subgroups of the high-risk group. [3]Peak anhedonia reflects the maximum score across 3 possible visits over up to 2 years (baseline, 12-months, 24-months).

were conducted by trained students and staff.

2.3. Measures and tasks

For each measure, sum score was used. Greater scores indicated greater severity, unless noted otherwise. All variables were standardized using z-scores prior to running the LASSO model.

2.3.1. Anhedonia

The Snaith Hamilton Pleasure Scale (SHAPS), the gold-standard anhedonia measure, has been well-validated within adolescent samples [56,57]. Participants' maximum score was identified for up to three annual timepoints (α_1=.84;α_2=.82;α_3=.81): baseline, 12 months, and 24 months (entry anhedonia: *M*(SD)=*25.45*(5.93), 12 months *M*(SD)=*25.16*(5.52), 24 months *M*(SD)=*23.73*(6.13)). 40 participants had anhedonia data across all timepoints, 22 participants had two timepoints of anhedonia data, and 11 participants had one timepoint of anhedonia data.

2.3.2. Demographic factors

Participants completed a survey of demographics, including age, gender, and race.

2.3.3. Clinical factors

Depression. Participants completed the Center for Epidemiological Studies–Depression (CES-D) Scale [58] (α=.89). **Anxiety.** Participants completed the Screen for Child Anxiety Related Disorders (SCARED) [59] (α=.93). **Psychosis-risk symptoms.** Participants completed the Prodromal Questionnaire–Brief (PQ-B) [60] (α=.83). **Impulsivity.** Participants completed the Barratt Impulsiveness Scale (BIS) [61] (α=.86) to indicate preference for impulsive behaviors. **Hypomania.** Trained staff administered the Young Mania Rating Scale (YMRS) [62]. **Sleep quality.** Participants completed the Patient Reported Outcomes Measurement Information System - Sleep Disturbance Scale (PROMIS-SD) [63] (α=.85). **Suicidal ideation.** Suicidal ideation (SI) was measured using the KSADS "current suicidal ideation" item (scored 1–3; 1: absence of any SI; 2: subthreshold SI; 3: definite SI).

2.3.4. Function in neural reward circuitry

Participants completed an fMRI scan during an event-related monetary reward card guessing task [53]. Each trial type included guessing, anticipation, and outcome phases associated with the potential to win money. The task consisted of four anticipation contexts (possible win, possible loss, possible win or loss, and neutral) and three outcome contexts (win, loss, and neutral outcome), with monetary values associated with each outcome ($1 per win; deduction of $0.50 for loss; $0 for neutral). Analyses focused on the reward outcome phase of the guessing reward task given anhedonia's standard and traditional definition—diminished experiences of pleasure and responses to pleasurable stimuli [52]—which is closely tied to consummatory response to reward. We have examined this task in several previous papers in our lab [37] and have found activation in reward regions implicated in reward receipt (e.g., ventral striatum) during this phase of the task [53]. Trial outcomes and order were pseudorandomized. Participants were unaware that trials were fixed. After using a button-press to guess whether a card number would be greater or less than "5" (4 s), an expectancy cue reflecting the anticipation context was presented (2–6 s, jittered; reward anticipation). The anticipation phase was modeled as the 2–6 s interval between the guess stimulus and display of the card outcome. The guess phase was modeled as the 4 s interval during card selection as "higher" or "lower". Participants were then shown the "actual" card number (selected randomly; 500 ms), followed by the trial outcome cue (500 ms) indicating whether they won money, lost money, or had no change in earnings (reward outcome). The task lasted approximately eight minutes and included 48 trials, with 12 trials per trial type and a 0.5–1.5 second inter-trial interval.

2.3.5. fMRI acquisition and processing

Functional neuroimaging data were collected using a 3.0 Tesla Siemens Trio MRI scanner. Images were acquired with a multi-band gradient echo EPI sequence (18 slices, 3-factor multiband; 2.3 mm isotropic voxels; TR=1500ms, TE=30ms; field of view=220 ×220 mm; matrix 96 ×96; flip angle 58°, bandwidth 1736 Hz Px–1). Structural 3D axial MPRAGE images (TR=1500ms, TE=3.19ms; flip angle 8°; FOV=256 ×256 mm; 1 mm isotropic voxels; 176 continuous slices) and spin-echo fieldmaps (2.3 mm isotropic voxels; TR=550ms, TE1 =4.92ms, TE2 =7.38ms; FOV=220 ×220 mm; flip angle 50°, bandwidth 380 Hz Px–1) were acquired in the same session. Preprocessing and fMRI image analyses were performed using Statistical Parametric Mapping software, version 12 ("SPM (Statistical Parametric Mapping)"). See supplement for more details on our standard preprocessing steps.

