REVIEW

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A Systematic Review: Investigating Biomarkers of Anhedonia and Amotivation in Depression and Cannabis Use

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Objective: To assess biological factors associated with anhedonia in depression and amotivation in cannabis use (PROSPERO: CRD42023422438).

Method: A systematic review was conducted of 8 electronic databases. Inclusion criteria included original research studies that investigated the association of biological factors or behavioral tasks with depression combined with concepts of anhedonia or cannabis combined with concepts of amotivation including apathy.

Results: The review included 44 articles that evaluated biological factors associated with anhedonia in depression and 2 articles that evaluated biological factors associated with amotivation in cannabis use. Overall, anhedonia was operationalized as loss of anticipatory pleasure or consummatory pleasure using a range of measures. No biological factor or behavioral task was consistently associated with anhedonia in depression. Neuroimaging studies encompassed heterogeneous study designs and analytic approaches, with little overlap among findings of brain regions associated with anhedonia. Regions of interest most frequently associated with anhedonia across functional and structural neuroimaging and tasked-based neuroimaging studies included the anterior cingulate cortex, nucleus accumbens, and medial prefrontal cortex. No biochemical marker, including interleukin-6 or C-reactive protein, was consistently associated with anhedonia, and most tested associations between biochemical markers and anhedonia were not significant.

Conclusion: Heterogeneous study designs and self-reported assessments of anhedonia have yielded variable findings across the literature. Neuroimaging studies of adolescents with depression and cannabis use reveal similar neurobiological deficits in reward processing. Prospectively examining these deficits may inform developmental pathways that underlie the etiology of these disorders and identify novel treatment targets.

Plain language summary: Depression and cannabis use are both common among adolescents. Clinical phenotypes of anhedonia in depression and amotivation in cannabis use may overlap, complicating diagnostic assessment and management. This systematic review identified 44 articles that evaluated biologic factors associated with anhedonia in depression and two articles that evaluated biologic factors associated with amotivation in cannabis use. Most articles were neuroimaging studies that encompassed mixed study designs. Neuroimaging studies of adolescents with depression and cannabis use revealed similar neurobiological deficits in reward processing. Prospectively examining these deficits may inform developmental pathways that underly the etiology of these disorders and identify distinct treatment targets.

Study preregistration information: A systematic review of anhedonia and amotivation in depression and cannabis use; https://www.crd.york.ac.uk/PROSPERO/view/CRD42023422438

Diversity & Inclusion Statement: One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented racial and/or ethnic groups in science. One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented sexual and/or gender groups in science. We actively worked to promote sex and gender balance in our author group. We actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our author group. While citing references scientifically relevant for this work, we also actively worked to promote sex and gender balance in our reference list. While citing references scientifically relevant for this work, we also actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our reference list.

Key words: amotivation; anhedonia; apathy; cannabis; depression

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Adolescence is a critical period of neurodevelopment that marks the onset of many mental health disorders, including depression and substance use disorders. Depression is one of the most common mental health concerns among youth and a leading cause of disability worldwide.[1] The prevalence of depression has risen sharply among youth over the past decade,[2] with 15% to 17% of youth ages 12 to 25 years developing a major depressive episode within the past year.[3] This is particularly concerning given the concurrent rise in suicide rates among youth over the past 2 decades.[4]

Depression encompasses a spectrum of difficulties, ranging from transiently low mood to major depressive disorder (MDD).[2] A diagnosis of MDD requires either

depressed mood or loss of interest or pleasure, in addition to other symptoms.[5] It is increasingly evident that persistent loss of pleasure leading to a reduced capacity for pleasure, or anhedonia, is associated with depression that is more difficult to treat.[6,7] Indeed, anhedonia in depression is associated with longer time until remission of depression, fewer depression-free days, increased depression severity, and increased suicidality.[6,7] Anhedonia may also be the most important symptom linking depression with common pleasure-seeking behaviors among adolescents, such as cannabis use.[8] While not specific to depression, anhedonia more often affects multiple pleasure domains in MDD compared with other psychiatric disorders[9] and may represent a precipitant or a consequence of cannabis use among adolescents who may be more vulnerable than adults to harmful effects of cannabis.[10] Anhedonia is also experienced across temporal phases of the reward cycle, conceptualized as anticipatory (in anticipation of an event) and consummatory (during an event) pleasure.[11]

Anhedonia has proven challenging to study as the concept comprises multiple constructs, including reward anticipation, motivation to exert effort to gain reward, consummatory pleasure, and integration of reward learning.[12] Studies of the neurobiological etiology of anhedonia in adults have primarily focused on the reward pathway and inflammatory alterations,[13,14] whereas adolescent studies have focused on pleiotropic genetic contributions and aberrant function in the dorsal striatum.[8] Extant studies in adults also implicate involvement of the mesocorticolimbic pathway within dopaminergic, glutamatergic, and γ-aminobutyric acidergic (GABAergic) neurons between the nucleus accumbens (NAc), ventral striatum, orbitofrontal cortex (OFC), and medial prefrontal cortex (PFC).[11,13,15–17] Cannabis use compounds these reward processing deficits, with distinct as well as interactive effects on the reward system.[18]

Adolescence is unquestionably a period marked by experimenting with substance use. Most problematic substance use begins before age 18 years.[3,19] Cannabis is among the most commonly used substances, with Monitoring the Future, a biennial survey of 8th-, 10th-, and 12th-grade students in the United States, reporting the lifetime prevalence of any cannabis use remaining steady around 38% among 12th-grade students in the United States in 2022.[20] However, rates have continued to increase over the past decade among emerging adults (ages 18-25 years),[3] who remain at risk for the neurodevelopmental impacts of cannabis use.[21] In addition to altered cognition,[22] the central concern of the effects of cannabis on motivation and reward processing complicate the evaluation and treatment of adolescents in psychiatric settings when recreational use crosses the threshold to pathological use.[18] Daily cannabis use during adolescence is associated with decreased motivation,[18] and use at a younger age has been associated with reduced reward learning in late adolescence and early adulthood.[22] This has been conceptualized as amotivation syndrome, which is a constellation of symptoms including introversion, passivity, and lack of achievement orientation.[23] However, the etiology of amotivation syndrome as a unique phenomenon has not been described or compared to concepts such as anhedonia.

Studies of cannabis use have not consistently described the phenomenon of amotivation syndrome, and some studies explain amotivation by the confounding effects of depression[23–25] or, more broadly, apathy.[24] Yet, alterations in reward processing during cannabis use appear phenotypically distinct from depression and have been described heterogeneously as amotivation, avolition, apathy, and anhedonia, with each likely representing different subsets of reward deficits.[26,27] Consequently, researchers have used a broad range of validated measures to assess complex phenotypes proximal to amotivation. Similar to the literature on depression, studies of amotivation in adults who use cannabis have implicated dopaminergic, opioidergic, and GABAergic systems within the mesocorticolimbic circuit.[27] Further understanding of how amotivation related to cannabis use compares and contrasts to anhedonia in depression would improve diagnostic clarity and facilitate treatment priorities.

When evaluating the depression and cannabis use literatures side by side, the clinical phenotypes of anhedonia in depression and amotivation in cannabis use may overlap, complicating diagnostic assessment and management. In this review, we aimed to assess biological similarities and differences between anhedonia in depression and amotivation in cannabis use. We hypothesized that neurobiological factors would clearly delineate depression from cannabis-related reward dysfunction; however, we anticipated that the synthesis of the literature may be limited to a few studies with disparate findings and methodologies. Nevertheless, we conducted this review to determine future directions for research on anhedonia and amotivation and to help to focus research on depression-related anhedonia to inform research on cannabis use–related amotivation while clarifying methods and brain systems that might be involved.

METHOD

The review protocol was registered in PROSPERO International Prospective Register of Systematic Reviews database (ID: CRD42023422438) before conducting the search and completed per PRISMA reporting guidelines (Supplement 1, available online).

Search Strategy

A health sciences librarian (E.S.) created search strategies based on depression combined with concepts of anhedonia or cannabis combined with concepts of amotivation that studied biological factors or behavioral tasks in adolescents. Searches were conducted in Ovid MEDLINE, PsycINFO, Cumulated Index to Nursing and Allied Health Literature (CINAHL), Embase, Web of Science, Cochrane Library, and Allied and Complementary Medicine. The search strategy for each database, including the native search syntax, is provided in Table S1, available online. The search was conducted in 2 stages, with the last search completed on June 27, 2023. Searches were limited to English language with no other limits applied.

