

Annual Research Review: Puberty and the development of anhedonia – considering childhood adversity and inflammation

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Anhedonia, or diminished pleasure and motivation, is a symptom of severe mental illness (e.g., depressive disorder, bipolar disorder, schizophrenia) that emerges during adolescence. Anhedonia is a pernicious symptom that is related to social impairments, treatment resistance, and suicide. As the mechanisms of anhedonia are postulated to include the frontostriatal circuitry and the dopamine neuromodulatory system, the development and plasticity of these systems during the vulnerable period of adolescence, as well as their sensitivity to pubertal hormones, suggest that pubertal maturation could play a role in the development of anhedonia. This review takes a developmental perspective, considering the possibility that anhedonia emerges in the context of pubertal maturation and adolescent development, with childhood adversity and chronic inflammation influencing neural reward systems to accelerate anhedonia's progression. Here, we review the relevant extant literature on the components of this model and suggest directions for future research. **Keywords:** Puberty; adolescence; neural reward systems; developmental psychopathology; risk factors.

Introduction

Anhedonia, a transdiagnostic symptom defined as a diminished experience of pleasure, reduced response to pleasurable stimuli, or difficulty with the motivation to pursue or experience rewards, emerges during adolescence (Pizzagalli, 2022a). This symptom has long been established as a state or trait vulnerability for several psychiatric disorders under the umbrella of severe mental illness (SMI), including schizophrenia, bipolar disorder, and depression (Dowd & Barch, 2010; Kring & Elis, 2013; Lambert et al., 2018; Pizzagalli, 2022b). SMI tends to emerge during late adolescence and early adulthood, while anhedonia first appears during adolescence and is thought to set the stage for SMI. The emergence of anhedonia prior to SMI lends urgency to understanding and preventing its development during adolescence, which is a time of increased neuroplasticity (i.e., neural reorganization) (Fuhrmann, Knoll, & Blakemore, 2015). Standard psychosocial and pharmacological treatments are generally ineffective in treating anhedonia, often aiming to reduce negative affect rather than enhance positive affect (Sandman & Craske, 2022). The lack of effective treatments for a symptom predictive of future SMI and poor functioning makes it imperative to understand anhedonia's mechanisms, develop targeted treatments, and prevent the progression from anhedonia to SMI.

Clinical neuroscience models identify the mechanisms for anhedonia in neural reward circuitry

(Forbes & Dahl, 2005; Pizzagalli, 2022b). Consistent with this, conceptual and empirical literature also suggest that neural reward circuitry is altered in depression (Davey, Yücel, & Allen, 2008; Forbes & Dahl, 2012), schizophrenia (Barch, Pagliaccio, & Luking, 2016; Strauss, Waltz, & Gold, 2014), and bipolar disorder (Gruber, 2011; Whitton, Treadway, & Pizzagalli, 2015), and stress contributes to reward deficits in the context of depression (Auerbach, Admon, & Pizzagalli, 2014). Furthermore, conceptual models propose adolescents exposed to child adversity may be at particularly heightened risk for psychopathology. More specifically, frameworks suggest that child adversity can lead to depressive symptoms through chronic inflammation and disrupted neural reward circuitry (Nusslock & Miller, 2016; Slavich & Irwin, 2014). Furthermore, research on pubertal development emphasizes the importance of considering how puberty plays a role in adolescent brain development (Berenbaum, Beltz, & Corley, 2015; Blakemore, Burnett, & Dahl, 2010; Forbes et al., 2010; Goddings, Beltz, Peper, Crone, & Braams, 2019; Ladouceur, 2012; Pfeifer & Allen, 2021; Vijayakumar, de Macks, Shirtcliff, & Pfeifer, 2018). Building on this foundation, a critical next step is to propose a conceptual model for the emergence of anhedonia from a developmental psychopathology and affective neuroscience perspective.

As the developmental psychopathology concept of equifinality suggests, many pathways may lead to the same outcome. In this paper, we present a conceptual model for one possible trajectory of the development of anhedonia, recognizing there may be

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other possible pathways to anhedonia, during adolescence that integrates relevant existing models, considers the supporting (and in some cases, underdeveloped) empirical literature, and extends this conceptual and empirical groundwork to the development of anhedonia. We examine support for our model, offering a perspective on scientific advancement and suggesting future directions. Rather than conduct a systematic review of a single literature, our goal was to qualitatively integrate several seminal and sometimes disparate literatures, examine new trends in these areas, and identify some clear gaps that could serve to inspire future directions. The model focuses on the putative neural mechanisms of anhedonia – frontostriatal circuitry (with regions including the medial prefrontal cortex, mPFC, and ventral striatum, VS), and the dopamine (DA) neuromodulatory system – as they develop during puberty and are shaped by childhood adversity and chronic inflammation. To set a foundation for our model, we first discuss (a) the emergence, nature, and clinical correlates of anhedonia; (b) the neural systems underlying anhedonia; and (c) the role of pubertal maturation on these systems. We then review evidence for the role of two important early developmental factors: childhood adversity and the sequelae of chronic inflammation. We take a strong developmental perspective, considering the possibility that anhedonia emerges as a result of the timing and alignment of these changes in the setting of vulnerability during this point in the lifespan.

Conceptual model

While there may be multiple pathways to anhedonia, our model highlights one possible trajectory. Our model suggests that frontostriatal circuitry and the DA neuromodulatory system are particularly sensitive, during the period of pubertal maturation, to the negative influence of chronic inflammation stemming from the experience of childhood adversity (Figure 1). As proposed by Slavich and Irwin (2014), stressful events (e.g., exposure to childhood adversity) and associations with later depressive symptoms are mediated by an increase in the immune response of pro-inflammatory markers (e.g., cytokines). Alterations in the immune response could influence the synthesis and availability of striatal DA and in turn influence plasticity (e.g., Felger & Treadway, 2017), inhibiting the ability of adolescents to adapt to their environment during a time of important social, physical, and biological changes. When puberty occurs, it could be that striatal DA availability is further influenced, accelerating alterations in neural reward circuitry, and dampening responses to reward for some adolescents. It could be that difficulties and frustrations with learning and adapting to one's environment impact motivation and experiences of joy. Studies of adolescent depression find that depression is associated with

low VS activation to reward but high mPFC activation, a pattern potentially reflecting overregulation of basic reward response within this circuitry, as has been proposed for adolescent depression (Forbes et al., 2009). Greater activation of the mPFC could reflect recruitment of the VS to enhance striatal DA response to reward. While understudied in anhedonia, these processes could not only worsen anhedonia but derail adolescents from typical neurodevelopmental pathways, with unfortunate costs. As adolescence is a developmental period characterized by consequential changes in positive emotions and reward processing – including increases in reward-driven behavior, prosocial behavior, sensitivity to rewards (including social rewards such as achievement, status, affiliation, and intimacy), and the experience of intense positive affect (Blakemore, 2008; Dahl, 2004; Davey et al., 2008; Forbes et al., 2010; Forbes & Dahl, 2012; Larson, Csikszentmihalyi, & Graef, 1980; Sawyer, Azzopardi, Wickremarathne, & Patton, 2018; Steinberg, 2005) – alterations could be a long-term detriment to affect regulation, social functioning, and navigation of the developmental tasks of adulthood.

Importantly, it could be that some adolescents are deviating from typical developmental trajectories regardless of life histories and inflammation in adolescence, experiencing a general vulnerability, which may have long-term consequences. While it is of course possible, here, we propose a more specific pathway of vulnerability to chronic inflammation effects that is created by the influence of pubertal maturation on neural reward circuitry.