1 st-level analyses of BOLD response entailed a fixed effect general

linear model (GLM) for each participant, including guess, anticipation, and outcome phases. Outcome was defined as the 1 s feedback period plus the jittered ITI, for a mean of 2 s across the task. The Artifact Detection Toolkit (https://www.nitrc.org/projects/artifact_detect/) identified high motion volumes (image intensity deviated>3 SD from the mean intensity, movement>.5 mm translation, or>.01° rotation from the previous image), which were included as regressors along with the six realignment parameters in the 1st-level model. A 128 s high-pass filter and autoregressive modelling were implemented during fitting. Analyses excluded seven participants with VS coverage< 50 % and two participants with movement≥ 3 mm/° in any direction [53]. For VS FC, whole brain Generalized Psychophysiological Interaction (gPPI) analysis was employed [64,65] with left and right VS as seed regions, defined from the Neurosynth meta-analytic database (https://neurosynth.org; association test map, thresholded at 50 %; Fig S1). Activation and FC within the sample is described elsewhere [53,65].

To broadly identify regions of reward activation or FC for inclusion in the LASSO model, and to avoid focus exclusively on canonical reward regions, 2nd-level, whole-brain regressions were run using peak anhedonia as a regressor and *win outcome>neutral outcome* as the contrast. For FC, 2nd-level gPPI analyses were conducted with VS seed. Significance was defined for both neural activation and FC as p_{unc}< .005 and minimum contiguity= 20 voxels. Typically, for imaging studies where meaningful inferences are drawn from the results of 2nd-level analyses performed within standard neuroimaging packages (e.g., SPM12), potential error is reduced through several practices: (a) using a correction for number of tests such as family-wise error (FWE), (b) minimizing the use of non-parametric cluster inference methods, (c) ensuring strong correction for motion-related and scanner-related noise, and (d) using task designs that support stronger signal acquisition (e.g., randomized event-related designs). In this study, while an FWE correction was not applied, we used a task with a pseudorandomized event-related design and followed practices of avoiding non-parametric methods and applying validated noise-reduction methods. The goal of these imaging analyses was not to draw conclusions about brain-anhedonia associations. Rather, these analyses identified potentially relevant regions whose responding to reward might vary with anhedonia in order to build the primary model, which was intended to select predictive features from among demographic, clinical, and neural variables. Importantly, the majority of the activation/connectivity clusters had peak voxel significance detectable at p_{unc}< 0.001. To characterize the principal component of whole-brain reward activation/FC (i.e., the value that explains the greatest variance related to anhedonia within a given cluster, without assuminghomogeneity of response across the cluster), the first eigenvariate was extracted from significant clusters for use in the LASSO model.

2.4. Data analysis plan

A four-step plan was employed: [1] examination of peak anhedonia and neural activation during reward outcome of the monetary reward task (*win outcome>neutral outcome*), [2] examination of peak anhedonia and FC (*win outcome>loss outcome*) of the monetary reward task, [3] use of a LASSO model to identify demographic, clinical, and neural factors associated with peak anhedonia, and [4] traditional hierarchical regression to parse the LASSO results and examine the effect size of variables selected in the LASSO model.

LASSO regression was conducted in R version 4.1.2 using package GLMNET Version 2.0–2 [66,67]. LASSO penalizes complex models with a regularization term (lambda=λ) that shrinks coefficients toward zero and eliminates unimportant features [66,67]. In GLMNET, $k = 5$ fold cross-validation [68] was completed to identify the optimal λ term (lambda.1se) that would minimize the mean cross-validated error for our model, minimize prediction error, reduce overfitting, and enforce sparsity [67]. The variables entered into the model were: demographics (age, gender, race), clinical features (high/low SMI risk status, depression, anxiety, impulsivity, sleep disturbance, psychosis-risk, suicidal ideation, hypomania symptoms), neural correlates from BOLD response to reward receipt and FC of left and right VS (see Table 2 for full list of neural features entered into LASSO model).

P-values and test statistics have not yet been developed for use with LASSO models due to the complexity of the null distributions [69]. Therefore, to describe the magnitude of the strength of the relationships between the identified non-zero variables after cross-validation and anhedonia, we used hierarchical linear regression: one model, with two steps (all non-neural variables entered at step one and all neural variables entered step two). This data analysis approach is similar to previous work [70–72].