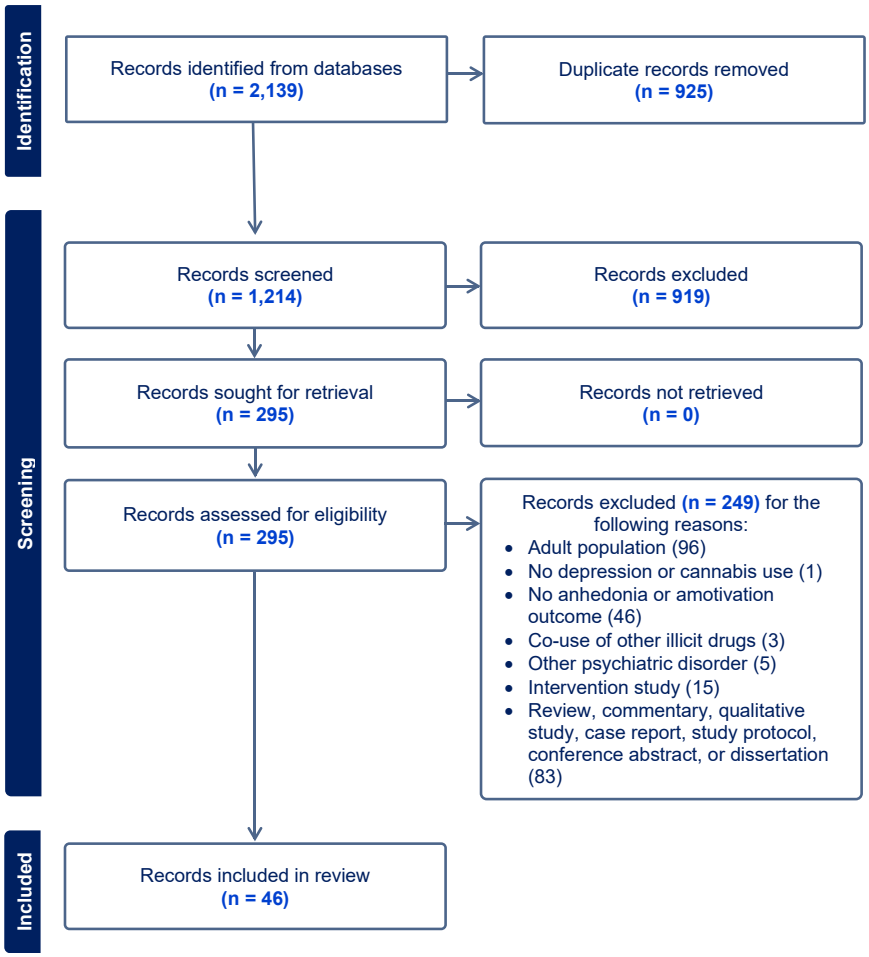
Study Selection and Data Extraction

A total of 2,139 records were retrieved and uploaded into Covidence (Figure 1). After deduplication, 1,214 unique citations were screened for inclusion. Inclusion criteria included peer-reviewed original research of human studies of youth cohorts (mean age $\leq$21 years) that investigated the association of study of anhedonia in depression or amotivation in nonmedical use of cannabis with a biological factor or behavioral task. Studies that recruited youth with other psychiatric disorders, studies of use of illicit drugs other than cannabis, and studies with medical disease cohorts were excluded. Screening of each title and abstract and full text was completed independently by 2 authors (J.H., B.C., R.M., P.A., D.B., E.E.S.). At each screening step, discrepancies were discussed and resolved by consensus. Two authors (J.H., B.C., R.M., P.A., D.B., E.E.S.) independently extracted data for the complete set of included articles using a shared template.

Study Quality

The quality of included articles was assessed adapting the well-validated QUADAS checklist derived from the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis.[28,29]

FIGURE 1 PRISMA Diagram



Two authors independently assessed quality criteria (J.H., B.C., R.M., P.A., D.B., E.E.S.) of each extracted article including selection, measurement, detection, and selective reporting biases, as well as limitation due to incomplete data (Table S2, available online). No studies were excluded based on quality rating.

RESULTS

Of the 1,214 unique records identified as possibly relevant (Figure 1), 295 were considered relevant, and full-text review was conducted (Table S3, available online). Of these, 249 studies were excluded because they did not meet inclusion/exclusion criteria. The most common reason for exclusion was adult-age study population. There were 44 articles that evaluated biological factors associated with anhedonia in depression across 37 primary studies with more than 8,335 participants (Table 1). There were 2 articles that evaluated biological factors associated with amotivation in cannabis use across 81 participants (Table 2). Data extracted for summary focused on analyses that related biological factors to anhedonia and amotivation. Detailed characteristics and references of the biological factors are provided in the full database of the 46 articles provided in Tables S4-S7, available online. Because reported results had a high degree of heterogeneity regarding several characteristics (variable sample sizes and demographics of study populations, variable measures and methods applied to biological factors, and variable operational definitions of anhedonia and amotivation), data extracted from articles were qualitatively summarized.

Depression and Anhedonia

The numerous measures used to assess anhedonia in the studies reviewed herein focused on loss of interest or pleasure as their operational definitions of anhedonia. A self-report measure of anhedonia was used in 21 (47.7%) studies, including the Revised Physical Anhedonia Scale (RPhA), which measures consummatory pleasure[76]; Revised Social Anhedonia Scale (RSAS), which measures social enjoyment[76]; Snaith-Hamilton Pleasure Scale (SHAPS), which measures consummatory pleasure[77]; and Temporal Experience of Pleasure Scale (TEPS), which measures anticipatory and consummatory pleasure.[78] The remaining 23 (52.3%) studies derived anhedonia from a subset of questions selected from standardized self-report measures of depression (eg, Beck Depression Inventory [BDI]) or semistructured interview (eg, Schedule for Affective Disorders and Schizophrenia for School-Age Children [K-SADS]).

Behavioral Tasks

Four articles were identified that used only behavioral tasks to understand anhedonia in depression (n = 224 participants, range 15-132). Of the 3 studies that reported gender, 67% to 100% of participants were female. Only 1 study reported ethnicity, with 75% of patients identifying as White (Table 1). Two studies identified anticipatory anhedonia as a significant predictor of diminished hedonic reactions. Specifically, Chentsova-Dutton and Hanley[30] measured heart rate in response to tasting chocolate samples in adolescents with and without MDD. Multiple logistic regression found that only anticipatory anhedonia was a significant predictor of heart rates (Table 1). Similarly, Frey *et al.*[31] explored both anticipatory and consummatory anhedonia related to "liking," "wanting," and "willingness to exert effort" of 3 reward types (gustatory, visual, and monetary), finding that high anticipatory anhedonia was correlated with lower liking and wanting ratings. These studies suggest that anticipatory anhedonia predicts response to hedonic reactions.

Two studies identified an association between anticipatory anhedonia and diminished learning or response to reward cues. Pizzagalli *et al.*[32] used a signal-detection task based on a differential reinforcement schedule that was designed to provide an objective assessment of participants' likelihood and ability to adjust behavior in response to rewards. Anhedonia was not significantly associated with change response bias (ie, change in response after undergoing reward cue) at baseline (Table 1). Further, participants failing to develop a response bias at the first testing reported high anhedonia symptoms at 1-month follow-up.[32] Likewise, using a task to assess maximization of reward with minimal physical effort, Frey *et al.*[31] found that anticipatory anhedonia was associated with lower reward learning accuracy. These results suggest that anhedonia is related to deficiencies in learning from rewarding cues.

Conversely, using a social emotional task, Setterfield *et al.*[33] found that anticipatory social anhedonia did not predict reduced helping behavior (Table 1). Whereas depression predicted reduced helping behavior among adolescent girls,[33] once controlling for depression, anhedonia was not associated with differences in helping behavior, suggesting that depressive symptoms other than anhedonia reduced the likelihood of helping behavior.

Neuroimaging

Neuroimaging paradigms were investigated in 28 studies comprising 6,268 participants (range 27-2,566) (Table 1). One study used the Adolescent Brain Cognitive Development (ABCD) Study,[43] and 3 used the IMAGEN study.[36,46,50] The majority of studies comprised predominantly female participants, with race/ethnicity ranging widely from 0% to 100% White. Figure 2 presents regions of interest (ROIs) that overlap across neuroimaging studies.

TABLE 1 Studies of Depression and Anhedonia

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
Chentsova-Dutton *et al.*, 2010[30]	United States	Cross-sectional	Undergraduate students. n = 61, mean (SD) age = 19.4 (1.4) y, 75% female, 75% White.	BDI, DID	TEPS	Hedonic reaction: anticipated, experienced (chocolate tasting), and recalled	Anticipatory anhedonia was associated with anticipated HRs (Pearson r = 0.35, $p < .001$), but not experienced or recalled HRs.[a] Experienced anhedonia was associated with recalled HRs (Pearson r = 0.26, $p <$ .01), but not anticipated or experienced HRs.[a] In multiple regressions models predicting HRs, only anticipatory anhedonia emerged as a significant predictor for anticipated HR (β = .37, B = .70, SE = 0.26, $p < .001$).
Frey *et al.*, 2023[31]	United Kingdom	Cross-sectional	Community-recruited youth experiencing depression. n = 132, mean (SD) age = 20 (2.74) y.	BDI	TEPS	Probabilistic instrumental learning task with monetary, visual, and gustatory rewards	High anticipatory anhedonia correlated with lower "liking" rating ($r = -0.22$, $p = .008$) and "wanting" rating ($r = 0.20$, $p = .012$) as well as lower reward learning accuracy ($r = 0.21$, $p = .009$).
Pizzagalli *et al.*, 2005[32]	United States	Cross-sectional	Undergraduate students. High BDI group: n = 15, mean (SD) age = 19.9 (1.4) y, 67% female. Low BDI group: n = 21, mean (SD) age = 20.8 (3.9) y, 67% female.	BDI-II	RPhA, RSAS	Signal-detection task	Change response bias was negatively correlated with total BDI score ($r = -0.46$, $p < .025$) and BDI melancholic subscore ($r = -0.41$, $p < .05$), but not social anhedonia or physical anhedonia.[a] Participants with negative change response at first testing reported high anhedonic symptoms at 1-mo follow-up (mean BDI anhedonic score 2.22 vs 1.06 in positive change response group; $p = .03$).
Setterfield *et al.*, 2016[33]	United Kingdom	Cross-sectional	Community-recruited female youth stratified by BDI score. High BDI: n = 16, mean (SD) age = 19.2 (1.2) y. Low BDI: n = 30, mean (SD) age = 20.2 (5.4) y.	BDI	RPhA, RSAS	SET with helping behavior assessment	In youth with high depressive symptoms, positive emotion ratings on SET were negatively correlated with RSAS ($r = -0.74$, $p = .001$) and RPhA scores ($r = -0.72$, $p = .002$). Negative emotion ratings