The nature of anhedonia: Anhedonia emergence and clinical correlates

Anhedonia is a serious, impairing symptom across moodily maturing neural reward circuitry including and psychotic disorders. In schizophrenia, anhedonia is considered a *negative symptom* in the sense that it reflects reductions in processes considered fundamental for adaptive behavior: positive emotions, motivation, effort, and reward responsiveness. Anhedonia is also a cardinal symptom of depressive disorders (along with depressed mood, either of which is required to be present for diagnosis of a major depressive episode; American Psychiatric Association, 2013) and can be present in those with bipolar disorder, particularly during depressive episodes (Dimick, Hird, Fiksenbaum, Mitchell, & Goldstein, 2021; Whitton et al., 2015). Anhedonia is a complex symptom because it can occur in different forms. For example, anhedonia can be divided into stages of consummatory (i.e., liking or enjoyment) and anticipatory (i.e., motivation or looking forward to potentially pleasant experiences). Social anhedonia – reduced pleasure and interest in social situations – has been considered a form that may

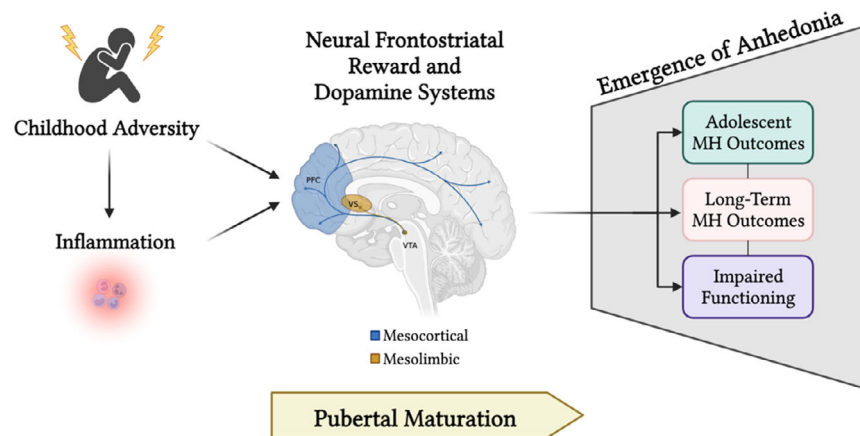


Figure 1 Conceptual model of a neurobiological pathway to anhedonia development in adolescence. This model suggests that childhood adversity and chronic inflammation—alone and as a consequence of childhood adversity—can contribute to disruptions in neural frontostriatal circuitry and dopamine systems, which serve as etiologic mechanisms for anhedonia. Frontostriatal circuitry includes the ventral tegmental area (VTA), which sends projections to the ventral striatum (VS) via the mesolimbic pathway and the prefrontal cortex (PFC) via the mesocortical pathway. Puberty can open a vulnerable developmental window (gray), in which the accumulation of developmental disruptions can trigger the emergence of anhedonia, which in turn can result in varying mental health (MH) outcomes

differ from other aspects of anhedonia and can lead people to experience isolation, withdrawal, loneliness, and other psychological challenges (Kwapil, 1998; Sagud et al., 2021; Tan, Shallis, & Barkus, 2020; Tarbox-Berry & Pogue-Geile, 2008). While social anhedonia is not a primary focus of this review, it is worth noting there are several typical processes involving social reward during adolescence – intimate friendships, affiliation with peer groups, status concerns, and romantic/sexual relationships (Crone & Dahl, 2012) – social anhedonia is potentially consequential and worthy of future focus.

Anhedonia predicts poor-functional outcomes and quality of life (Amr & Volpe, 2013; Auerbach, Pagliaccio, & Kirshenbaum, 2022; Blanchard, Mueser, & Bellack, 1998; Eckstrand et al., 2019; Lambert et al., 2018). It is a harmful clinical symptom that contributes to higher depression severity, longer depressive episodes, greater recurrence rates, and suicide (Auerbach et al., 2022; McMakin et al., 2012; Pizzagalli, 2022a). In those at risk for psychotic disorders such as schizophrenia, anhedonia predicts psychosis onset: it is related to the emergence of attenuated positive symptoms (e.g., perceptual abnormalities) and precedes the emergence of the full-blown syndrome (Cannon et al., 2002, 2008; Fusar-Poli et al., 2013). People who experience anhedonia as part of schizophrenia have higher substance use, duration of untreated illness, disability, unemployment, and challenges developing close relationships (Birnbaum, Wan, Broussard, & Compton, 2017; Foussias & Remington, 2010; Strauss et al., 2013).

While there is a sizable literature examining anhedonia in adults, we still know little about the development of its phenomenological, physiological, and behavioral aspects in adolescence. What is known is that Major Depressive Disorder (MDD)

has a peak onset in adolescence (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015) and anhedonia has a high prevalence in adolescents with MDD (i.e., 65%–76%) (Lewinsohn, Petit, Joiner Jr., & Seeley, 2003; Yorbik, Birmaher, Axelson, Williamson, & Ryan, 2004). Anhedonia can occur as early as age 3 (Prabhakar, Nielson, & Stringaris, 2022), and is even observed in community samples of adolescents without a depressive disorder (Stringaris et al., 2015). Furthermore, epidemiological evidence suggests that 58% of adolescents with anhedonia report a depressive disorder later in life (Wilcox & Anthony, 2004). In addition, it is well-known that depression is more common in girls than boys (Bennik, Nederhof, Ormel, & Oldehinkel, 2014; Grigoriadis & Robinson, 2007) with this sex difference apparent starting at around age 13 (Hankin et al., 1998). However, anhedonia tends to occur at greater rates in boys than girls (Dodell-Feder & Germine, 2018), and boys show an increase in anhedonia in mid-adolescence (Bennik et al., 2014). Importantly, adolescent suicide attempters report more anhedonia compared to suicidal ideators (Auerbach, Millner, Stewart, & Esposito, 2015), and anhedonia is related to an escalation in substance use (Leventhal et al., 2017), and predicts later psychopathology (Gabbay et al., 2015; Pine, Cohen, Cohen, & Brook, 1999; Yang, Guo, Harrison, & Liu, 2022). Anhedonia is thus present and damaging early in life, underscoring the need to understand its mechanisms and ultimately reduce its harm.

Treatments directly targeting anhedonia, especially during adolescence, are unusual and perhaps insufficiently disseminated. There may be promise in newer treatments such as neuromodulation (e.g., repetitive transcranial magnetic stimulation) and ketamine, both of which can target the mechanisms

of anhedonia (Downar et al., 2014; Fukuda et al., 2021; Nogo et al., 2022; Rodrigues et al., 2020) and can be administered safely to adolescents (Croarkin & MacMaster, 2019; Dwyer et al., 2021). Critically, these treatments are only given to individuals experiencing treatment-resistant depression, which is typically defined as having failed traditional, first-line treatments (e.g., SSRI medications). Consequently, access to effective treatments can be delayed, which is particularly troubling when the lost years are likely valuable and formative ones in affective, social, and identity development. Positive Affect Treatment (Craske et al., 2019; Craske, Meuret, Ritz, Treanor, & Dour, 2016; Sandman & Craske, 2022), which targets the anticipation and experience of reward, is both effective for enhancing positive affect and rare among cognitive-behavioral treatments for its focus on positive, rather than negative, affect. This could easily be offered to young people with anhedonia. Elucidating anhedonia's development could propel the application of treatments that are developmentally informed and targeted toward a symptom or subtype rather than a heterogeneous syndrome.

The Hallmark of developmental processes during adolescence: Puberty

What marks the transition from childhood into adolescence is pubertal development, which is a biological maturational process occurring over the course of 4–5 years, beginning between the ages of 8 and 15 years of age, and present earlier in girls than boys (Blakemore et al., 2010). Puberty is a time of substantial neurocognitive, social, and physical change as adolescents develop to meet the demands of adulthood. The increase in the pursuit of rewards during adolescence is hypothesized to be due in part to the influence of adrenarche. Adrenarche is an early stage of puberty marked by the maturation of the adrenal glands and production of adrenal androgens, whereas gonadarche refers to the maturation of the ovaries and testes with subsequent release of sex steroids (Dorn, 2006). Biological changes such as alterations in gonadal steroid hormones – estrogen and testosterone – as well as adrenal androgens promote pubertal maturation. Activation of gonads in girls leads to the secretion of estradiol (in the ovaries), progesterone, and ovarian androgens, and eventually to the development of ovulatory menstrual cycles. In boys, these processes can lead to testicular secretion of testosterone (Blakemore et al., 2010; Dorn, 2006; Schulz & Sisk, 2006).