3. Results

3.1. Neural activation during reward

Higher peak anhedonia across up to two years was associated with greater activation to reward receipt in the right sub-gyral temporal lobe, right cuneus, and left caudate and putamen (Table 2).

3.2. Functional connectivity during reward

Negative FC between left VS and the following regions was associated with peak anhedonia: bilateral thalamus, right middle cingulate gyrus, right visual cortex, and left SMA/dorsal ACC (Table 2). Negative FC between right VS and three regions emerged as related to peak anhedonia: bilateral thalamus and left SMA (Table 2).

Table 2
Associations Between Peak Anhedonia and Regional Activation and Functional Connectivity with Ventral Striatum during Reward Outcome.

Region	Voxels	*t*	*p*	Coordinates		
				x	y	z
Neural Activation						
Sub-gyral temporal lobe	36	3.19	.001	32	-70	8
Visual cortex/cuneus (BA 17)	97	3.15	.001	18	-80	18
Caudate body	28	3.24	.001	-20	2	18
Putamen	36	3.03	.002	-22	0	8
Functional Connectivity						
Seed: Left Ventral Striatum						
Thalamus (Red Nucleus/ Subthalamic Nucleus/ Ventral Posterior Thalamus)	36	3.64	< .001	8	−10	−2
Thalamus (Ventral Anterior Nucleus)	32	3.91	< .001	−6	−14	−4
Thalamus (Ventral Posterolateral Nucleus)	111	4.00	< .001	18	−26	−2
Middle Cingulate Gyrus	26	3.33	.001	16	−2	42
Thalamus (Pulvinar)	62	3.32	.001	−14	−28	2
Associative Visual Cortex	70	3.29	.001	32	−74	−10
Supplementary Motor Area/ Dorsal Anterior Cingulate Cortex	26	3.02	.002	−8	2	46
Seed: Right Ventral Striatum						
Supplementary Motor Area/ Motor Cortex	36	3.67	< .001	−56	4	38
Thalamus (Pulvinar)	29	3.16	.001	−14	−28	2
Thalamus (Ventral Posterolateral Nucleus)	34	3.91	< .001	20	−24	−2

Note. Neural variables were collected at baseline. Specifically, regional response for reward receipt and functional connectivity during win > loss were computed from a monetary reward fMRI task. The noted neural variables in this table were associated with peak anhedonia, extracted, and entered into the LASSO model. BA: Brodmann Area.

3.3. Demographic, clinical, and neural predictors of anhedonia: LASSO model

When demographics, clinical features, and neural variables (from the models already described above) were entered into the LASSO model, at lambda.1se (λ=.23853), 10 predictors emerged as non-zero coefficients (Table 3, Fig. 1): higher impulsivity; greater activation in caudate, subgyral temporal lobe, and cuneus (Fig. 2A); and negative FC between VS and thalamus (five subregions) and SMA (Figs. 2B and 2C). Model statistics indicated that the model was a good fit for GLM (Figure S2). In summary, these variables were found to be uniquely associated with peak anhedonia in the context of the other demographic, clinical, and neural factors entered into the model.

3.4. Post-hoc hierarchical regression

Post-hoc hierarchical regression was employed to determine if the neural predictors that emerged in the LASSO model were predictive of peak anhedonia even in the context of clinical predictors, with impulsivity entered as a predictor in the first step of the hierarchical regression and neural variables added in the second step to examine correlations to peak anhedonia. Additionally, two of the 10 variables (from the LASSO model) were associated with peak anhedonia in the traditional statistical sense: impulsivity and caudate activation (Table 4).

4. Discussion

The current study sought to understand individual differences in adolescent anhedonia through examining the predictive contributions of neural, demographic, and clinical factors. The study included a sample at a developmental point of vulnerability that varied in risk for anhedonia-related disorders. Adolescents with higher severity of anhedonia were those with high impulsivity; greater activation in a set of reward-processing regions; and negative FC between the VS and several secondary reward-system regions that support cognitive and behavioral functioning. Notably, neural activation and FC were related to anhedonia even when considering demographic and clinical factors, and demographic factors themselves were unrelated to anhedonia. Additionally, the combination of impulsivity and function in reward-relevant systems had greater predictive value for peak anhedonia than impulsivity alone, with neural factors explaining an additional 40 % of variance. Altogether, our findings indicate that neural factors could be robust predictors of peak anhedonia over up to two years and that regions beyond traditional neural reward systems could be particularly valuable for understanding the development of anhedonia. Our findings emphasize the importance of defining anhedonia using multiple domains, with the need to consider motor and decision-making aspects of reward in addition to traditional phenomenological aspects.