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
							were positively correlated with RSAS ($r = 0.51$, $p = .043$) and RPhA ($r = 0.61$, $p = .012$) scores. In youth with low depressive symptoms, positive emotion ratings on SET were negatively correlated with RSAS ($r = -0.42$, $p = .020$) and RPhA ($r = -0.62$, $p < .001$) scores.
Neuroimaging							
Auerbach *et al.*, 2017[34]	United States	Longitudinal	Community-recruited adolescent female participants. $n = 50$, mean (SD) age = 13.0 (0.8) y, 78% White.	K-SADS-PL, MFQ	SHAPS	fMRI, Chatroom Task	There was a significant relation between smaller right nucleus accumbens volume and greater anhedonia severity ($b = -.45$, $p = .01$, $pr = -0.37$). Smaller left ($\Delta F_{1,31} = 8.82$, $p = .006$; $\Delta R_2 = 0.14$) and right ($\Delta F_{1,31} = 7.16$, $p = .01$; $\Delta R_2 = 0.11$) putamen volume predicted greater anhedonia severity at 3-mo follow-up, accounting for 53% and 51% of the variance, respectively. Neither caudate nor nucleus accumbens volume predicted anhedonic symptoms.[a] Putamen volume significantly moderated relation between peer feedback and anhedonia (putamen × acceptance interaction, left putamen: $\Delta F_{1,29} = 4.90$, $p = .03$, $\Delta R_2 = 0.06$; right putamen: $\Delta F_{1,29} = 5.16$, $p = .03$, $\Delta R_2 = .05$).
Bradley *et al.*, 2018[35]	United States	Cross-sectional	Adolescents with MDD and health controls. MDD: n = 20, mean (SD) age = 15.5 (2.5) y, 40% female, 60% White. Control: n = 16, mean (SD) age = 15.6 (2.6) y, 50% female, 56% White.	K-SADS-PL, CDRS-R, BDI	2 items from BDI and 1 item from CDRS-R	GABA-edited ^{1}H-MRS	Within the MDD group, striatal GABA was not correlated with anhedonia.[a] Striatal GABA was significantly higher in youth with MDD compared with controls ($t_{34} = -3.81$, $p = .001$).
Eckstrand *et al.*, 2019[36]	United States	Longitudinal	Clinical cohort. n = 52, mean (SD) age = 21.4 (2.3) y, 81% female, 40% White.	HAM-D, MASQ-AD	SHAPS	Monetary reward fMRI task	Left ventral striatum activation to reward prediction error was negatively associated with change in self-reported anhedonia symptoms during a 6-mo period ($\beta = -6.152$, $p = .04$).

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
Freed *et al.*, 2017 (USA)[37]	United States	Cross-sectional	Community-recruited adolescents. Depression: n = 19, mean (SD) age = 15.7 (2.5) y, 42% female, 32% White. HC: n = 8, mean (SD) age = 16.1 (3.4) y, 63% female, 38% White.	CDRS-R	SHAPS	Structural MRI: measuring occipital glutathione and comparing with neurometabolites choline, creatine, and *N*-acetylaspartate by ^{1}H-MRS	No correlation was found between glutathione levels and SHAPS scores in the full sample or in the MDD group.[a] Occipital glutathione levels were lower in adolescents with depression compared with HCs (HC = $2.39 \times 10^{-3} \pm 0.66 \times 10^{-3}$, MDD = $1.80 \times 10^{-3} \pm 0.29 \times 10^{-3}$, $p = .04$). No group differences were found in other neurometabolites in the occipital cortex (choline, creatine, *N*-acetylaspartate).
Gabbay *et al.*, 2012[38]	United States	Cross-sectional	Clinical cohort and community-recruited controls. Depression: n = 20, mean (SD) age = 16.7 (2.7) y, 60% female, 40% White. HC: n = 21, mean (SD) age = 16.2 (1.6) y, 68% female, 43% White.	Individual assessment, CDRS-R, K-SADS, and BDI-II	2 items on BDI-II and 1item on CDRS-R	Structural MRI: anterior cingulate cortex GABA levels	Anterior cingulate cortex white matter percentage trended lower in anhedonic MDD subgroup compared with HC (mean [SD] = 36.2% [6.6%] vs 39.8% [5.8%]; $t = 1.82$; $p = .08$). Anterior cingulate cortex GABA decreased in anhedonic subgroup compared with HC (2.14×10^{-3} [0.37×10^{-3}] vs 2.68×10^{-3} [0.27×10^{-3}]; $df = 33$; $t = 4.08$; $p < .001$; $p_{Tukey} < .001$) and nonanhedonic MDD subgroup (2.14×10^{3} [0.37×10^{-3}] vs 2.60×10^{-3} [0.43×10^{-3}]; $df = 33$; $t = 2.35$; $p = .02$; $p_{Tukey} = .06$). Significance persisted controlling for white matter differences. GABA and anhedonia trends were not confounded by MDD severity.[a]
Gabbay *et al.*, 2013[39]	United States	Cross-sectional	Clinical cohort and community-recruited controls. Depression: n = 21, mean (SD) age = 17.1 (2.5) y, 57% female, 48% White. HC: n = 21, mean (SD) age = 16.3 (1.4) y, 57% female, 48% White.	*DSM-IV-TR* diagnostic criteria and CDRS-R	2 items on BDI-II and 1 item on CDRS-R	Resting-state fMRI measured intrinsic functional connectivity among bilateral striatal seeds (dorsal caudate, ventral caudate, nucleus accumbens, dorsal-rostral putamen, dorsal-caudate putamen, ventral-rostral putamen), and remaining brain regions	Anhedonia positively correlated with intrinsic functional connectivity strength of ventral and dorsal caudate seeds with supplementary motor area (left dorsal caudate supplementary motor area: $Z = 4.18$, $p < .001$; left ventral caudate supplementary motor area: $Z = 4.14$, $p < .001$), middle frontal gyrus ($Z = 4.92$, $p = .001$), supramarginal gyrus ($Z = 3.58$, $p = .003$), precuneus ($Z = 3.88$, $p < .001$), and

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
							pregenual anterior cingulate cortex ($Z = 4.06$, $p = .004$). Anhedonia was positively correlated with intrinsic functional connectivity strength of right dorsal rostral putamen and supramarginal gyrus ($Z = 4.01$, $p = .003$). Anhedonia was negatively correlated with intrinsic functional connectivity strength between left nucleus accumbens and subgenual anterior cingulate cortex and left caudate ($Z = 4.70$, $p < .001$). Anhedonia was negatively correlated with intrinsic functional connectivity strength between right nucleus accumbens and occipital fusiform cortex ($Z = 3.82$, $p = .005$).
Gabbay *et al.*, 2017[40]	United States	Cross-sectional	Clinical cohort. MDD: n = 44, mean (SD) age = 16.3 (2.6) y, 52% female, 39% White. HC: n = 36, mean (SD) age = 15.8 (2.1) y, 64% female, 36% White.	K-SADS-PL, CDRS-R	2 items from BDI and 1 item from CDRS-R	GABA-edited ^{1}H-MRS	GABA levels were different between anhedonic and non-anhedonic MDD subgroups and HC ($F_{2,72} = 6.47$, $p = .003$). GABA levels were lower in anhedonic youth with MDD compared with HC in pairwise comparisons ($p = .002$). However, GABA levels did not differ between anhedonic and non-anhedonic MDD subgroups or between non-anhedonic MDD and HC groups.[a] Within the MDD group, anhedonia ($\beta = -.43$, $p = .02$), but not depression severity, anxiety, or suicidality, significantly predicted GABA in MDD.[a]
Hager *et al.*, 2022[41]	United States	Cross-sectional	Undergraduate cohort. High depression: n = 30, mean (SD) age = 21.5 (5.5) y, 83% female, 43% White. Low depression: n = 61, age = 22.5 (6.2) y, 66% female, 49% White.	BDI-II	SHAPS	Reward positivity estimated from Modified Doors Task and Source Memory Task, EEG event-related potential	Reward positivity was not associated with depression or anhedonia.[a] There were no main effects of depression severity, depression group, or anhedonia severity on event-related potential response and no interaction of feedback with depression severity, depression

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
							group, or anhedonia severity.[a] Time domain event-related potential analyses found no main effects of depression severity, depression group, or anhedonia severity on either delta or theta and no interactions with feedback.[a]
Healey *et al.*, 2014[42]	United States	Cross-sectional	Community-recruited adolescents. n = 27, mean (SD) age = 20.4 (0.80) y, 52% female, 78% White.	CES-D	CES-D anhedonia subscale, RSAS	Block design social reward (likability) fMRI task	Greater social anhedonia associated with increased response to likability ratings within a specific cluster within the mPFC (4,826 voxels, [1,44,41], $t = 4.01$, $p < .05$). This cluster includes the dorsal mPFC, rostral mPFC, and pregenual anterior cingulate. Higher social anhedonia was associated with greater positive connectivity between the bilateral nucleus accumbens and mPFC in response to mutual liking > received liking (peak in BA9, 1,110 voxels, [−12,41,33], $t = 3.44$, $p < .05$; peak in BA32, 292 voxels, [−12,29,36], $t = 3.26$, $p < .05$). This cluster included the dorsal mPFC, pregenual anterior cingulate, rostral mPFC, and anterodorsal anterior cingulate.
Henderson *et al.*, 2013[43]	United States	Cross-sectional	Community- and clinic-recruited adolescents. Depression: n = 17, mean (SD) age = 16.8 (2.2) y, 47% female, 53% White. Control group: n = 16, mean (SD) age = 16.4 (1.4) y, 63% female, 38% White.	CDRS-R, BDI-II	2 items on BDI-II and 1 item on CDRS-R	fMRI	Increased anhedonia was positively related to fractional anisotropy in a cluster in posterior cingulum near the hippocampus (cluster size = 13) and negatively related to fractional anisotropy in anterior limb of the internal capsule (cluster size = 14), OFC projection fibers (cluster size = 12), and posterior cingulum (cluster size = 10). Increased anhedonia was positively related to mean diffusivity in OFC projection fibers (cluster size = 14), external capsule (cluster size = 11), sagittal stratum (cluster size = 11). Anhedonia was positively correlated with axial diffusivity in the corticospinal tract (cluster size = 34) and projection fibers into the occipital cortex (cluster size = 12).