Adolescent reward development

Puberty starts in the developmental stage of adolescence. Adolescence is a period of brain maturation, particularly in neural reward systems

(Steinberg, 2005; Crone & Dahl, 2012; Forbes et al., 2010). Adolescence is also a unique time of novelty, change, and identity formation: adolescents engage in new experiences, social relationships are salient, exploring new hobbies and interests is a priority, new passions such as music or social justice are discovered, romantic relationships are pursued, and future goals are developing (Crone & Dahl, 2012; Dahl, Allen, Wilbrecht, & Suleiman, 2018). Adolescents tend to respond to rewards more intensely (Steinberg, 2008). However, while adolescents are more sensitive and responsive to rewards, this is not the complete picture. For instance, adolescents' baseline mood is characterized by lower positive affect than children's (Larson et al., 2002), and typical adolescents experience a level of depressive severity that corresponds to mild depression in adults (Lewinsohn, Rohde, Seeley, 1998). Along with other changes in reward valuation and responding, such as the shift to a focus on social reward (Davey, Allen, Harrison, Dwyer, & Yücel, 2010), this heightened sensitivity could create a vulnerability to an intense, maladaptive response such as anhedonia when goals are thwarted. Perhaps additional factors such as inherited risk or exposure to childhood adversity may then shift some adolescents toward a dysregulated processing of rewards.

Pubertal maturation may contribute to this pathway, creating a vulnerable state for alterations to – and also directly influencing (Holder & Blaustein, 2014; Sisk & Foster, 2004) – rapidly maturing neural reward circuitry including the perception, pursuit, and enjoyment of rewards (Goddings et al., 2019; Steinberg, 2008). In some adolescents, these alterations can contribute to the development of anhedonia (Auerbach et al., 2014; Brent & Birmaher, 2002; Forbes & Dahl, 2012). With anhedonia, the joy of life, the energy to pursue pleasant activities, and the experience of meaning and purpose in life are diminished, and the influence of this alteration on typical experiences can be long-lasting. Given the ramifications of anhedonia during adolescence, the need to understand anhedonia during this developmental period is of vital importance.

Neural reward systems Frontostriatal circuitry

Neural reward systems are responsible for identifying, anticipating, experiencing, responding to, and generating motivation to obtain rewards. Regions of frontostriatal circuitry include the VS (the hub of reward; responding to rewarding or pleasurable stimuli, hedonics, and prediction error), dorsal striatum (i.e., caudate and putamen; decision-making), mPFC (valuation of rewards as relevant to oneself and regulation of VS responding), amygdala (identifying the valence and salience of rewards after receipt), ventrolateral prefrontal cortex (reward-

related decision making), orbitofrontal cortex (computing reward value), and dorsal anterior cingulate cortex (regulating cognition and behavior in response to rewards) (Haber & Knutson, 2010).

Disruptions in frontostriatal circuitry could be the mechanisms underlying anhedonia. As mentioned, early work suggested that in response to monetary rewards, adolescents with depression tend to have low VS activation but high mPFC activation (Forbes et al., 2009; Keren et al., 2018; Stringaris et al., 2015). There are several possible interpretations of this pattern. For example, an adolescent may experience pleasure from social interactions, which activates the VS, but there may be an overregulation of the VS by the mPFC, which could result in attenuated intensity and duration of the affective response. Disrupted frontostriatal circuitry could also be a result of mPFC signaling VS in efforts to recruit more DA responses to a reward (Forbes & Dahl, 2012). Alternatively, disrupted hedonic capacity could be a result of not assigning a high value (i.e., the desire or preference) to a reward, which in turn can contribute to reduced drive and motivation to pursue rewards (van der Meer & Redish, 2011). Another possibility is that the mPFC, given its role in rumination (Zhou et al., 2020) is overactivated and has poor flexibility for shifting out of negative, self-focused thought patterns, making it unlikely for an individual to fully enjoy rewarding experiences.

Importantly, anhedonia can also include other components of reward including motivation, reward learning, motor actions, effort expenditure, and decision-making (Cooper et al., 2018; Treadway & Zald, 2011; Lemke et al., 1999). Given the differences in stages and contexts, the underlying mechanisms of anhedonia may differ. For example, consummatory anhedonia is thought to include disruptions in reward regions such as the VS and the OFC while anticipatory anhedonia is thought to include disruptions in the mPFC, ACC, OFC, and basal ganglia (Der-Avakian & Markou, 2012).

Dopamine neuromodulatory system

Dopamine pathways originate in the midbrain in either the ventral tegmental area (VTA) or substantia nigra. Two relevant pathways for our model are (a) the mesolimbic pathway, which projects to the VS from the VTA and is involved in wanting rewards as well as engaging in behaviors to obtain rewards, and (b) the mesocortical pathway, which extends from the VTA to the mPFC (Berridge, 2018). The mesocortical pathway is involved in processes such as affective processing and executive function. Anhedonia is thought to be characterized by disruptions in the mesolimbic pathway such as decreased availability of striatal DA (Keller et al., 2013). Animal models show that DA neuron firing increases during adolescence (McCutcheon et al., 2012) and the balance of DA pathways shifts from mesolimbic

(e.g., VTA to VS) to mesocortical (e.g., VTA to medial PFC) (Berridge, 2018), likely subserving increased self-control and cognition. DA release, which occurs in response to unexpected and salient rewards, generates new learning and motivated actions (Berridge & Robinson, 1998; Schultz, 2002, 2007).

Mesocorticolimbic DA circuitry and related processes such as DA signaling undergo maturation in adolescence and into early adulthood (Reynolds & Flores, 2021). The DA system is a critical component of several reward-related processes during adolescence, including reward learning, behavioral control, motivation, and event salience (Reynolds & Flores, 2021; Schultz, 2007; Spanagel & Weiss, 1999). The DA system has also been referred to as the system essential to experience-induced neural plasticity (Reynolds & Flores, 2021) in areas of higher-order cognition, such as regions of the PFC (e.g., dorsolateral prefrontal cortex, dlPFC) (Larsen & Luna, 2018; Peters & Naneix, 2022; Widge, Heilbrunner, & Hayden, 2019). Development of this system during adolescence is considered to promote flexible self-control into adulthood (Peters & Naneix, 2022). Furthermore, human studies using striatal tissue iron as a proxy for DA availability indicate that DA can underlie changes in sensitivity to reward that occur into adulthood (Parr et al., 2021).

Factors influencing anhedonia development during adolescence

This section provides background and support for our proposed model across several relevant literature. Generally, findings from research on pubertal maturation, neural reward system development, chronic inflammation, and childhood adversity suggest preliminary but incomplete evidence in favor of the model.

Puberty, reward, and anhedonia development

Pubertal maturation influences neural systems (Goddings et al., 2019; Pfeifer & Allen, 2021; Vijayakumar et al., 2018) and could accelerate anhedonia development. In the context of neural reward systems and among young adolescents, pubertal maturation is associated with less striatal and more mPFC activation during reward outcomes (Forbes et al., 2010). Additionally, higher levels of estradiol in girls are associated with less VS activation to reward cues (Ladouceur et al., 2019). Hormones such as testosterone and estrogen may influence neurotransmission of DA, which in turn can impact the way in which neural circuitry matures and the way in which reward processing and cognition (and cognition e.g., working memory) proceed during adolescence (Sinclair, Purves-Tyson, Allen, & Weickert, 2014). Rodent studies using sucrose preference tests – a test thought to capture anhedonia – find

that exposure to amphetamine before puberty can induce DA availability in the mPFC, and after withdrawal from amphetamine, anhedonia is most severe closest to the onset of puberty (Kang, Wu, Galvez, & Gulley, 2016).