Table 3
LASSO Regression Non-Zero Variables Associated with Peak Anhedonia.

Variable	LASSO Derived Coefficient
Non-Neural Variables	
Impulsivity	.088
Neural Variables	
Caudate Body Activation	.095
Sub-Gyral Temporal Lobe Activation	.022
Cuneus Activation	.037
Left VS-Thalamus (Ventral Posterolateral) Negative FC	.131
Left VS-Thalamus (Left Ventral Anterior Nucleus) Negative FC	.037
Left VS- Thalamus (Right Ventral Anterior Nucleus) Negative FC	.028
Right VS-Thalamus (Ventral Posterolateral Nucleus) Negative FC	.015
Right VS-SMA Negative FC	.0004
Right VS-Thalamus (Pulvinar) Negative FC	.0303

Note. Ten predictors emerged as significantly associated with peak anhedonia (i.e., maximum score across 3 timepoints) at lambda.1se in the LASSO regression. FC: Functional connectivity; VS: Ventral Striatum; SMA: Supplementary motor area.

Higher impulsivity predicted greater anhedonia, providing clues regarding the previously documented [73] but ambiguous relationship between anhedonia and unplanned reward-driven behavior. Growing theories in this area [44] suggest that adolescents may engage in potentially risky behaviors to escape an aversive state of non-pleasure, avoid intolerable affective states, and experience greater positive affect [41]. According to the Urgency, Premeditation, Perseverance, Sensation Seeking, and Positive Urgency (UPPS-P) model, a key component of impulsivity is negative urgency, which entails an unpleasant affective state leading to rash behavior through difficulty tolerating distress [74]. Interestingly, adults with depression and disruptions in corticostriatal circuitry underlying anhedonia may more readily engage in impulsive behaviors when they perceive negative experiences, possibly due to diminished salience of rewards and hypersensitivity to losses [75–77]. Potentially, anhedonia-related disruptions in reward learning and corticostriatal circuitry may prompt people to engage in impulsive decisions that further limit their exposure to rewards and reinforce anhedonia. Anhedonia could also lead to devaluing one's well-being and discounting potential dangers when initiating behaviors, consistent with an interpretation that poor motor regulation could be an important aspect of anhedonia.

In terms of neural factors, as mentioned, the nine neural variables selected by the LASSO model explained an additional 40 % of the variance in peak anhedonia even after accounting for impulsivity, which on its own explained 10 % of the variance. Additionally, the effect sizes for the neural factors, such as caudate activation and left VS-thalamus connectivity, were in the small-medium range, suggesting these predictors had moderate effects on anhedonia. The collective contributions of neural predictors were large, indicating that findings appear to be robust and that neural response to reward has predictive value for the development of anhedonia. These data provide a foundation for which neural systems may be most relevant to anhedonia in youth at risk for SMI, contributing to an improved conceptualization of anhedonia. Furthermore, identifying associated neural factors of anhedonia can allow us to develop brain-targeted interventions. Lastly, the neural findings may also provide possible biomarkers for assessing the effectiveness of interventions for anhedonia.

A common thread of our findings on the development of anhedonia is the involvement of neural regions implicated in motor and decision-making processes relevant to reward. The dorsal caudate, a region involved in reward-based movements and decisions and habitual behavior [78–81] (and the only neural factor that survived a traditional regression along with the LASSO model) was, like impulsivity, surprisingly associated with anhedonia in a positive direction. This finding underscores the complexity of the neural mechanisms that underlie reward processing in adolescent anhedonia. One possible explanation of associations between anhedonia and increased activation of the caudate in response to rewards is that the caudate may be overactive to compensate for the reward system's weaknesses in generating a pleasant hedonic response and appropriate motor responses to rewards. Impulsivity is associated with altered patterns of functional connectivity in the caudate [79,80], and when considering the connection between anhedonia and higher impulsivity, it is also worth noting that impulsive behaviors might contribute to overactivation of the reward system, including the caudate. Although we cannot infer causality and directionality from these analyses, it is possible that impulsivity could exacerbate the caudate's heightened activation (or vice versa) further compounding the experience of anhedonia. In sum, these findings may point toward an emerging clinical and neural profile of anhedonia for certain adolescents: those with greater impulsivity and caudate overactivation, both of which could reflect adaptations to diminished reward experiences.