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
Liang *et al.*, 2023[44]	China	Cross-sectional	Clinical cohort. Melancholic MDD group (MDD-MEL): n = 57, mean (SD) age = 15.3 (2.2) y, 67% female. Nonmelancholic MDD group (MDD-nMEL): n = 44, mean (SD) age = 16.3 (2.3) y, 68% female. Control group: n = 58, mean (SD) age = 19.2 (2.5) y, 85% female.	HAM-D	SHAPS	fNIRS, RBANS	RBANS attention score was negatively correlated with SHAPS score ($r = -0.388$, $p = .034$) in MDD-MEL group. There were significant differences in 5 channels in MDD-MEL group compared with controls ($p < .05$). In the MDD-MEL group, β values of 2 channels were negatively correlated with SHAPS score ($p = .027$ and $p = .004$). One channel showed a partial mediating effect between SHAPS score and attention score ($c' = -1.419$, $p < .001$).
Liu *et al.*, 2022[45]	China	Cross-sectional	Community-recruited. Depression: n = 33, mean (SD) age = 20.8 (1.75) y, 61% female. Control group: n = 31, mean (SD) age = 20.8 (1.75) y, 45% female.	BDI-II	Anhedonia subscale of *DSM-5* personality inventory	EEG with gambling task	Anhedonia had an indirect effect on reward sensitivity (0.173, bootstrap SE = 0.068).
Luby *et al.*, 2018[46]	United States	Longitudinal	Community-recruited children ages 3-6 y at baseline oversampled for depression. Scan 1: n = 175, mean (SD) age = 10.3 (1.27) y, 48% female, 55% White. Scan 2: n = 160, mean (SD) age = 11.8 (1.23) y. Scan 3: n = 139, mean (SD) age = 13.0 (1.16) y. Scan 4: n = 135, mean (SD) age = 16.3 (1.11) y.	CDI	CDI anhedonia subscale	fMRI	There was a significant interaction of anhedonia by age in multilevel linear model of OFC volume and thickness, with higher levels of anhedonia being associated with steeper decline in OFC volume ($\beta = -.0102$, SE = 0.0033, $t = -3.06$, $p = .0025$) and thickness ($\beta = -.0032$, SE = 0.0011, $t = -2.96$, $p = .0036$) with age. Anhedonia at scan 3 was weakly correlated with alcohol/cannabis use frequency ($r = 0.19$, $p = .0474$). Residualized OFC volume was positively associated with onset of cannabis use ($\beta = 2021.9$, SE = 610.7, $t = 3.31$, $p = .0009$), whereas OFC thickness was negatively associated with onset of cannabis use ($\beta = -12198.0$, SE = 0.0069, $t = .00$, $p < .0001$) in zero-inflated Poisson regression models incorporating time-varying anhedonia scores. OFC thickness was negatively associated with

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
							frequency of cannabis use ($\beta = -54.2$, SE = 17.8, $t = -3.04$, $p = .0024$); OFC volume was not associated with frequency of cannabis use.[a]
Luking *et al.*, 2016[47]	United States	Cross-sectional	Community-recruited children. High risk: n = 16, mean (SD) age = 9.1 (1.1) y, 50% female, 75% White. Low risk: n = 32, mean (SD) age = 9.3 (1.0) y, 53% female, 75% White.	CDI	CDI anhedonia subscale	fMRI with gambling task card guessing game	Anhedonia negatively predicted response to gain-loss within the insula and anterior cingulate in the voxelwise regression (insula: $\beta = -.75$ and $\beta = -.70$, $t = -4.29$ and $t = -3.88$, $p \leq .001$ and $p < .001$; anterior cingulate: $\beta = -.61$, $t = -3.19$, $p = .003$). Anhedonia predicted reduced deactivation to loss feedback in the anterior cingulate ($\beta = .54$, $t = 2.69$, $p = .01$).
McVoy *et al.*, 2019[48]	United States	Cross-sectional	Clinical cohort. MDD: n = 25, mean (SD) age = 16.0 (0.9) y, 80% female, 84% White. Control: n = 15, mean (SD) age = 15.4 (1.0) y, 73% female, 87% White.	CDRS-R	SHAPS	Resting-state EEG	SHAPS total score was correlated with average alpha coherence overall [$r_s(33) = -0.41$, $p = 0.014$]. SHAPS total score was also correlated with frontal alpha [$r_s(38) = -0.48$, $p < .01$], theta [$r_s(38) = -0.40$, $p = .02$], and beta [$r_s(38) = -0.35$, $p = .04$] coherence.
Murray *et al.*, 2023[49]	United States	Cross-sectional	Community-recruited. Anhedonia: n = 41, mean (SD) age = 15.7 (1.8) y, 73% female, 71% White. Control: n = 41, mean (SD) age = 16.0 (2.0) y, 73% female, 71% White.	K-SADS	SHAPS	Probabilistic reward fMRI task with ROI analysis including nucleus accumbens and mPFC, followed by 5-day ecological monetary assessment	SHAPS score was not associated with impaired behavioral reward learning or with nucleus accumbens or mPFC activity (no significant clusters identified).[a] Compared with typically developing youth, youth with anhedonia showed reduced nucleus accumbens activity during win vs neutral trials ($t = 4.10$).
Pan *et al.*, 2022[50]	Europe	Longitudinal	Community cohort, IMAGEN study. n = 303, mean age = 14.5 y, 48% female, 100% White	DAWBA	DAWBA	Resting-state fMRI	Left ventral striatum connectivity associated with anhedonia at baseline (OR 1.78 [95% CI 1.06, 3.01]. $p = .030$). Future anhedonia was not predicted by left or right ventral striatum connectivity scores (4-y follow-up not reported).[a] Anhedonia was associated with left ventral striatum connectivity at 2-y follow-up (OR 2.20 [95% CI 1.54, 3.14], $p =$

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
							.001) and with right ventral striatum connectivity at 4-y follow-up [OR 1.87 [95% CI 1.09, 3.21], $p = .023$).
Pornpattananangkul *et al.*, 2019[51]	United States	Cross-sectional	Community-recruited, ABCD Study. fMRI group: n = 2,455, mean (SD) age = 10.0 (0.62) y, 48% female. MID task: n = 2,566, mean (SD) age = 10.0 (0.62) y, 49% female. N-back task: n = 2,465, mean (SD) age = 10.0 (0.62) y, 47% female.	Clinical assessment, K-SADS	K-SADS	Resting-state fMRI connectivity, MID task, and N-back task	For children with anhedonia vs without, the brainstem had stronger positive correlations with the cinguloparietal network ($\ln[BF_{10}] = 3.37$) and had weaker positive correlations with the right pallidum ($\ln[BF_{10}] = 1.97$). The salience network showed weaker anticorrelations with the left ventral diencephalon ($\ln[BF_{10}] = 2.81$); the dorsal attention network had weaker anticorrelations with the default mode network ($\ln[BF_{10}] = 3.29$) and left hippocampus ($\ln[BF_{10}] = 5.06$); the retrosplenial-temporal network showed weaker within-network connectivity ($\ln[BF_{10}] = 3.99$) and weaker positive correlations with the right cerebellum ($\ln[BF_{10}] = 2.15$).
Rzepa and McCabe, 2016[52]	United Kingdom	Cross-sectional	Community-recruited adolescents stratified by MFQ score. High risk: n = 17, mean (SD) age = 16.6 (1.2) y, 69% female. Low risk: n = 18, mean (SD) age = 16.3 (1.6) y, 50% female.	BDI, MFQ	FCPS, SHAPS, TEPS	Resting-state fMRI	Increased resting-state functional connectivity of the pregenual anterior cingulate cortex and the insula/OFC was negatively correlated with anticipatory pleasure in both high-risk ($r = -0.65$, $p = .004$) and low-risk ($r = -0.48$, $p = .04$) groups.
Rzepa and McCabe, 2018[53]	United Kingdom	Cross-sectional	Community-recruited adolescents. Depression: n = 44, mean (SD) age = 18.1 (1.8) y, 77% female. Control: n = 42, mean (SD) age = 18.0 (1.9) y, 76% female.	BDI, MFQ	FCPS, SHAPS, TEPS	Resting-state fMRI	Resting-state functional connectivity of right dorsal mPFC with anterior cingulate cortex/paracingulate gyrus negatively correlated with TEPS-ANT score ($r = -0.28$, $p = .009$). Resting-state functional connectivity of right dorsal mPFC and left precuneus positively correlated with TEPS-ANT ($r = 0.365$, $p = .001$).
Rzepa and McCabe, 2019[54]	United States	Cross-sectional	Community-recruited adolescents. Depression: n = 43, mean (SD) age = 18.2 (1.8) y, 77% female. Control: n = 41, mean (SD) age = 18.0 (2.0) y, 76% female.	BDI, MFQ	TEPS	fMRI with effort-based reward task	Anticipatory pleasure positively correlated with effort on hard reward trials ($r = 0.26$, $p = .008$). Anticipatory anhedonia was positively correlated with effort to avoid aversion in the precuneus (axial = 4, sagittal = −56,

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
							coronal = 46; $z = 3.67$, $p = .01$) and insula (axial = −36, sagittal = −6, coronal = 2; $z = 4.19$, $p < .05$). Consummatory anhedonia was negatively correlated with neural response during the aversive taste in the caudate (X = −14, Z = −4, Y = 26; $z = 4.39$, $p = .006$, $b = -0.09$, $f^2 = 0.83$).
Santopetro *et al.*, 2020[55]	United States	Longitudinal	Community-recruited female youth. n = 199, mean (SD) age = 12.3 (1.76) y.	CDI	CDI anhedonia subscale	EEG with flanker task	Baseline P300 amplitude was negatively correlated with anhedonia scores ($r_{197} = -0.163$, $p = .021$). Baseline P300 amplitude ($t199 = -2.58$, $b = -.05$, $p = .011$) and baseline anhedonia scores ($t_{199} = 9.99$, $b = .57$, $p < .001$) were also associated with anhedonia at 2-y follow-up.
Sato *et al.*, 2023[56]	Japan	Cross-sectional	University cohort, training dataset. Subthreshold depression (BDI-II ≥13): n = 30, mean (SD) age = 18.2 (0.4) y, 37% female. Control: n = 61, mean (SD) age = 18.4 (0.5) y, 48% female. University cohort, test dataset. Subthreshold depression: n = 16, mean (SD) age = 18.6 (0.7) y, 38% female. Control: n = 27, mean (SD) age = 18.5 (0.6) y, 33% female.	BDI-II	4 BDI-II items	Resting-state fMRI	8 of 29 subthreshold depression classifier functional connections were selected via a sparse classification algorithm based on their contribution to the classifier. Of those, functional connection 1 (right pallidum to left pallidum, $r = -0.469$, $p < .001$) and functional connection 2 (right fusiform gyrus to right cuneus, $r = -0.321$, $p = .002$) were significantly associated with anhedonia. The remaining functional connections were not significantly associated with anhedonia after Bonferroni correction.[a]
Stringaris *et al.*, 2015[57]	Europe	Longitudinal	Community-recruited, IMAGEN study. n =1,576, mean (SD) age = 14.4 (0.4) y.	DAWBA at baseline, ADRS at follow-up	1 DAWBA item	fMRI with MID task at baseline and follow-up	At baseline, adolescents with anhedonia showed significantly decreased activation in the ventral striatum bilaterally compared with adolescents without anhedonia (left: $\beta = 20.20$, $p < .001$; right: $\beta =$