Clinical symptoms such as depression, emotional distress, and anxiety are related to pubertal development (Angold, Costello, Erkanli, & Worthman, 1999; Barendse et al., 2022; Berenbaum et al., 2015). Given these literatures, it is possible that pubertal maturation could accelerate the progression of anhedonia in adolescence. Theories suggest that increases in adrenal and gonadal hormones contribute to psychopathology (Angold et al., 1999; Barendse et al., 2022; Byrne et al., 2022; Sinclair et al., 2014). Interestingly, it appears that only during mid-later pubertal maturation – and not earlier, even in young people of the same age – does low VS activation during reward anticipation predict an increase in depression severity (Morgan, Olino, McMakin, Ryan, & Forbes, 2013). This highlights that perhaps puberty facilitates associations between frontostriatal circuitry and clinical symptoms.

Drawing from studies of adolescents with depression (Keenan, Culbert, Grimm, Hipwell, & Stepp, 2014), it is also possible that both pubertal timing (the age at which puberty begins) and pubertal tempo (the rate at which puberty progresses) play a role in the association between changes in neural reward systems and anhedonia. For example, early pubertal timing predicts the onset of a first depressive episode in boys and girls (Copeland et al., 2019; Hamlat, McCormick, Young, & Hankin, 2020), and faster pubertal tempo is related to depression severity later in adolescence (Keenan et al., 2014). A recent review found an association between pubertal stage and depression in girls but not boys, with robust effects in White girls, in particular (Stumper & Alloy, 2023). Findings on the role of pubertal timing in boys are mixed, with some work suggesting that early pubertal timing contributes to depressive symptoms and other work reporting no association (Ge et al., 2001; Mendle et al., 2012). See Table 1 for selected studies discussed.

As mentioned, sex differences in anhedonia are prevalent and have been observed starting at age 13, with boys reporting more anhedonia and even an increase in anhedonia during mid-late adolescence. Given the timing of increases in anhedonia during early adolescence (Hankin et al., 1998), it has been suggested that one explanation for sex differences in depressive symptoms is pubertal maturation. Puberty may play a role in the emergence of depressive symptoms especially for girls due to reasons such as an increase in pubertal hormones and early physical changes (Angold, Costello, & Worthman, 1998). However, this is not well-understood in the context of anhedonia and may be

especially critical to understand in future work in the context of boys' mental health, given anhedonia's higher prevalence in boys than girls.

Social processes. While not a direct focus of our model, it is important to note that a pathway from pubertal maturation to anhedonia could be through social processes. Pubertal maturation may allow plasticity to be shaped by factors such as adolescents' peer social environment in contrast to the family-focused plasticity of childhood (Piekarski et al., 2017). Pubertal maturation may open a window in which responses to social processes become disrupted behaviorally and neurally (Pfeifer & Allen, 2021). Social behavior has distinct phases that are driven by changes in the central social circle (e.g., parent, peer, romantic partner) (Nelson, Jarcho, & Guyer, 2015), with parents at the center of the social environment during childhood and a shift from parents to peers in adolescence. Adolescents' pursuit of social behaviors is thought to be based on social concern and social status (Steinberg & Morris, 2001). Earlier pubertal onset may contribute to problematic psychological outcomes, possibly for social reasons such as the pressure of exhibiting greater maturity in appearance compared with one's peers. For example, earlier pubertal maturation can set girls apart, even contributing to isolation or bullying (Mendle, 2014) while later pubertal onset in boys could contribute to similar outcomes due to the stigma of not appearing fully mature (e.g., muscle growth, body size, facial hair) (Mendle & Ferrero, 2012). There are a range of social responses to the changes in physical appearance that result from puberty which can occur during a time in which there is already heightened sensitivity to social interactions, a desire to affiliate, and a wish to receive social approval from peers. Pubertal maturation also influences (and is influenced by) adverse social contexts including sexual abuse and exposure to surroundings with high levels of interpersonal violence (Graber, 2013; Sumner, Colich, Uddin, Armstrong, & McLaughlin, 2019; Zhang, Zhang, & Sun, 2019). There is also recent work globally examining the influences of the COVID-19 pandemic on puberty, showing an increase in precocious puberty in girls and altered biological changes such as lower ovarian volume (Oliveira Neto et al., 2022) and increased pubertal progression. These effects are perhaps due to the influences of environmental changes and stressors resulting from the lockdown (e.g., sedentary lifestyle, use of electronic devices, increased body mass index) (Stagi et al., 2020).

Taken together, the influence of pubertal changes on social domains could be a factor that contributes to adolescents' anhedonia in typically developing youth. However, for some, perhaps the earlier exposure to child adversity and changes in the immune response may accelerate the progression

Table 1 Selection of studies discussed of constructs proposed in the model

Pathway	Author	N, sample type/clinical status	Age	%Women/ girls, %Racial composition	Design and relevant constructs	Relevant findings supporting proposed model?
Puberty → Neural Reward Systems	Forbes et al. (2010)	- N = 77 - Healthy adolescents, 26 pre/early pubertal, 51 mid-late pubertal	11–13 years	50% Girls 75% White 5% Black 1% Asian 1% Native American	- Longitudinal - Self-reported depression - Physical examination and pubertal hormone collection - fMRI guessing reward task	<u>Yes</u> - Advanced pubertal maturation related to less VS and more mPFC activation during reward outcome compared to adolescents with less advanced pubertal maturation - Higher testosterone levels were related to more VS activation during reward anticipation in boys; negative correlation with VS activation in girls and boys during reward outcome
	Ladouceur et al. (2019)	- N = 79 - Community adolescents, varying in pubertal status	10–13 years	59% Girls 65% White 22% Black 1% Asian 4% Hispanic or Latino 10% More than one race	- Cross-sectional - Tanner staging, self-reported pubertal development, pubertal hormone collection - fMRI reward cue processing task	<u>Yes</u> - Girls with higher estradiol levels showed less activation in the left/right caudate and more nucleus accumbens-putamen connectivity - Girls with more testosterone showed more VS-anterior cingulate cortex and insula connectivity, but no associations in boys
Puberty → Anhedonia	Hamlat et al. (2020)	- N = 603 - Community adolescents, typically developing	12.09 years (Avg ^a)	56% Girls 69% White 10.5% Black 9.2% Asian or Pacific Islander 0.8% Native American or Alaskan Native 12.8% Hispanic or Latino 10.5% Other	- Longitudinal - Self-reported pubertal timing - Interview assessing depression	<u>Mixed</u> Earlier pubertal timing predicted the onset of a first, depressive episode and recurrent episodes following
	Keenan et al. (2014)	- N = 2,450 - community sample of adolescents, oversampling of households in low-income neighborhoods	9–17 years	- Girls only 41% White 52% Black	- Longitudinal - Tanner staging estimations, self-reported physical development - Self-reported depression	<u>Yes</u> - In those with earlier pubertal timing, there were also more depressive symptoms at age 10 years; slower tempo was related to higher depressive symptoms at this age as well - Faster tempo was related to more depression ages 10–13 years

(continues)

Table 1 (continued)

Pathway	Author	N, sample type/clinical status	Age	%Women/ girls, %Racial composition	Design and relevant constructs	Relevant findings supporting proposed model?
Inflammation → Neural Reward Systems	Bradley et al. (2019)	- N = 46 - diverse psychiatric symptoms from out-patient clinic	12–20 years	54% Girls 41% White 37% Black 2% Asian 20% Other	- Cross-sectional - Inflammatory markers - fMRI reward flanker task	<u>Yes</u> Reduced frontostriatal activation during reward attainment associated with increased cytokine levels
	Eisenberger et al. (2010)	- N = 39 - without psychiatric disorders	18–36 years	51% Women 39% White 7% Black 18% Hispanic 18% Asian 18% Other	- Cross-sectional, randomized - Endotoxin administration - Observer rated and self-reported depression - fMRI monetary reward task	<u>Yes</u> - After endotoxin administration, more depressed mood - Reduced VS response to reward was also observed after administration
	Felger et al. (2016)	- N = 48 - MDD primary diagnosis	18–65 years	70.8% Women 37.5% White 62.5% Black	- Cross-sectional - Inflammatory markers - Resting-state fMRI	<u>Yes</u> Elevated levels of CRP and cytokines were related to lower functional connectivity between the VS and vmPFC
	Liu et al. (2020)	- N = 64 - with psychiatric symptoms	12–20 years	69% Girls 48.4% White 27.7% Black 21.9% Other	- Cross-sectional - Self-reported anhedonia - Clinician ratings and self-reported depression - Inflammatory markers - fMRI reward flanker task	<u>Mixed</u> - No relationship between CRP levels and anhedonia and depression - Elevated CRP was related to activation of reward regions (e.g., VS) during anticipation, attainment, prediction error
	Rengasamy et al. (2023)	- N = 36 - high risk for depression	13–19 years	55.6% Girls 69.4% White 13.9% Black 5.6% More than one race 11.1% Unknown	- Cross-sectional - Inflammatory markers - fMRI guessing reward task	<u>Yes</u> Inflammatory markers linked to greater FC between VS and regions of the DMN during win anticipation
	Swartz et al. (2021)	- N = 70 - community sample of adolescents	12–15 years	32 Girls, 2 Nonbinary 37% White 4% Black 9% Asian 4% Native Hawaiian or Pacific Islander 7% Hispanic or Latino 34% More than two races	- Cross-sectional - Inflammatory markers - Resting-state fMRI	<u>No</u> Higher TNF-α was related to increased amygdala-VS and prefrontal-parietal resting-state connectivity