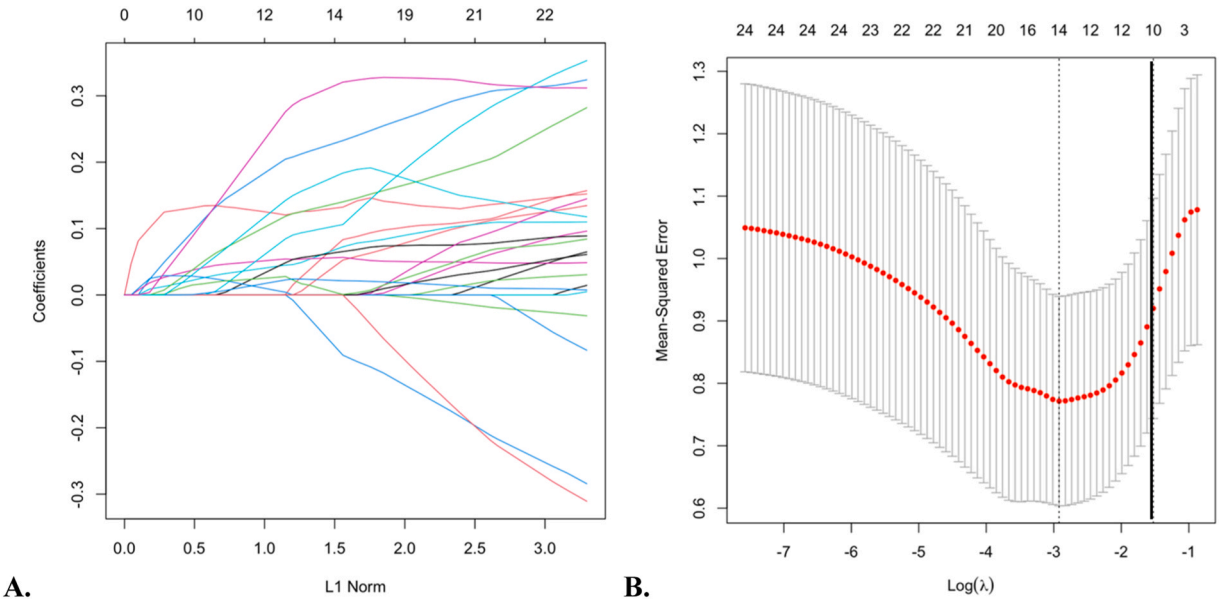


Fig. 1. LASSO Fit and Cross Validation Plots. Note. A. Plot of variable fit. Each curve represents a predictor variable in the full model before optimization. Curves show path of each variable coefficient as λ *changes. Values across the top of the graph indicate number of variables included in the model. B. Plot of non-zero variable fit after 5-fold CV cross validation (CV). Values across the top of the graph indicate number of variables included in the model. Mean-Squared Error (MSE) declines with cross-validation as penalization increases, reflecting better fit. At lambda.1se (solid line), there were 10 non-zero variables.*