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
							20.16, $p = .015$). At follow-up, decreased activation in the left ventral striatum predicted having concurrent anhedonia and low mood over low mood only (OR 0.84 [95% CI 0.73-0.98]). No significant differences in positive or negative outcomes were found for adolescents with clinical depression or low mood.
Whalen *et al.*, 2020[58]	United States	Cross-sectional	Clinical cohort. Depression: n = 99, mean (SD) age = 5.7 (0.8) y, 34% female, 79% White. Control: n = 65, mean (SD) age = 5.4 (0.9) y, 37% female, 78% White.	K-SADS-EC, Preschool Feelings Checklist	Sum of boredom, anhedonia, and amotivation items of K-SADS-EC	EEG with event-related potential to picture-viewing task	Event-related potential mean scores during pleasant and neutral picture viewing were not significantly correlated with MDD core symptoms or anhedonia sum score.[a]
Willinger *et al.*, 2022[59]	Switzerland	Cross-sectional	Clinically recruited adolescents and community-recruited controls. Depression: n = 30, mean (SD) age = 16.1 (1.4) y, 67% female. Control: n = 33, mean (SD) age = 16.2 (1.9) y, 70% female.	K-SADS-PL	CDI anhedonia subscale	fMRI with MID task	Magnitude-modulated loss prediction error signaling was negatively associated with anhedonia scores in the medial thalamus/habenula (k = 268, peak $Z = 4.54$, $p < .001$), posterior cingulate cortex, left and right postcentral gyrus (k = 1,492, peak $Z = 4.51$, $p < .001$ and k = 866, peak $Z = 4.94$, $p < .001$, respectively), and right fusiform gyrus (k = 175, peak $Z = 4.81$, $p = .05$). Loss-related outcome error signal in the posterior insula was negatively associated with anhedonia scores (peak $Z = 4.73$, $p < .001$).
Xie *et al.*, 2021[60]	Europe	Longitudinal	Community-recruited, IMAGEN study. Baseline (14 y): n = 1,877, 51% female, 100% White. Follow-up (19 y): n = 1,140, 53% female, 100% White.	DAWBA at baseline, ADRS at follow-up	1 ARDS item	MID with fMRI	Medial OFC activation was associated with anhedonia ("nothing really interests or entertains me") ($r = -0.075$, $p = .010$), whereas lateral OFC activation was not.[a]

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
Zhang *et al.*, 2016[61]	China	Cross-sectional	Community cohort, right-handed. Younger (11-13 y): n = 18, 39% female. Middle (13-14 y): n = 18, 33% female. Older (15-16 y): n = 17, 35% female.	BDI	TEPS	Implicit emotional Go/NoGo task with EEG	TEPS score was positively correlated with NoGo P3 amplitudes elicited by positive faces ($r = 0.38$, $p < .05$) but not those elicited by negative and neutral faces.[a] After controlling for age, these correlation coefficients were still significant (all $p < .05$).
Biochemical							
Chat *et al.*, 2023[62]	United States	Longitudinal	Community-recruited adolescents. n = 265, mean (SD) age = 12.5 (0.8) y, 52.5% female, 43% White.	CDI	4 CDI-items	Circulating IL-6 and CRP	Concentrations of IL-6 and CRP were not significantly correlated with anhedonia at baseline.[a] Structural equation modeling identified that CRP was negatively associated with concurrent anhedonia when controlling for BMI and sex ($\chi^2 = -0.124$, $p < .05$). Neither IL-6 nor CRP was prospectively associated with anhedonia.[a]
Franklyn *et al.*, 2022[63]	Canada	Cross-sectional	Undergraduate students. n = 539, mean (SD) age = 19.4 (2.2) y, 77% female, 59% White.	BDI, DASS-21	SHAPS	Circulating levels of cortisol, CRP, IL-6, and TNF-α	No significant differences were found between students with anhedonia and students without anhedonia.[a] CRP levels in the neurovegetative cluster were significantly greater compared with HCs ($p < .0001$) or anhedonia ($p = .0003$). Cortisol, IL-6, and TNF-α were not significantly associated with anhedonia.[a]
Freed *et al.*, 2019[64]	United States	Cross-sectional	Clinical cohort. Psychiatric group: n = 54, mean (SD) age = 15.4 (2.2) y, 56% female, 44% White. Control: n = 22, mean (SD) age = 15.5 (2.8) y, 59% female, 50% White.	BDI-II	SHAPS	In vitro functional immune response assay	Controlling for BMI, age, sex, and depression severity, SHAPS scores were significantly positively correlated with post-LPS values of 19 of 41 cytokines at the FDR corrected threshold: FGF-2, Flt3-L, fractalkine, G-CSF, GM-CSF, IL-1a, IL-2, IL-3, IL-4, IL-7, IL-9, IL-10, IL-12p40, IL-12p70, IL-15, IL-17α, MCP-3, TNF-β, and VEGF (ρs 0.334-0.572, *ps* <0.001-0.023).

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
Gabbay *et al.*, 2012[65]	United States	Cross-sectional	Clinical cohort. MDD: n = 36, mean (SD) age = 15.9 (1.7) y, 58% female, 44% White. Control: n = 20, mean (SD) age = 16.1 (2.7) y, 60% female, 55% White.	K-SADS-PL, BDI-II, CDRS-R	2 items from BDI, 1 item from CDRS-R, and 2 items from K-SADS-PL	IDO activity (blood KYN/TRP ratio) and KYN pathway neurotoxicity (blood 3-HAA/KYN and 3-HAA)	IDO activity was correlated with anhedonia scores in all participants ($r = 0.30$, $p = .02$) and in medication-free participants ($r = 0.44$, $p = .004$). In youth with MDD, there was a trend toward significant correlation between anhedonia scores and IDO activity while controlling for severity ($r = 0.31$, $p = .06$). When medicated participants were excluded, IDO activity was significantly correlated with anhedonia scores ($r = 0.42$, $p = .05$). There were no significant correlations between TRP, KYN, 3-HAA, or 3-HAA/KYN blood levels and anhedonia in the whole sample or MDD group.[a]
Liu *et al.*, 2020[66]	United States	Cross-sectional	Clinical cohort. n = 64, mean (SD) age = 15.2 (2.1) y, 43% MDD, 11% dysthymia, 69% female, 48% White.	K-SADS-PL, BDI-II, CDRS-R	SHAPS, TEPS	Circulating fasting CRP	No associations were identified between blood CRP levels and measures of anhedonia (SHAPS, TEPS-CON, or TEPS-ANT).[a] CRP levels were also not correlated with BDI-II or CDRS-R scores.[a]
Liu *et al.*, 2021[67]	United States	Cross-sectional	Clinical cohort. n = 127, mean (SD) age = 15.2 (2.2) y, 61% female, 57% White; 76% clinical with 41% MDD and 8% with dysthymia, 24% HC.	BDI-II, CDRS-R	SHAPS, TEPS	Circulating fasting CRP	No associations were identified between blood CRP levels and measures of anhedonia (SHAPS, TEPS-CON, or TEPS-ANT) or overall depression (BDI, CDRS-R) severity in the whole sample.[a] No differences in CRP levels were detected in depressive (CDRS-R score $\geq$35) or anhedonic (SHAPS score $\geq$26) adolescents relative to controls.[a]
Luby *et al.*, 2004[68]	United States	Cross-sectional	Clinic-recruited preschool-age children. Depression: n = 54, mean (SD) age = 4.6 (0.7) y, 55% female, 85% White. ADHD/ODD group: n = 46, mean (SD) age = 4.3 (0.8) y, 44% female, 91% White. Control group: n = 56, mean (SD) age = 4.5	DISC-Young Child	DISC-Young Child anhedonia items	Salivary cortisol, stress cortisol reactivity	Anhedonic depression subgroup had significantly decreased stress cortisol reactivity compared with ADHD/ODD ($U = 246.0$, $z = -2.15$, $p < .05$) and HC ($U = 319.0$, $z = -2.35$, $p < .05$) groups.