(continues)

Table 1 (continued)

Pathway	Author	N, sample type/clinical status	Age	%Women/girls, %Racial composition	Design and relevant constructs	Relevant findings supporting proposed model?
Inflammation → Puberty	Stumper et al. (2020)	- N = 155 - community sample of adolescents	12–20 years	52.4% Girls 42.6% White 57.4% Black	- Cross-sectional - Self-reported pubertal development - Inflammatory markers	Mixed - Advanced pubertal status was associated with lower levels of TNF-α and IL-8 - More mature girls, but not boys, had higher CRP levels
Inflammation → Anhedonia	Rengasamy et al. (2021)	- N = 36 - with a depressive disorder diagnosis	12–18 years	75% Girls 77.8% White 22.2% Non-white^b	- Longitudinal - Depressive disorder based on clinician ratings - Self-reported anhedonia - Inflammatory markers	Yes Higher TNF-α levels predicted depression and anhedonia severity at follow up
Childhood Adversity → Neural Reward Systems	Tabatabaeizadeh et al. (2018)	- N = 563 244 with depressive symptoms, 319 healthy adolescents	12–18 years	- Girls only %100 Iranian	- Cross-sectional - Self-reported depression - Inflammatory markers	Mixed Higher hr-CRP levels were related to depression severity
	Colich et al. (2017)	- N = 137 - early pubertal development, Tanner Stage 3 or below	9–13 years	57% Girls 44% White 9% Black 12% Asian 2% Native American 13% Hispanic or Latino 18% Other	- Cross-sectional - Adversity interview - Tanner staging - fMRI emotion label task	Mixed - Positive association between adversity and vPFC and internalizing problems in girls - Associations between adversity and lower right vPFC-bilateral amygdala connectivity in boys and girls
	Peverill et al. (2019)	- N = 57 - sample includes variability in violence exposure	16.93 years (Avg) ^a	61.4% Girls 28.1% White 29.8% Black 8.8% Asian 19.3% Hispanic or Latino 14% Other	- Longitudinal - Adversity was assessed with self-report and interview - fMRI emotion regulation task	Yes Greater vmPFC-amygdala negative FC in those exposed to adversity (e.g., physical abuse) than those without exposure
	Zhu et al. (2019)	- N = 202 - adults, community sample	23.2 years (Avg) ^a	58.4% Women 69% White 9% Black 16% Asian 13% Hispanic or Latino 12% Other	- Retrospective cohort study - Maltreatment scale - fMRI task of viewing angry and fearful faces vs. neutral or shapes	Yes - Retroactive reports of exposure to maltreatment during early life was related to activation of the amygdala in response to emotional faces vs. shapes - Early exposure related to blunted amygdala response; later exposure associated with augmented response

(continues)

Table 1 (continued)

Pathway	Author	N, sample type/clinical status	Age	%Women/ girls, %Racial composition	Design and relevant constructs	Relevant findings supporting proposed model?
Childhood Adversity → Puberty	Colich et al. (2023)	• N = 227 adolescents	10–13 years	• 48% Girls • 63.8% White • 12.3% Black • 7.9% Asian • 11% Hispanic or Latino • 4.85% Other	• Cross-sectional • Threat and deprivation assessments • Tanner staging • fMRI task of passive viewing of fearful and calm faces	Mixed • Earlier pubertal development was related to childhood trauma • Earlier pubertal timing was associated with lower activation of limbic regions (e.g., amygdala) when viewing fearful and calm faces • Pubertal timing was not related to amygdala-mPFC connectivity
						Mixed • Girls exposed to trauma before onset of puberty were more likely to have a depressive disorder diagnosis whereas those exposed to trauma during puberty were more likely to have an anxiety disorder
Childhood Adversity → Anhedonia	Marshall (2016)	• N = 2,899 adolescents	13–18 years	• Girls only • 55.05% White • 19.39% Black • 19.73% Hispanic or Latino • 5.83% Other	• Longitudinal • Exposure to trauma collected using clinical interview • Self-report age of menarche • Clinical diagnoses from interview	Mixed • Girls exposed to trauma before onset of puberty were more likely to have a depressive disorder diagnosis whereas those exposed to trauma during puberty were more likely to have an anxiety disorder
						Mixed • Exposure to threat (e.g., violence) was related to advanced pubertal stage but deprivation (e.g., food insecurity) was not
Childhood Adversity → Anhedonia	Sumner et al. (2019)	• N = 247 • children and adolescents from the community	8–16 years	• 48% Girls • 38.9% White • 27.9% Black • 21.1% Other	• Cross-sectional • Exposure to adversity (e.g., violence) • Tanner staging	Mixed • Exposure to threat (e.g., violence) was related to advanced pubertal stage but deprivation (e.g., food insecurity) was not
						Yes • Early life unpredictability was associated with greater anhedonia during adulthood over 6 months
Childhood Adversity → Inflammation	Spadoni et al. (2022)	• N = 156 • adults exposed to lifetime trauma	21–90 years	• 38% Women • 65.38% White • 21.79% Black • 8.33% Asian • 2.56% Native Hawaiian/Pacific Islander • 21.15% Hispanic or Latino • 3.21% Other/unknown	• Longitudinal • Anhedonia self-report • Adversity assessed using self-report measures	Yes • Early life unpredictability was associated with greater anhedonia during adulthood over 6 months
						Yes • Adverse events occurring in early or middle childhood and cumulative adversity up to 8 years predicted elevated CRP in mid adolescence
Childhood Adversity → Inflammation	Slopen et al. (2013)	• N = 5,802 adolescents	Prior to 8 years, 10–15 years	• 50% Girls • 95% White • 5% Non-white ^b	• Prospective, longitudinal • Parent report of child's acute adverse events • Inflammatory markers	Yes • Adverse events occurring in early or middle childhood and cumulative adversity up to 8 years predicted elevated CRP in mid adolescence
						Mixed • Early adversity moderated the relationship between cytokines (e.g., IL-6) and decreases in the pursuit of reward and reward response bias
Childhood Adversity → Inflammation Neural Reward Systems	Kuhlman et al. (2023)	• N = 80 • oversampled for adversity	12–15 years	• 45% Girls • 77.5% White • 8.8% Black • 8.8% Asian • 35% Hispanic or Latino	• Cross-sectional • Parent report of child's exposure to adversity • Inflammatory markers • Behavioral pirate reward task	Mixed • Early adversity moderated the relationship between cytokines (e.g., IL-6) and decreases in the pursuit of reward and reward response bias

(continues)

Table 1 (continued)

Pathway	Author	N, sample type/clinical status	Age	%Women/ girls, %Racial composition	Design and relevant constructs	Relevant findings supporting proposed model?
Childhood → Adversity → Inflammation → Anhedonia	Slavich et al. (2020)	- N = 116 - with mental health concerns over the past 2 years	12–16 years	- Girls only 65.5% White 34.5% Non-white^b	- Longitudinal - Life stress interview, laboratory social stress test - Self-reported depression - Inflammatory markers	Mixed TNF-α and IL-18 increases moderate recent interpersonal stress exposure on the development of depressive symptoms

Findings are listed in alphabetical order within sections “Yes” = supports model, “Mixed” = mixed evidence in support of model, “No” = does not support the model. Sample characteristics (age, %girls/women, %racial composition) are presented when this information was available and/or calculated. The table highlights selected studies in the text but do not include all studies (e.g., animal studies) in the literature. Findings discussed in the table do not include all findings from each article but instead, findings relevant for the proposed model and topic of this Review. CRP, C-reactive protein; DMN, default mode network; FC, functional connectivity; IL, interleukin; MDD, major depressive disorder; mPFC, medial prefrontal cortex; TNF, tumor necrosis factor; vPFC, ventral lateral prefrontal cortex; vmPFC, ventral medial prefrontal cortex; VS, ventral striatum.