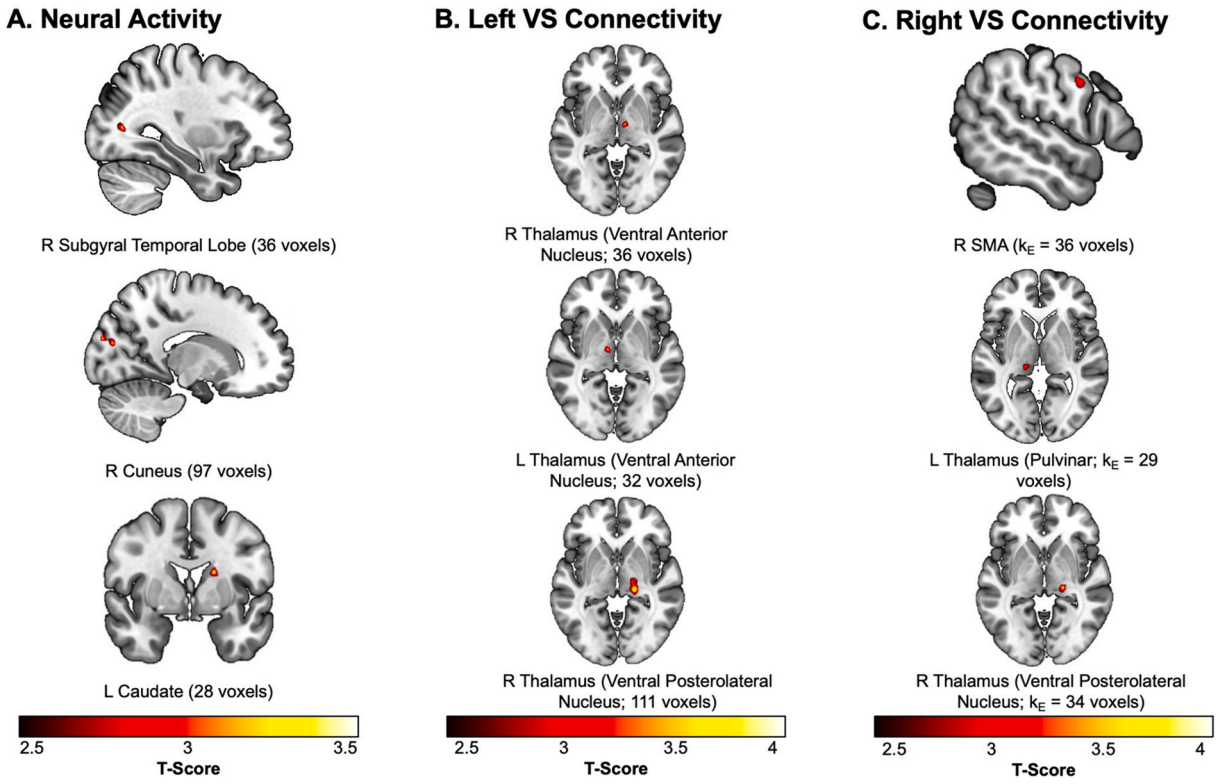


Fig. 2. Regions of Activity/Connectivity Significantly Associated with Peak Anhedonia in LASSO Regression. Note. The nine neural regions that emerged as a significantly associated with peak anhedonia (i.e. maximum score across three timepoints) at lambda.1se in the LASSO regression are presented in this figure. There are 3 separate regions under each of the sub-headers (A,B,C). Only one view of each region is shown, rather than a multi-planar view of 3 regions. **A.** activation in the right subgyral temporal lobe (32, −70, 8), right cuneus (18, −80, 18), and left caudate (-20, 2, 18); **B.** left ventral striatum (VS) connectivity to the bilateral ventral anterior nuclei of the thalamus (R: 8, −10, −2; L: −6, −14, −4) and right ventral posterolateral nucleus (18, −26, −2); and **C.** right VS connectivity to the right supplemental motor area (SMA) (-56, 4, 38), left pulvinar region of the thalamus (-14, −28, 2), and right ventral posterolateral nucleus of the thalamus (20, −24, −2); All extractions were thresholded at $p < .005$ and contiguity of 20 voxels.

Table 4
Post-hoc Hierarchical Regression Coefficients Associated with Peak Anhedonia.

Variable	Unstandardized B	*SE*	Standardized *B*	*t*	*p*
(Constant)	−.074	.110		−.675	.502
Impulsivity	.357	.103	.357	3.460	< .001 * *
Caudate Activation	.315	.141	.222	2.229	.029 *
Sub-gyral Temporal Lobe Activation	.068	.140	.055	.481	.632
Cuneus Activation	.084	.075	.126	1.126	.264
Left VS-Thalamus (Left Ventral Anterior Nucleus) Negative FC	.189	.136	.208	1.391	.169
Left VS-Thalamus (Right Ventral Anterior Nucleus) Negative FC	.009	.143	.010	.065	.949
Right VS-Thalamus (Ventral Posterior Lateral Nucleus) Negative FC	.042	.185	.035	.225	.823
Right VS-SMA Negative FC	.024	.050	.057	.481	.632
Right VS-Thalamus (Pulvinar) Negative FC	.190	.122	.189	1.552	.126
Left VS-Thalamus (Ventral Posterior Lateral) Negative FC	.164	.201	.130	.819	.416

Note. A hierarchical regression was preformed after conducting the LASSO model in order to identify the amount of variance explained with peak anhedonia as the outcome. Model 1 included impulsivity as the only predictor variable (R^2 =.100), and Model 2 included impulsivity and important neural correlates of anhedonia, as determined by the penalized regression outcome (R^2 =.501). *Significant at $\alpha = 0.05$; * *Significant at $\alpha = 0.01$; FC: Functional connectivity; VS: Ventral Striatum; SMA: Supplementary motor area.