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
			(0.7) y, 55% female, 82% White.				
Peters *et al.*, 2021[69]	United States	Cross-sectional	Clinical cohort. Depression: n = 34, mean (SD) age = 14.5 (1.7) y, 56% female, 56% White. Control: n = 29, mean (SD) age = 14.7 (1.4) y, 62% female, 55% White.	K-SADS, CDRS-R	2 CDSR-R items	Circulating IL-6, IL-1β, and TNF-α	TNF-α was positively associated with somatic symptoms across all participants (Cohen $d = 0.25$, $p < .05$), but not reported depressed mood, CDRS-R total score, or anhedonia.[a] IL-6 was significantly elevated in depression group relative to control group (Cohen $d = 0.64$, $p = .017$) and positively associated with reported depressed mood across all participants (Cohen $d = 0.28$, $p < .05$), but not CDRS-R total score or anhedonia.[a] IL-1β was not associated with any symptom scale or reported depressed mood.[a]
Rengasamy *et al.*, 2021[70]	United States	Longitudinal	Clinical cohort with unipolar depression. n = 36, mean (SD) age = 16.1 (1.9) y, 75% female, 78% White.	CDRS-R, MFQ	SHAPS	Circulating IL-6 and TNF-α measured at baseline and a follow-up time point	Baseline TNF-α was positively associated with baseline SHAPS score ($B = 11.28$, $p = .012$) as well as follow-up SHAPS score ($B = 6.8$, $p = .043$) and CDRS-R score ($B = 33.62$, $p = .029$). Baseline IL-6 was not associated with any symptom scale.[a] No cytokine level changes were associated with symptom scales over time, and no follow-up cytokine levels were associated with follow-up symptom scales.[a]
Zhang *et al.*, 2023[71]	China	Cross-sectional	Clinical cohort of youth (15-24 y). Melancholic depression: n = 150. Nonmelancholic depression: n = 150. HC: no information provided.	HAM-D	SHAPS, TEPS	Circulating IL-1β, IL-2, IL-6, IFN-γ, and TNF-α	Increased serum levels of IL-1β, IL-6, and IFN-γ were positively correlated with anhedonia in melancholic patients with MDD (statistics not provided).
Other							
Ahles *et al.*, 2017[72]	United States	Cross-sectional	Community-recruited adolescents. n = 76, mean (SD) age = 13.3 (0.8) y, 52% female, 79% White.	CDI-2	6 CDI-2 items	Cardiac PEP, delayed match-to-sample reward task	Smaller PEP changes to reward were associated with greater concurrent anhedonia ($b = .23$, SE = 0.04, $t = 2.00$, $p = .049$). PEP reactivity to reward was not associated with the non-anhedonic depressive symptom cluster.[a]

(*continued*)

TABLE 1 Continued

Study	Location	Design	Demographics	Depression measure	Anhedonia measure	Assay	Key findings
Behavioral task							
Mareckova *et al.*, 2020[73]	United States	Cross-sectional	University cohort. n = 482, mean (SD) age = 19.8 (1.2) y, 53% female, 100% White.	MASQ short form	MASQ-AD	T-PRS characterizing depression-related changes in corticolimbic circuit, PGC-PRS, and BOLD fMRI during face-matching task	T-PRS was associated with widespread reductions in neural response to neutral faces in female participants and increases in neural response to emotional faces and shapes in male participants ($p < .01$). In female participants, brain scores reflecting T-PRS–associated ($R^2 = 0.03$, $p = .007$) and PGC-PRS–associated ($R^2 = 0.03$, $p = .009$) blunting of neural response to neutral faces were associated with higher anhedonia.

Note: *[1]H-MRS = proton magnetic resonance spectroscopy; 3-HAA = 3-hydroxyanthranilic acid; ABCD = Adolescent Brain Cognitive Development; ADHD = attention-deficit/hyperactivity disorder; ADRS = Adolescent Depression Rating Scale; BDI = Beck Depression Inventory; BMI = body mass index; BOLD = blood oxygen level–dependent; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale–Revised; CES-D = Center for Epidemiologic Studies Depression Scale; CRP = C-reactive protein; DASS-21 = Depression Anxiety Stress Scale-21; DAWBA = Development and Well-Being Assessment; DID = Diagnostic Inventory for Depression; DISC = Diagnostic Interview Schedule for Children; FCPS = Fawcett-Clark Pleasure Scale; FDR = false discovery rate; FGF = fibroblast growth factor; Flt3-L = FMS-like tyrosine kinase 3 ligand; fMRI = functional magnetic resonance imaging; fNIRS = functional near-infrared spectroscopy; GABA = γ-aminobutyric acid; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; HAM-D = Hamilton Depression Scale; HC = healthy control; HR = hedonic response; IDO = indoleamine 2,3-dioxygenase; IL = interleukin; IFN = interferon; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version; KYN = kynurenine; LPS = lipopolysaccharide; MASQ = Mood and Anxiety Questionnaire; MASQ-AD = Mood and Anxiety Questionnaire anhedonic depression subscale; MCP-3 = monocyte chemotactic protein 3; MDD = major depressive disorder; MFQ = Mood and Feelings Questionnaire; MID = monetary incentive delay; mPFC = medial prefrontal cortex; MRI = magnetic resonance imaging; ODD = oppositional defiant disorder; OFC = orbitofrontal cortex; OR = odds ratio; PEP = pre-ejection period; PGS-PRS = Psychiatric Genomics Consortium polygenic risk score; RBANS = Repeatable Battery for the Assessment of Neuropsycholgical Status; ROI = region of interest; RPhA = Revised Physical Anhedonia Scale; RSAS = Revised Social Anhedonia Scale; SET = Social emotion task; SHAPS = Snaith-Hamilton Pleasure Scale; TEPS = Temporal Experience of Pleasure Scale; TEPS-ANT = Temporal Experience of Pleasure Scale anticipatory pleasure scale; TEPS-CON = Temporal Experience of Pleasure Scale consummatory pleasure scale; TNF = tumor necrosis factor; T-PRS = Transcriptome-based polygenic risk score; TRP = tryptophan; VEGF = vascular endothelial growth factor.*
[a]Indicates nonsignificant results (p > .05).

TABLE 2 Studies of Cannabis and Amotivation

Study	Location	Design	Demographics	Cannabis measure	Amotivation measure	Assay	Key findings
Bloomfield *et al.*, 2014[74]	United Kingdom	Cross-sectional	Community-recruited current cannabis users with at least weekly use of cannabis and the induction of psychotic-like symptoms in response to smoking cannabis. n = 14, mean (SD) age = 20.4 (1.3) y, 7% female.	Self-report timeline follow-back, Cannabis Experience Questionnaire	AES-S	[^{18}F]-DOPA PET scan 1 h following administration of oral carbidopa 150 mg and entacapone 400 mg. ROI analysis of bilateral whole striatum and subdivisions including associative, limbic, and sensorimotor striatum	All participants scored more than 34 points on AES-S, indicative of significant apathy. AES-S was not significantly associated with current cannabis consumption.[a] Dopamine synthesis capacity was inversely correlated to AES-S score in the whole striatum (Spearman $\rho = -0.64$, $p = .015$) and associative subdivision (Spearman $\rho = -0.69$, $p = .006$). There were no significant relations between AES-S and volumes of any ROIs examined.[a]
Shollenbarger *et al.*, 2015[75]	United States	Cross-sectional	Community-recruited current cannabis users and demographically matched controls. Cannabis: n = 33, mean age = 21.2 y, 36% female, 67% White. Control: n = 34, mean age = 21.2 y, 59% female, 68% White.	Self-report timeline follow-back	Frontal Systems Behavioral Scale apathy score	Fractional anisotropy and mean diffusivity for corpus callosum forceps minor and bilateral anterior thalamic radiation and uncinate fasciculus	In cannabis users, increased self-reported apathy symptoms were associated with decreased fractional anisotropy in bilateral uncinate fasciculus (right: $r = -0.52$, $p = .002$; left: $r = -0.59$, $p < .001$). Higher BDI-II scores were associated with decreased fractional anisotropy in bilateral anterior thalamic radiation (right:

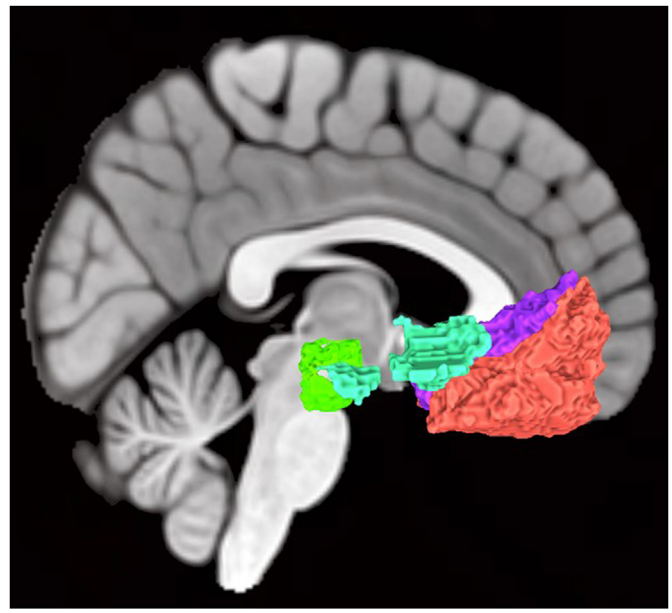
(*continued*)

TABLE 2 Continued

Study	Location	Design	Demographics	Cannabis measure	Amotivation measure	Assay	Key findings
							$r = -0.36$, $p = .04$; left: $r = -0.35$, $p = .04$), fractional anisotropy in right uncinate fasciculus ($r = -0.34$, $p = .05$), and increased mean diffusivity in left anterior thalamic radiation ($r = 0.45$, $p = .009$).

Note: [18F]-DOPA = 3,4-dihydroxy-6-[(18)F]-fluoro-L-phenylalanine; AES-S = Apathy Evaluation Scale self-report; BDI = Beck Depression Inventory; PET = positron emission tomography; ROI = region of interest.
[a]Indicates nonsignificant results ($p > .05$).

FIGURE 2 Regions of Interest Relevant to Relations Between Depression and Anhedonia and Cannabis and Amotivation



Note: Red indicates the ventromedial prefrontal cortex, including the medial orbitofrontal cortex; purple indicates the anterior cingulate cortex; dark green indicates the nucleus accumbens; and light green indicates the ventral tegmental area.

Longitudinal Studies

Three longitudinal reports described associations between anhedonia and activity in the ventral striatum.[36,50,57] Specifically, decreased activity in the left ventral striatum was positively associated with anhedonia, higher anhedonia was associated with increased OFC characteristics,[46,60] smaller overall putamen volume and smaller left NAc volume were positively associated with SHAPS score,[34] and baseline P300 amplitude was reduced in relation to higher anhedonia symptoms at baseline and at 2-year follow-up.[55] One study reported a significant interaction between lower overall putamen activity and peer feedback predicting higher anhedonia scores.[34]

Cross-Sectional Studies

Functional and Structural Connectivity Magnetic Resonance Imaging. In 6 studies, relations between anhedonia and resting-state functional or structural connectivity were examined in youth.[39,43,51–53,56] Findings indicate multiple paths involving the NAc and the ACC related to anhedonia. However, there was little overlap and often conflicting directionality in the functional connectivity findings (Table 1).