^aAverage age reported only.

^bWhite and Non-white were reported only.

and severity of anhedonia which will be discussed next.

Chronic inflammation, puberty, reward, and anhedonia development

While puberty influences neural reward systems (Goddings et al., 2019) and perhaps accelerates the development of anhedonia, both animal and human models indicate that chronic inflammation also disrupts neural reward systems and is a possible pathophysiological pathway to anhedonia (Bekhbat et al., 2022; Lucido et al., 2021; Swardfager, Rosenblat, Benlamri, & McIntyre, 2016). At a starting point, while there are multiple pathways likely at play, pubertal hormones such as estrogen and testosterone likely alter the immune system (Cutolo & Wilder, 2000; Stumper et al., 2020). Immunomodulatory proteins play an important role in regulating immune system function and include C-reactive protein (CRP) and cytokines [e.g., interleukins (IL), interferons (IFN), tumor necrosis factors (TNF), transforming growth factors (TGF)] (Kany et al., 2019).

After puberty, girls experience increases in inflammatory responses compared to boys (Yang & Kozloski, 2011). Additionally, earlier pubertal onset is related to lower levels of TNF-α and IL-8 in girls but not boys (Stumper et al., 2020). From more established literature, adolescents with physical conditions *resulting* in persistent inflammation (e.g., Crohn’s disease) tend to experience alterations in pubertal maturation such as delays in onset (Brain & Savage, 1994; Grob & Zacharin, 2020; Jin et al., 2021). Taken together, there may be a bidirectional effect between pubertal maturation and chronic inflammation although the details of these relationships (e.g., earlier pubertal onset, lower levels of pro-inflammatory cytokines) need to be further elucidated.

Pro-inflammatory cytokines influence neural reward systems (Miller, Maletic, & Raison, 2009); however, this literature is somewhat mixed. In animal studies, administering vaccines or endotoxins that induce an immune response leads to disruptions in frontostriatal circuitry, including altered VS response to rewards (Bekhbat et al., 2022; Eisenberger et al., 2010). In a study of humans, while no associations were observed with anhedonia, increased CRP was related to increased activation in the left lateral occipital, posterior, and superior parietal cortices during reward attainment but not reward anticipation in adults (Liu et al., 2020). In other work in adults, CRP was not associated with neural activation during a neural reward task (Bradley et al., 2019). However, using principal component analyses, specific factors of cytokines (e.g., IL-3, IL-4) were negatively associated with precuneus/posterior cingulate cortex activation during anticipation of neural rewards, and another

factor (e.g., IL-9 and IL-15) was negatively associated with angular gyrus activation during reward attainment (Bradley et al., 2019). In the context of DA, a hypothesized pathway to anhedonia includes the process by which chronic inflammation targets presynaptic DA in regions with high concentrations of DA such as the striatum (Felger & Treadway, 2017). Animal models show that chronic inflammation can reduce striatal DA availability (Felger & Lotrich, 2013), with experimental work suggesting that cytokines in particular cause reductions in the release of DA (Felger, Hernandez, & Miller, 2015).

While the literature is complex, chronic inflammation and anhedonia are likely associated especially given the possible role of chronic inflammation in the pathogenesis of depression (Miller & Raison, 2016). Theoretical models have noted that there is an intuitive connection between chronic inflammation and anhedonia, given that the behavioral phenotype of anhedonia—fatigue, low motivation, reduced engagement in pleasant activities—mimics “general sickness behavior” (Dantzer & Kelley, 2007). In studies of adults, patients given IFN- α to treat hepatitis C virus tend to report anhedonia (Capuron et al., 2002). In animal studies, depressive-like behaviors such as decreases in sucrose preference emerge after introducing inflammatory insults (e.g., chronic inoculation with *Bacillus Calmette-Guerin*) (Moreau et al., 2008). Rhesus monkeys exposed to chronic IFN- α show increases in depressive symptoms including huddling behavior (Felger et al., 2007). In human studies, among adolescents given in-vitro lipopolysaccharide stimulation (which stimulates the immune response), anhedonia is associated with elevated levels of pro-inflammatory cytokines (see Freed et al., 2018 full list). Additionally, there is evidence that anti-cytokine therapies, which reduce chronic inflammation, decrease the severity in depressive symptoms in adults with depression (Kappelmann, Lewis, Dantzer, Jones, & Khandaker, 2018). Importantly, the prevailing model for the association between chronic inflammation and psychopathology conceptualizes acute inflammatory response as a component of an adaptive response while emphasizing that psychopathology most likely arises from the chronic, long-term influence of non-optimally regulated inflammation (Goldsmith, Bekhbat, Mehta, & Felger, 2023).

While somewhat outside the scope of this review, there are also additional possibilities such as the impacts of chronic inflammation on white matter integrity which can lead to altered brain function and anhedonia. For example, in adults with depression, there is a negative association between TNF- α and fractional anisotropy (Lim, Sohn, Kwon, & Kim, 2021). This idea is further supported by studies suggesting associations between anhedonia and white matter tracts of neural reward processing in adolescent depression (Henderson et al., 2013).

Another possibility is that chronic inflammation may damage and decrease microglia in reward circuitry (Miller, Haroon, & Felger, 2017).

Childhood adversity, puberty, reward, and anhedonia development

So far, we have discussed literature on pubertal maturation and its influence on neural reward systems, chronic inflammation, and the progression to anhedonia in adolescence. Social and contextual factors can shape these relationships. Exposure to childhood adversity is one such factor that, in some individuals, may shape how pubertal maturation influences the neural mechanisms of anhedonia. Consistent with the developmental psychopathology principle of multifinality, wherein an event may trigger multiple pathways and outcomes (Klahr, Burt, & Nikolas, 2012), not all those exposed to childhood adversity will experience anhedonia in adolescence. Some youth exposed to adversity may develop prosocial or hypervigilant responses. However, in those who are vulnerable—perhaps those with certain stress phenotypes or those exposed to certain types of adversity (e.g., deprivation)—such exposures may cause disruptions in neural reward circuitry, alterations in the immune response, and the emergence of anhedonia (Hostinar, Swartz, Alen, Guyer, & Hastings, 2023; Kasperek et al., 2023).