Interestingly, anhedonia was also related to function in secondary reward systems that support behavior and cognition. Sub-gyral temporal lobe, a region involved in reward-related memory [81], and cuneus, a region involved in visual processing and reward response [82], both exhibited lower activation in people with higher anhedonia. At a systems level, predictors included negative VS FC with SMA, a region involved in body movements [83] and reward expectancy [24], and thalamic regions like the pulvinar nucleus, a higher-order subregion involved in cognition through cortico-cortico loops [84] which activates with reward anticipation [85], and the ventral anterior nucleus, which provides direct afferent input to the VS [17,86]. Putative functions of these regions suggest a role for disruptions of cue-reward association, goal-driven behaviors, reward decision-making, or updating behaviors during changing reward contexts [87]. Decision-making and motor disturbances are notable in other groups who exhibit alterations in reward-based circuitry [88] such as in people with—and at risk for—schizophrenia [89], providing further justification for investigating anhedonia as a symptom with a strong motor component. In summary, the traditional focus on experiential features of anhedonia paired with the literature's neglect of its behavioral aspects, might have limited our knowledge of the pathways to its development. Our findings involving motor regions, such as the SMA, suggest that anhedonia relates to reduced behavioral pursuit of reward, or, potentially, a higher threshold for motor response.

These findings offer insights regarding the larger role of regions such as the caudate and SMA in cognitive and motor aspects of anhedonia. Emerging models of depression emphasize the role of alterations in cost/benefit decision-making [90–92] and motor activity [93]. Effort-based decision-making involves choosing whether to engage motor processes to achieve a reward and has been suggested as a key component of anhedonia and reward motivation [92]. Studies using the Effort-Expenditure for Rewards Task, for example, have found that adults with anhedonia choose greater-effort/greater reward options less often compared with people without anhedonia, especially when rewards are uncertain [90]. In contexts involving the decision to act to obtain a possible reward, the caudate is postulated to weigh the cost and benefits of rewards [94], while the SMA is involved in motor planning, initiation, and coordination of reward-driven action [95]. Consistent with this, typically developing adults exhibit caudate and SMA activation during effort-based tasks [96,97]. Similarly, psychomotor slowing, which includes features such as lower overall activity level, occurs with depression [98] and is associated with altered function in neural systems that contribute to both reward and motor processes [99]. Corticostriatal pathways, whose regions include SMA and caudate, are involved in coordinating reward, cognitive, and motor processes in the service of goal-directed behavior [100]. Disruptions in these pathways are postulated to contribute to both decision-making and behavioral aspects of anhedonia [101].

Within this context, while our findings of higher activation in the caudate and SMA in those with higher anhedonia are surprising in light of other studies' findings of lower caudate activation during cost-benefit decision-making in people with depression [102], the pattern in the current study may reflect overestimation of motor effort required to initiate actions towards goals and rewards. This could indicate a mismatch between the perceived coordination of motivation, effort, and motor engagement needed to attain rewards and the actual value of the rewards experienced, leading to a combination of increased activation in the caudate and SMA, yet little satisfaction from the outcome (i.e., anhedonia). Given that we observed effects in these cognitive and motor-related regions of reward systems during reward receipt, we are constrained in interpreting how they might reflect alterations in the pursuit of rewards. However, the patterns in the current study could reflect alterations that feed forward to influence impairments in motivation, decision-making, and response initiation in the context of potential future rewards. The integration of the effort-based decision-making and reward processing literatures may serve as a foundation for future work to continue to disentangle unexpected findings of overactivation of reward and motor circuitry and associations with anhedonia.

In tandem, common findings of neural reward correlates of adolescent depression and anhedonia, such as higher VS-mPFC FC [28] or higher mPFC [103], did not emerge as predictors. Perhaps coordinated FC beyond traditional neural reward systems has influence on the development of anhedonia, a symptom linked not only to reduced pleasure but to reduced motivation and activity level [104]. Contrary to our hypotheses, anhedonia was unrelated to demographic characteristics and clinical factors. Potentially, age, gender, and race/ethnicity differences in anhedonia may change across adolescence, as with experience sampling evidence that sex differences in the experience of day-to-day pleasure are more evident in early than late adolescence [105]. Gender differences could also emerge for specific subtypes such as social anhedonia, as boys but not girls with lower sociability at age 3 report more social anhedonia in adolescence [106]. Developmental studies should continue to employ long-term, longitudinal designs to better understand these relationships. Furthermore, the lack of clinical predictors (beyond impulsivity) could reflect inclusion of participants who varied in risk but were generally healthy. Future work with adolescents varying in current psychopathology and risk for SMI will be informative.