One study identified 2 resting-state functional connections related to anhedonia: right pallidum to left

pallidum functional connection and right fusiform gyrus to right cuneus functional connection.[56] Two studies showed negative correlations between increased resting-state functional connectivity of the pregenual ACC, the insula, and the OFC and decreased anticipatory anhedonia,[52] as well as resting-state functional connectivity of the right dorsal medial PFC with the ACC and paracingulate gyrus with anticipatory anhedonia.[53] However, the same study also showed that functional connectivity of the right dorsal medial PFC seed and left precuneus positively correlated with anticipatory anhedonia.[53]

Finally, 1 study used diffusion tension magnetic resonance imaging (MRI) structural connectivity analyses and found that increased anhedonia was positively related to fractional anisotropy in a cluster in the posterior cingulum near the hippocampus and negatively related to fractional anisotropy in the anterior limb of the internal capsule, OFC projection fibers, and posterior cingulum.[43] The investigators also found that increased anhedonia positively related to mean diffusivity in OFC projection fibers, external capsule, and sagittal stratum. Anhedonia was positively correlated with axial diffusivity in the corticospinal tract and projection fibers into the occipital cortex.

Task-Based Functional MRI Studies. Multiple ROIs have been identified using task-based functional MRI studies to examine associations between anhedonia and neural activation. However, similar to the aforementioned functional connectivity studies, there is little overlap between studies. Rzepa and McCabe[54] used exposure to rewarding (Belgian chocolate) and aversive (Belgian chocolate mixed with beet juice) stimuli related to button press task effort to assess relations between specific ROIs and anticipatory and consummatory anhedonia. Anticipatory anhedonia was positively correlated with effort to avoid exposure to the aversive stimuli in the precuneus and insula (as anticipatory anhedonia increased, ROI activity decreased). Conversely, increased activity in the caudate was associated with decreased consummatory anhedonia during aversive taste trials (as experienced pleasure decreased, caudate activity increased). Healey *et al.*[42] found that increased social anhedonia was associated with increased response to likability ratings on a picture viewing task within the dorsal medial PFC, rostral medial PFC, and pregenual ACC. During the liking task, higher social anhedonia was associated with greater positive connectivity between the basolateral NAc and medial PFC structures. In another functional MRI study using a probabilistic reward task, Murray *et al.*[49] found that anhedonia was not associated with impaired behavioral reward learning or with NAc or medial PFC activity; however, youth with anhedonia showed reduced NAc activity during win vs neutral trials. Willinger *et al.*[59] demonstrated that depression symptoms correlated with loss-related error signals in the posterior insula and habenula. Luking *et al.*[47] found that anhedonia negatively predicted response to gain-loss within the insula and ACC in the voxelwise regression, and, in the ACC, anhedonia positively predicted reduced deactivation to loss feedback. Of note, the ACC has shown significant relation to anhedonia across multiple neuroimaging studies.

Structural MRI Studies. Gabbay *et al.*[40] showed that white matter percentage was lower in youth with anhedonia compared with healthy controls.

Magnetic Resonance Spectroscopy Studies. Two magnetic resonance spectroscopy studies investigating GABA in the ACC in relation to depression and anhedonia in youth with depression found that lower levels of GABA are associated with anhedonia when examined dimensionally and categorically.[38,40] The remaining studies showed nonsignificant effects.

EEG and Functional Near-Infrared Spectroscopy Studies. We identified 5 studies that used EEG techniques and 1 study that used functional near-infrared spectroscopy to determine associations between brain activity and anhedonia in children and adolescents. The EEG studies showed that anhedonia was positively correlated with average alpha coherence overall and frontal alpha, theta, and beta coherence.[48] Zhang *et al.*[61] used an implicit emotional EEG task with valanced faces and found that anhedonia was positively correlated with P300 amplitudes elicited by positive faces but not by neutral or negative faces. This result is contrary to the association between P300 amplitude and anhedonia reported by Santopetro *et al.*[55] Liu *et al.*,[45] using a simple gambling task event-related potential study found that anhedonia had an indirect effect on the relation between reward sensitivity and overall depression symptoms. Two studies reported no significant effects for anhedonia.[41,58] Liang *et al.*[44] reported functional near-infrared spectroscopy results comparing adolescents with major depression and melancholia, adolescents with major depression without melancholia, and healthy controls using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and found that the attention score was negatively correlated with anhedonia in the group with melancholia.

Biochemical Assays

Biochemical assays were evaluated in 10 studies comprising 1,532 participants (range 36-539) (Table 1). Nine studies reported baseline gender and race/ethnicity, with most

TABLE 3 Biochemical Markers Associated With Anhedonia

Study	IL-1β	IL-2	IL-6	IFN-γ	TNF-α	CRP	Cortisol	Kynurenine pathway
Chat *et al.*, 2023[62]	—	—	NS	—	—	↓	—	—
Franklyn *et al.*, 2022[63]	—	—	NS	—	NS	NS	NS	—
Freed *et al.*, 2019[64,a]	NS	↑	NS	NS	NS	—	—	—
Gabbay *et al.*, 2012[65]	—	—	—	—	—	—	—	↑
Liu *et al.*, 2020[66]	—	—	—	—	—	NS	—	—
Liu *et al.*, 2021[67]	—	—	—	—	—	NS	—	—
Luby *et al.*, 2004[68,b]	—	—	—	—	—	—	↓	—
Peters *et al.*, 2021[69]	NS	—	NS	—	NS	—	—	—
Rengasamy *et al.*, 2021[70]	—	—	NS	—	↑	—	—	—
Zhang *et al.*, 2023[71,c]	↑	NS	↑	↑	NS	—	—	—

Note: *CRP = C-reactive protein; IL = interleukin; IFN = interferon; NS = not significant; TNF = tumor necrosis factor.*
[a]*Cytokine levels measured after in vitro stimulation with lipopolysaccharide.*
[b]*Stress cortisol reactivity; authors do not report baseline cortisol levels.*
[c]*No cytokine levels or statistical tests reported by authors.*

participants being female (range 52%-77%) and identifying as White (range 43%-85%). Circulating cytokines were the most evaluated biochemical assays. However, no cytokine was consistently associated with anhedonia, and most tests exploring associations with anhedonia were not significant (Table 3). Interleukin (IL)-6, a proinflammatory cytokine that has been most strongly associated with depression in adults,[79,80] was significantly elevated in a clinical cohort of youth with depression compared with healthy controls (Table 1).[69] However, no significant associations were identified between IL-6 and anhedonia in youth with depression[69,70] or with anhedonia in general population studies of younger[62] or older[63] adolescents. Although Zhang *et al.*[71] reported IL-6 levels were positively correlated with anhedonia in youth with melancholic MDD, they did not present biochemical or statistical results to evaluate the association. Similarly, the majority of studies measuring tumor necrosis factor (TNF)-α found no significant association with depression[69] or with anhedonia.[63,69,71] However, in a longitudinal study of adolescents with depression, Rengasamy *et al.*[70] found that baseline TNF-α was positively associated with baseline and follow-up SHAPS score, as well as baseline depression score (Table 1). These findings are discrepant with data from the study by Peters *et al.*,[69] which did not establish a significant association between TNF-α and depression or anhedonia.

Freed *et al.*[64] more broadly evaluated peripheral inflammatory cytokines in a study of 54 psychotropic medication–free adolescents with psychiatric conditions, of whom 59.3% had a *DSM-IV* lifetime diagnosis of depressive disorder and 51.9% had a diagnosis of anxiety disorder, and 22 healthy control youth. Peripheral blood mononuclear cells were stimulated in vitro with lipopolysaccharide (LPS), a bacterial endotoxin that activates innate immune response. Immune response as measured by post-LPS cytokine values did not differ when comparing youth with psychiatric conditions with healthy controls. Of the 41 cytokines measured, anhedonia was positively correlated with post-LPS values of 19 cytokines (Table 1). Post-LPS values of IL-6 and TNF-α were not associated with SHAPS score (Table 3).

Another systemic marker of inflammation that has been positively associated with MDD in adults is C-reactive protein (CRP), an acute-phase plasma protein.[79] Similar to cytokines, 3 studies found no significant association between CRP levels and anhedonia,[63,66,67] whereas 1 study reported a significant negative association (Table 3).[62] Chat *et al.*[62] used structural equation modeling to examine concurrent and prospective relations between IL-6 and CRP, 5 depressive symptom factors including anhedonia, and frequency of substance use in a longitudinal study of adolescents. At the follow-up visit, CRP was negatively associated with concurrent anhedonia (Table 1). However, neither IL-6 nor CRP was associated with anhedonia at baseline or prospectively associated with anhedonia.

Two studies evaluated associations between anhedonia and the stress response steroid hormone cortisol (Table 3),[81] which is implicated in the dysregulation of the hypothalamic-pituitary-adrenal axis leading to depressive symptoms.[82] Luby *et al.*[68] evaluated salivary stress cortisol reactivity following parental separation in preschool-age children with an anhedonic subtype of depression compared with children with attention-deficit/hyperactivity disorder or oppositional defiant disorder or healthy control children. Children with anhedonic depression had significantly decreased stress cortisol reactivity relative to either comparison group. In contrast, Franklyn *et al.*[63] found no significant association between plasma cortisol levels and

anhedonia or depression symptoms in a general population cohort of undergraduate students.

Finally, Gabbay *et al.*[65] evaluated the kynurenine pathway, a neuroimmunological pathway implicated in the development of depression via the production of oxygen radicals and neurotoxins.[83–85] The authors estimated the activity of indoleamine 2,3-dioxygenase, the rate-limiting enzyme in the kynurenine pathway, and downstream neurotoxins.[65] Indoleamine 2,3-dioxygenase activity was correlated with anhedonia scores in all participants and medication-free participants (Table 1). The authors reported indoleamine 2,3-dioxygenase activity was correlated with anhedonia in the subset of medication-free youth with MDD when controlling for depression severity, with a trend toward significant correlation in all youth with MDD. There were no significant correlations between circulating neurotoxin levels and anhedonia.