Exposure to adversity during childhood has been consistently associated with psychopathology (Anda et al., 2006; Francis, Tsaliopoulou, Stock, Pingault, & Baldwin, 2023) including anhedonia in adolescents (O'Brien et al., 2023) and adults (Spadoni et al., 2022). The additional influence of adversity on physiologic functioning—specifically functions associated with pubertal maturation—may contribute to the development of psychopathology in those exposed to adversity. Life history and adaptive models posit that individuals develop in response to early life experiences to adapt effectively to the environmental demands they may continue to experience later in life (Ellis, Figueredo, Brumbach, & Schlomer, 2009; Ellis, Sheridan, Belsky, & McLaughlin, 2022; Nettle, Frankenhuys, & Rickard, 2014). Individuals exposed to significant environmental threats or harsh conditions during childhood may have an accelerated pubertal onset, possibly to achieve the physical and socioemotional characteristics of adulthood required to exist independently separate from a harsh environment; in contrast, those exposed to environmental deprivation may have an unaffected or delayed pubertal onset (Callaghan & Tottenham, 2016; Colich et al., 2020; Johnson et al., 2018; Negriff, Blankson, & Trickett, 2015; Sumner et al., 2019). For example, girls who have experienced childhood sexual abuse also experience early pubertal onset (Noll et al., 2017). Some of these changes in pubertal maturation are associated with psychopathology, where earlier pubertal

onset in girls mediates the association between childhood exposure to threat and increased risk for psychological distress (Colich et al., 2020). While continued exposure to adversity is an ongoing risk for the development of psychopathology, including during the pubertal period (Bosch et al., 2012), some animal research has demonstrated that a shift from a stressful early-life environment to a supportive environment may offer a window for pubertal recalibration of stress response systems, potentially leading to resilient outcomes (for review, see DePasquale, Herzberg, & Gunnar, 2021). Specifically, in the absence of continued adversity, the heightened plasticity of the peripubertal period may reset the tone of physiologic and neural stress-response systems that have been altered by prior childhood adversity. The dynamic nature of puberty and adversity may impact the developing frontostriatal circuits and, subsequently, the emergence of anhedonia.

The association between childhood threat and earlier pubertal status is postulated to be due to changes in hypothalamic–pituitary–adrenal (HPA) axis function, which may trigger earlier maturation of the hypothalamic–pituitary–gonadal axis (Belsky, Ruttle, Boyce, Armstrong, & Essex, 2015; Engel & Gunnar, 2020; Saxbe, Negri, Susman, & Trickett, 2015). While a critical review of this literature is beyond the scope of this review, the intersection of HPA axis function, inflammation, and reward circuitry is relevant to understanding how childhood adversity and puberty may impact frontostriatal circuits and anhedonia. In addition to the hypothalamus, where stress stimulates the eventual release of cortisol via the HPA axis, corticotropin-releasing hormone (CRH) plays a neuromodulatory role in the VS. Specifically, CRH-expressing projections from the basolateral amygdala and mPFC to the VS (Itoga et al., 2019) may play a role in blunting frontostriatal DA release in the setting of stress (Birnie et al., 2020). This is supported by rodent research showing that male rats experiencing stress during puberty have lower striatal DA turnover and higher anhedonia-like behaviors during a sucrose preference test (Harris, Villalobos-Manriquez, Melo, Clarke, & O’Leary, 2022). Specifically, rodents exhibited reduced locomotor and exploratory behavior, similar to reduced motivation, reduced pleasure-seeking, and psychomotor slowing, all of which are considered homologous to anhedonia.

Human neuroimaging studies in young adults further demonstrate adversity-associated changes in mPFC connectivity that are associated with anhedonia (Eckstrand et al., 2019), and that both VS and amygdala reward function interact with childhood adversity to impact mood symptoms (Eckstrand et al., 2021). While this supports the hypothesis that altered VS–mPFC connectivity, influenced by dysfunctional CRH signaling from the amygdala in the setting of prior stress, may be a

mechanism for the development of anhedonia following childhood adversity (Birnie et al., 2020), no research has tested this explicit hypothesis in relation to puberty.

The timing of childhood adversity in relationship to puberty may play an important role in how brain–mood relationships are impacted. In a longitudinal study examining the timing of trauma exposure on the development of psychiatric disorders, girls exposed to trauma before the onset of puberty were more likely to have a depressive disorder diagnosis, whereas those exposed to trauma during puberty were more likely to have an anxiety disorder (Marshall, 2016). Similarly, cortisol profiles differ based on the timing of adversity relative to puberty, where childhood adversity is associated with higher cortisol during adolescence but adolescent adversity is associated with lower cortisol (Bosch et al., 2012). Last, when considering neural affective circuitry, threat exposure prior to puberty may blunt amygdala function and accelerate amygdala–mPFC connectivity (Colich et al., 2017; Peverill, Sheridan, Busso, & McLaughlin, 2019). Preliminary animal research suggests that alterations in amygdala function and amygdala–mPFC connectivity mediate the association between early-life adversity and anhedonia (Bolton et al., 2018), but only one study has examined this hypothesis in humans, with null results (Colich et al., 2023).

The role of chronic inflammation in associations between childhood adversity and adolescent anhedonia

Chronic inflammation may mediate outcomes of childhood adversity and the emergence of psychopathology (Slavich & Irwin, 2014). This could be due to the fact that pro-inflammatory cytokines, especially TNF- α and IL- β , are mediators of “sickness behaviors” (Dantzer, 2009; Slavich, 2020). Relatedly, the Social Signal Transduction Theory of Depression (Slavich & Irwin, 2014) posits that exposure to interpersonal stressors can lead to pro-inflammatory cytokines to increase the immune response leading to changes in behavior including the emergence of depressive symptoms. Furthermore, changes in neural reward systems might form the mechanistic basis for this association. Longitudinal evidence suggests that exposure to adversity in early and mid-childhood predicts elevations in CRP in adolescence (Slopen et al., 2013). Relatedly, one theory, “the neuroimmune network hypothesis”, posits that exposure to childhood adversity increases the communication between the immune system and neural circuits underlying reward and threat processing, leading to low-grade inflammation and then long-term physical and mental health challenges (see Nusslock & Miller, 2016). Importantly, anhedonia has not been tested in these models. This is a necessary future direction of this research.

Other work has approached early adversity as a moderator, indicating that chronic inflammation-reward or inflammation-anhedonia associations are present only in those with a history of adversity. In adolescents, exposure to early adversity may moderate the link between elevated IL-6 and a decrease in tolerating risk when pursuing rewards (assessed with a computerized reward task) (Kuhlman et al., 2023). Another study in adolescent girls found increases in TNF- α and IL-1 β moderate the relationship between recent interpersonal stress and depressive symptoms (Slavich et al., 2020).

Evaluation of the evidence for the proposed model

As shown in the overview of studies highlighted above in Table 1, there is evidence supporting our proposed model. However, there are important limitations of the current literatures. For example, there is a need for studies with more rigorous designs and more diverse samples. Many of the studies to date have cross-sectional designs, tend to have small sample sizes, and include mostly White individuals. To truly investigate and draw generalizable conclusions about the development of anhedonia requires samples that represent the population of adolescents; prospective, longitudinal designs; and application of computational models to unpack indirect and direct effects of the putative pathways. Using a developmental framework is particularly useful so we can better steer youth toward a healthy trajectory of neural, social, and affective development. This is especially important given that certain points in the lifespan involve vulnerability to experiences, neural plasticity, and the onset of psychopathology. Interestingly, several relevant studies include large age ranges or arbitrarily divided age ranges of adolescence and adulthood, limiting the availability to focus conclusions on adolescence. While the age range is a central factor of some of the studies discussed, further consensus on what constitutes “adolescence” will allow for more powerful interpretations of findings.

A few links in our model are understudied, providing key opportunities for further research. The influence of chronic inflammation on puberty is not well understood, and the limited empirical findings preclude a clear conclusion or hypothesis. We discussed findings suggesting that advanced pubertal status is associated with *lower* pro-inflammatory cytokine levels in an adolescent sample (Stumper et al., 2020), yet *higher* levels of pro-inflammatory cytokines appear to mediate or moderate the relationship between interpersonal stressors and depressive symptoms (Slavich et al., 2020; Slavich & Irwin, 2014). Furthermore, elevated levels of pro-inflammatory markers have been linked to both increased and reduced activation of frontostriatal circuitry (Felger et al., 2016; Swartz

et al., 2021). These findings highlight the complex nature of these relationships and the importance of teasing apart causality and directionality. Furthermore, while there are some findings of the effects of both childhood adversity and chronic inflammation on frontostriatal circuitry, less is known about their influence on the DA neuromodulatory system. In fact, it would be compelling to investigate whether effects on frontostriatal circuitry are driven by changes in DA signaling. In addition, studies of DA are more commonly conducted in animals than in humans possibly because of the ability to adequately measure anhedonia using approaches discussed such as sucrose preference tests. It will be important to continue to draw from animal studies and develop models of anhedonia in humans.