Our study was not designed to examine pathways to developing specific disorders, and the enrollment of adolescents across varying types of family psychopathology was intended to enhance transdiagnostic representation rather than allow comparison of subgroups. As our sample primarily consisted of participants at familial risk for depression, our results might have greater relevance to the development of anhedonia in the context of depression than in the context of bipolar

or schizophrenia spectrum psychopathology. Predictors of adolescent anhedonia could certainly differ among these three populations or could vary based on other factors, such as overall severity, functional impairment, or pattern of comorbidity. Future research should consider whether the association of anhedonia with neural, clinical, or demographic factors varies with the severity or type of psychopathology among first-degree relatives. Additionally, the potential predictors we studied may differ from those associated with conversion to a full-blown affective or psychotic disorder, various stages of clinical course, or treatment response. Studies designed to distinguish differences in development of anhedonia in affective and psychotic disorders are thus welcome. Although our findings hint at risk for psychopathology, given anhedonia's role as a precursor of SMI [5], next steps should include prospective longitudinal assessment beyond the onset of SMI to examine the interplay of anhedonia, brain development, and demographic and clinical factors.

Our findings about the possible prominence of neural reward systems in the development of anhedonia (i.e., neural factors explaining 40 % of variance in peak anhedonia in our post hoc regression model) could have clinical applications, for instance by potentially informing strategies for the early identification or stratification of youth at risk for anhedonia. This application could also be relevant to identifying youth likely to develop related syndromes such as depression. While MRI scanning is not currently a feasible option for assessing risk for psychopathology—in terms of cost, access, or person-level value—it is worth considering the clinical implications of these findings beyond MRI assessment. For example, self-report or behavioral assays that are strongly related to function in neural reward systems could be developed for identifying youth likely to experience anhedonia. In concert with this, implications for assessment could include tempering the emphasis on traditional clinical or demographic indicators, which might have limited utility compared with neural indicators. At an intervention level, these findings suggest that youth with clinically meaningful anhedonia could benefit from brain-focused treatments or psychosocial treatments known to influence physiologic components of reward (e.g., Positive Affect Treatment; [107]). In line with this, several of our ongoing studies investigate the use of Transcranial Magnetic Stimulation (TMS) targeting reward systems to address anhedonic depression in youth (e.g., [108]). Finally, a more specific and practical approach derived from these findings could be monitoring impulsivity through adolescence to prevent possible progression to anhedonia.

While the study has many strengths—including the multi-modal approach, longitudinal design, age range, use of a machine-learning technique, and transdiagnostic definition of risk—our conclusions are limited by several factors. The ethnic/racial composition of the local population precluded us from fully investigating ethnicity differences in anhedonia severity. Furthermore, our approach also points to the value of capturing elaborated versions of clinical symptoms (e.g., gradations in suicidal thoughts and behaviors). Examining peak anhedonia captures within-person fluctuations in anhedonia across adolescence more directly than a single timepoint or mean across multiple timepoints. However, future work should examine anhedonia using more frequent and higher-duration assessment schedules and real-world measurement (e.g. ecological momentary) assessment to model more nuanced fluctuations. Additionally, our approach to identifying neural regions for inclusion in the main model relied on statistical thresholds selected for detecting regions that could be broadly relevant to anhedonia and was not intended for drawing meaningful inferences about activation and FC associations with anhedonia in absolute terms. Combining the aforementioned imaging methods with the rigorous strategy of LASSO penalized regression added additional confidence to our findings by reducing the number of neural factors from 14 to 9, including one that remained significant using traditional statistical methods (i.e., caudate activation). These data-driven results should be validated in independent, larger samples. Lastly, future work should examine other correlates and putative causes of anhedonia, including childhood maltreatment and social adversity [109–111]

5. Conclusion

In sum, this longitudinal, transdiagnostic study considered demographic, clinical, and neural factors in the development of anhedonia. The findings that neural response to reward contributed to adolescents' peak anhedonia beyond the contributions of demographic and clinical factors indicate that neural reward functioning could play key role in progression toward affective psychopathology. The involvement of regions relevant to motor systems could reframe anhedonia as a symptom of dysrupted motor function. Together, findings underscore reward processing as a mechanism in the development of anhedonia, suggest promising directions for developmental psychopathology, and emphasize the value of discovery efforts for neural markers.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and the World Medical Association Declaration of Helsinki.

Declaration of Competing Interest

The authors have nothing to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.xjmad.2025.100116.

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