Other Studies

Mareckova *et al.*[73] used a Psychiatric Genomics Consortium polygenic risk score (PRS), a postmortem transcriptomic corticolimbic circuit signature of depression, to generate a novel transcriptome-based PRS consisting of functional single nucleotide polymorphisms that alter corticolimbic circuit activity. In a cohort of university students, the Psychiatric Genomics Consortium PRS and transcriptome-based PRS were mapped onto whole-brain activity patterns during perceptual processing of social stimuli to understand the association of PRSs with depression variants and with anhedonia. Among female participants with functional alleles similar to the corticolimbic circuit signature of depression, anhedonia was associated with blunted neural activity to social stimuli (Table 1). Ahles *et al.*[72] studied cardiac pre-ejection period (PEP) and performance on delayed match-to-sample reward tasks in a general population cohort of youth with high vs low depression scores. Smaller PEP changes to reward were associated with greater anhedonia symptoms, whereas no association was found between PEP reactivity to reward among the non-anhedonic depressed cluster (Table 1). Thus, the relation between PEP reactivity and reward may be specific to anhedonic symptoms in youth.

Cannabis and Apathy

After screening, 2 reports on relations between cannabis and apathy as a related construct using neuroimaging were retained (Table 2).[74,75] Both studies were cross-sectional and collected data on cannabis use via self-report using timeline follow-back methods. Apathy was measured as a phenotype proximal to amotivation. Bloomfield *et al.*[74] conducted 3,4-dihydroxy-6-[(18)F]-fluoro-L-phenylalanine ([^{18}F]-DOPA) positron emission tomography imaging studies of bilateral whole striatum and associative, limbic, and sensorimotor subdivisions of the striatum. Results indicated that the apathy score was not significantly associated with cannabis use. Whereas dopamine synthesis capacity was negatively correlated with apathy score in the whole striatum, the authors found no associations between any ROIs and self-reported cannabis use or apathy. Shollenbarger *et al.*[75] used fractional anisotropy and mean diffusivity in the corpus callosum forceps minor and bilateral anterior thalamic radiation and uncinate fasciculus. The authors found a significant association between increased apathy and decreased fractional anisotropy in the bilateral uncinate fasciculus in youth who use cannabis.

In a previously mentioned study of depression and anhedonia by Luby *et al.*,[46] the authors also examined cannabis use among youth with and without anhedonia using fMRI (Table 1). Luby *et al.*[46] found that OFC volume was positively associated with onset of cannabis use, whereas OFC thickness was negatively associated with onset of cannabis use controlling for time-varying anhedonia scores; however, OFC volume was not significantly associated with frequency of cannabis use.

DISCUSSION

In our systematic review, we found evidence from 44 articles that anhedonia in adolescent depression may have a host of biological underpinnings, but only 2 articles evaluated biological factors associated with amotivation in cannabis use. Thus, a comparison of motivational dysfunction between depression and cannabis was ultimately not possible. Further, studies of depression and anhedonia nearly universally exclude individuals who use cannabis or do not report on substance use. As such, investigation of anhedonia and motivation in individuals with comorbid depression and cannabis use was also not possible.

No biological factor or behavioral task was consistently associated with anhedonia in depression. Neuroimaging studies encompassed heterogeneous study designs and analytic approaches, with little overlap among findings of brain regions associated with anhedonia. ROIs most frequently associated with anhedonia across functional and structural neuroimaging and tasked-based neuroimaging studies include the ACC, NAc, and medial PFC. Coherence between structural and functional connectivity findings allude to the centrality of the ACC, OFC, and striatum in anhedonia, all of which have been therapeutic targets for neuromodulation in individuals with refractory depression and/or anhedonia with inconsistent efficacy.[86–88] Notably, studies of anhedonia in adults have reported similar ROIs as

those identified in adolescents herein.[9,11,14–16] The NAc has also been identified as an ROI in studies of cannabis use and motivation in adults,[26] suggesting reward circuitry may be fundamental to both anhedonia and amotivation.

Circuit models of anhedonia and amotivation support transdiagnostic applications in that multiple disorders with anhedonia features have conserved deficits in medial prefrontal and striatal regions.[89,90] However, recent studies suggest that brain-based findings may be a marker of severity rather than of a specific pathophysiological phenomenon.[91] As such, comparing impaired motivation associated with depression vs with cannabis use may simply confirm that anhedonia is reward related but otherwise is not a diagnostically specific marker of symptom severity or persistence.[10,18] Clinical phenomenological differences may alternatively be a function of how motivation manifests in various disorders. Reduced willingness to exert cognitive effort for higher rewards in psychotic disorders (schizophrenia and bipolar disorders) resulted in greater clinician-rated motivation impairments, worse working memory and cognitive performance, and reduced engagement in goal-directed activities compared with that in major depressive disorders.[92] However, heterogeneity across studies also limits the interpretability of an overall model of what neurobiological deficits are consistently associated with anhedonia, much less its differential relation to depression or cannabis use. Thus, data generated from more refined methods are necessary to develop individually tailored therapies based on clinical and neurobiological profiles of patients.[17] For example, reviewed and emerging data suggest that temporally sensitive and higher-resolution imaging as well as novel task-based assessments that represent validated reward constructs[93] may facilitate novel pathophysiological insights. Further, measurement of anhedonia over time using psychometrically validated constructs and subconstructs,[94] while considering variations that are clinically meaningful and across sociodemographic factors,[95,96] may result in more positive and convergent findings that could inform individually tailored treatments.

Peripheral biomarker studies investigating inflammatory, stress cortisol, and oxidative stress (kynurenine pathway) have to date yielded weak and inconsistent results. No biochemical marker, including IL-6 or CRP, was consistently associated with anhedonia, and most tested associations between biochemical markers and anhedonia were not significant. Nevertheless, several lines of evidence exist to illustrate the impact of inflammation and stress on the CNS function. For example, increased inflammation in depression has been linked to disruptions in corticostriatal reward circuit connectivity and symptoms of anhedonia, which are thought be related to the impact of inflammation on the synthesis and release of dopamine.[97] In addition, other signaling pathways may mediate the relation between inflammation, depression, and anhedonia, including the endocannabinoid system.[98,99] There remains a need to establish reproducible methods to assess inflammation-associated circuit dysconnectivity, perhaps using biomarkers in clinical trials with primary outcomes relating to reducing the negative effects of inflammation on the brain.[100]

Finally, it is difficult to draw conclusions based on the results of 2 imaging studies in youth with cannabis use and apathy with different methods applied and hypotheses tested on different ROIs. In addition, both studies we identified were cross-sectional, relied on self-report, and collected data only on cannabis use frequency. Cannabis products have markedly changed over the past decade, with commercialization in legal markets leading to a sharp rise in Δ^9-tetrahydrocannabinol potency[101,102] and increased availability and consumption of Δ^9-tetrahydrocannabinol concentrates by youth.[102] More studies assessing associations between cannabis use and behavioral assessments of amotivation are needed, particularly longitudinal studies that measure cannabis use quantity and potency.

Although we identified several biological factors associated with anhedonia in depressive and cannabis use disorders, there was considerable heterogeneity among the reviews that satisfied our eligibility criteria. Further, there may be conceptual frameworks and etiologies other than reward processing for understanding motivational disruptions across these disorders.[8] Overall, these findings highlight the need for future studies to continue investigating anhedonia and depression through neuroimaging techniques while prioritizing specificity in assessing anhedonia. Reassuringly, most findings reported were not affected by publication bias.

Limitations in study design include limited and diverse objective outcome measures, some lack of normative comparison samples (in some studies), lack of corroborating physiological data, and high rates of attrition in prospective studies. Inconsistencies reported across studies were likely influenced by the diverse measures used to assess anhedonia, indicating that different regions of the brain could be responsible for different experiences of anhedonia as well as the mechanisms through which different types of anhedonia are activated. Assessment of anhedonia may also be limited by the use of self-report scales rather than behavioral tasks that more objectively assess domains underlying anhedonia and motivation. Studies of depression most often exclude or do not report on cannabis use, which also limits the evaluation of anhedonia and motivation within individuals with comorbid depression and cannabis use. In addition, for studies of depression and anhedonia, most participants were

female, whereas the 2 studies of cannabis and amotivation consisted of primarily male participants. To date, studies have not adequately evaluated sex as a biological covariate of anhedonia or amotivation. Further, little is known about the effect of race/ethnicity on the clinical manifestations of these phenotypes.

This review conducted an expansive search across multiple databases, though relevant studies may have been missed due to search term limitations. Further, in some studies examining biological factors associated with transdiagnostic motivational disruptions, the biological outcomes may have been tempered by intervention. However, from our analysis, most studies were not designed to quantify the effects of an intervention and/or did not specify exposures and their dynamics in relation to anhedonia. Consequently, many of these articles were excluded from full-text review. Finally, generalizability of the findings is limited due to the variation across study context, variations in biomarker measurement, and complex ensuing neurodevelopmental trajectories leading to diverse outcomes.

There is significant potential for key neurobiological factors to characterize youth with anhedonia within and across depressive and cannabis use disorders. Advances in neuroscience and computational tools have enabled fine-grain assessments to improve our ability to detect subtypes of reward dysfunction that might delineate etiologies related to depression vs cannabis use. This may be useful, especially in the context of cognitive impairment and poor insight, which can interfere with accurate symptom reporting or obscure diagnostic presentations. However, such advancements are overshadowed by the heterogeneity in studies with small sample sizes and self-report measures of anhedonia. Studies examining structural and functional brain connectivity that elucidate the relations among brain networks involved in complex and transdiagnostic symptoms are informative for understanding the developmental scaffolding needed to prevent or reduce the severity of adolescent depression or the emergence of cannabis use. Repeated prospective assessments require replication and clinical translation to advance understanding of ways to prevent progression to treatment refractory states. We anticipate that the next generation of advancements in neuroscience tools and measurement of context-dependent anhedonia constructs will facilitate new mechanistic insights allowing more accurate diagnosis and more effective treatment among youth with these disorders.

CRediT authorship contribution statement

Jesse D. Hinckley: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Bradley T. Conner:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Roseanne Mauch:** Writing – review & editing, Writing – original draft, Data curation. **Patrice A. Arkfeld:** Writing – review & editing, Writing – original draft, Data curation. **Devika Bhatia:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Emma E. Smith:** Data curation. **Ellie Svoboda:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Manpreet K. Singh:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

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