Overwhelmingly, research on childhood adversity, puberty, and neural systems as factors in developmental psychopathology has focused on neural threat systems with a relative omission of reward systems. Recent growth in the study of reward systems starting to close this gap. This research should also unpack different outcomes – both adaptive and maladaptive – resulting from exposure to child adversity to understand long-term risk and resilience. Identifying trajectories of outcomes of childhood adversity and using sophisticated, within-person computational approaches will be valuable in this regard. Consistent with pubertal recalibration models (see above section on “Childhood Adversity, Puberty, Reward, and Anhedonia Development”), this research should also examine how factors associated with puberty, or the removal or remediation of adversity, may restore function in DA/neural reward circuitry or even attenuate anhedonia.

Furthermore, depressive disorders are heterogeneous. While anhedonia and depressed mood are criteria for MDD, they should be investigated as distinct outcomes. There are differences between the two symptoms in terms of risk factors (e.g., associations between anhedonia and suicidal ideation independent of depression; see meta-analysis; Ducasse et al., 2021) and treatment (Craske et al., 2019). In 564 adults who had experienced MDD in their lifetime collected from the Oregon Adolescent Depression Project, over half reported experiencing both anhedonia and depressed mood while 28% reported depressed mood only and 5% reported anhedonia only (Lewinsohn et al., 2003). In epidemiologic data from the National Survey on Drug Use and Health (Cohen & Thakur, 2022), 15% reported experiencing anhedonia in their lifetime, compared with 10% who reported depressed mood. Most studies of anhedonia in people with schizophrenia examine anhedonia as a part of a total negative symptom profile (e.g., the sum of anhedonia, asociality, and other symptom domains collected from a clinical interview). This approach, while valuable, can also limit the ability to isolate and understand individual negative symptom domains.

Altogether, the field may be too bound by traditional categories and classes of psychopathology. Perhaps moving toward examining anhedonia transdiagnostically can allow for the ability to clarify anhedonia phenotypes and identify who may be at heightened risk of developing anhedonia, and in turn, other psychopathology, or psychiatric outcomes later in life.

It will be important to focus attention on how pathways to anhedonia may be influenced in adolescents experiencing marginalization due to identities such as ability, sex, gender, sexual orientation, race, ethnicity, and culture. For example, there is evidence that sexual minority youth report more anhedonia and more victimization for sexual orientation than heterosexual youth (Eckstrand et al., 2022). Additionally, from studies of racial disparities, Black and Hispanic children experience more adversities such as financial hardship compared to White children in the United States (Slopen et al., 2016). In other work, children of immigrants tend to have higher poverty rates relative to children of parents born in the United States (Mendoza, 2009; Slopen et al., 2016). It is important to acknowledge the value of considering individual differences and heterogeneity in the study of anhedonia. A future direction is to examine anhedonia considering these noted contexts at play. Similarly, understanding how identities intersect and how intersectionality influences anhedonia will be informative as well.

Understanding early-onset anhedonia is an important future direction. As mentioned, anhedonia is rare before adolescence but can occur as early as age 3 (Prabhakar et al., 2022). Preschoolers' odds of having a depression diagnosis are substantially higher when the symptom of anhedonia is present, and children with anhedonia show greater sensitivity to stress (Luby et al., 2004). Given the developmental importance of experiencing joy and pleasure during childhood, the emergence of anhedonia early on in development is thought to signal an increased likelihood of developing later, severe psychopathology (Prabhakar et al., 2022) while recurrent depression is the more likely outcome when depression emerges during adolescence (Harrington et al., 1990). Anhedonia could develop early in childhood, especially among children who have experienced child adversity. In addition, children with anhedonia exhibit hypoactivation during reward anticipation in reward and salience regions including the dorsal striatum and cingulo-opercular network (Pornpattananangkul et al., 2019). Together, this early sensitivity to stress and altered frontostriatal response to the anticipation of rewards may represent a pre-existing, early vulnerability that is further exacerbated during pubertal maturation, leading to long-term consequences. Understanding the emergence of anhedonia earlier on in development will be important to disentangle in future research.

There are also important differences in the cultural norms and expectations (e.g., Western, Eastern

cultures) of the experience and expression of positive affect that should be considered in the study of anhedonia. Cultural differences exist in the experience and expression of affect with evidence of Japanese Americans showing lower positive affect (Kanazawa, White, & Hampson, 2007) and Mexican Americans showing higher levels compared to Whites (Ruby, Falk, Heine, Villa, & Silberstein, 2012). There are also differences in the desire to experience some emotions vs others. For example, in individualistic cultures, there tends to be a desire to experience more pride and less guilt than in collective cultures (Eid & Diener, 2001). While it has been argued that culture shapes how positive affect is both experienced and expressed (Tsai, Knutson, & Fung, 2006), this notion is not well integrated into the existing anhedonia literature. This also may influence the way in which studies exhibit bias in their samples; perhaps studies include individuals that come from cultures in which there is a norm and acceptance around expressing challenging emotional experiences. While culture likely matters in the context of anhedonia for the reasons discussed, as a field, we do not know “*how*” culture matters (Ryder, Ban, & Chentsova-Dutton, 2011) when considering this symptom domain.

A timely and imperative future direction is to consider in what ways changes in social attitudes and the evolution of social movements (e.g., Black Lives Matter) may reduce or enhance the risk for developing anhedonia. For example, perhaps communities joining together to promote social causes may enhance motivation toward social behaviors (e.g., city meetings and gatherings) and one's sense of meaning and purpose. Additionally, broader local and regional decisions (e.g., abortion laws, gun laws) could influence the rates and severity of anhedonia during adolescence. Other societal factors such as access to treatment may also be a factor contributing to anhedonia emergence and progression and should be examined in future work. Notably, racial and ethnic minorities and adolescents without health insurance have lower rates of treatment for depression (Lu, 2019). Perhaps if resources are available when anhedonia first emerges, that may change the course of anhedonia and long-term outcomes for youth. This initiative would also benefit from educating members (e.g., teachers, family members) at the center of adolescents' social environments on anhedonia phenotypes.

Conclusion

Taken together, our model draws from several bodies of literature highlighting the multidimensional role of neural, biological, and social factors that may be at play in the emergence of anhedonia during adolescence. Specifically, the model focuses on the putative neural mechanisms of anhedonia – frontostriatal circuitry and the DA neuromodulatory system – as they develop during puberty and are shaped by

childhood adversity and chronic inflammation. Our model suggests that frontostriatal circuitry and the DA neuromodulatory system, during the period of pubertal maturation, are particularly sensitive to the negative influence of chronic inflammation stemming from the experience of childhood adversity. Alterations in the immune response could influence concentrations and availability of striatal DA and in turn influence plasticity, inhibiting the ability of adolescents to adapt to their environment during a time of social, physical, and biological changes. When puberty occurs, it could be that striatal DA availability is further influenced, accelerating alterations in neural reward circuitry, dampening responses to reward for some adolescents. While the developmental mechanisms underlying anhedonia have been traditionally neglected, the hope is that this model provides a possible framework and a path forward for future investigations. Research continuing to elucidate our understanding of the

emergence, mechanisms, course, and treatment of anhedonia has the meaningful and important potential to reduce pernicious mental health outcomes by keeping adolescents on – or re-directing them toward – pathways toward healthy neural and social development.

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Key points

- Adolescence is a developmental period in which there are several processes rapidly occurring in tandem (e.g., neural, social, and biological changes).
- What marks the transition from childhood into adolescence is pubertal development. Puberty is a time of substantial neurocognitive, social, and physical change as adolescents develop to meet the demands of adulthood.
- Anhedonia, or diminished pleasure and motivation, is a symptom of severe mental illness (e.g., depressive disorder, bipolar disorder, schizophrenia) that emerges during adolescence. Anhedonia is related to several poor outcomes including suicide and emerges during adolescence.
- This review takes a developmental perspective, considering the possibility that anhedonia emerges in the context of pubertal maturation and adolescent development, with childhood adversity and chronic inflammation influencing neural reward systems to accelerate anhedonia's progression.

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