Characterizing Reward Function During Social Feedback:
Associations with Anhedonia in Socially Anxious Adolescents

Corinne Nicole Carlton-Smith

Dissertation submitted to the faculty of the Virginia Polytechnic Institute and State University in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

In

Psychology

John A. Richey, Chair

Rosanna Breaux

Jungmeen Kim-Spoon

Thomas H. Ollendick

May 3rd, 2023

Blacksburg, Virginia

Keywords*:* reward, social anxiety, adolescence, social stress, peer victimization, anhedonia

Characterizing Reward Function During Social Feedback:

Associations with Anhedonia in Socially Anxious Adolescents

Corinne N. Carlton-Smith

ABSTRACT

The present study aimed to: (1) Characterize markers of reward sensitivity during periods of social stress using a well validated social feedback paradigm; (2) Evaluate clinical relations between reward markers and anhedonia; and (3) Investigate if elevated levels of baseline prior exposure to stress (i.e., peer victimization) are associated with the degree of ventral striatum suppression and anhedonia symptoms in a social stress context. A total of 29 adolescents between the ages of 13 and 17 years old (M_{age} = 15.31; *SD* = 1.51; 55.2% cisgender girls) participated in the present study. Participants were asked to complete a semi-structured interview; fill out self-report questionnaires regarding social anxiety, stress, depression, and anhedonia; and complete a magnetic resonance imaging scan while playing the Island Getaway task. Ventral striatum (VS) BOLD signal activation estimates were then extracted during discrete phases of the game (e.g., anticipation of social feedback and outcome of social feedback) and statistically compared within-subjects via paired samples *t*-tests and correlated to social anxiety measures. Additionally, regression analyses assessed the effect of VS activation on anhedonia as well as the associative effect of peer victimization on VS activation and anhedonia. Results revealed that when in the presence of social stress (defined as the potential for negative feedback), socially anxious adolescents demonstrated significantly suppressed VS activation relative to baseline when anticipating feedback. Additionally, results indicated that the degree of reduced VS activation during anticipation was correlated to total changes in anhedonia severity across the task. Lastly, results demonstrated that overt peer victimization is a significant predictor of suppressed VS activation during anticipation of social feedback, but not during social outcomes. Taken together, these results identify potentially novel mechanisms associated with anhedonia and blunted reward processing in socially anxious youth that could be improved via interventions that target positive-valence systems.

Characterizing Reward Function During Social Feedback:

Associations with Anhedonia in Socially Anxious Adolescents

Corinne N. Carlton-Smith

GENERAL AUDIENCE ABSTRACT

Socially anxious teens may be at a heightened risk for developing anhedonia – which means that they are showing a significant lack of interest in things they used to find interesting or rewarding. This is problematic, because the presence of anhedonia is associated with not doing as well in therapy and even with higher rates of suicide attempt. One area that may be linked to the development of anhedonia in socially anxious teens is social stress induced disrupted reward processing in certain regions of the brain that generally activate when people anticipate a reward. Despite this, there is very little research on the development of anhedonia is socially anxious teens and even less that focuses on biological and behavioral experiences of reward processing when under social stress. This study examines this potential stress-to-anhedonia pipeline by looking at a key region of the brain, called the ventral striatum, to see if social stress does disrupt reward processing in socially anxious teens, and, if so, if this disrupted reward processing is related to anhedonia. Through evaluating a total of 29 socially anxious teens who underwent a social stress task while completing brain scanning, the present study demonstrated evidence for diminished brain activation in the ventral striatum when anticipating rewards. Additionally, the present study showed that reduced brain activation in the ventral striatum was associated with changes in anhedonia severity. Lastly, results from this study indicated that peer victimization (or bullying) was a significant predictor of diminished brain activation in the ventral striatum. Taken together, these results identify potentially new markers associated with anhedonia and blunted reward processing in socially anxious youth that could be improved via interventions.

Acknowledgements

I would like to express my sincerest gratitude to those who have played an integral role in supporting my personal and academic growth. First, I would like to thank my family and friends for always supporting my dreams. Specifically, I'd like to recognize my mother, Maryann, who sacrificed so much to make sure I could pursue higher education and has been my cheerleader since day one, and my sister Jackie, who has brought immeasurable joy to my life. Second, I want to thank my husband, Zack, who has been a constant pillar of support and companionship in my life. Third, I'd like to recognize the rest of my family, Krista, Louise, Greg, and Spencer for their continuous love and support. I would also like to recognize my cohort-mates, Jennifer Bertollo and Janey Dike; peers, Brianna Ermanni, Morgan Lindenmuth, Brandon Minton, Alex Faunce, Jennifer Phillips, and Doug Harrison; and past and present lab-mates, Dr. Ligia Antezana, Katelyn Garcia, and Mara Villalongo Andino for always being a source of much needed levity and encouragement.

Additionally, I want to thank the many mentors that have made a significant impact in my life through their guidance and support; my first research mentor, Dr. Elizabeth Hammock, who took a chance on me as a curious young undergraduate who asked way too many questions and helped mold those questions into careful science, and my post-baccalaureate mentors Drs. Jesse Cougle and Alex Meyer who taught me how to enhance my scientific thinking and encouraged me to pursue this path. I'd further like to thank my mentors and committee members at Virginia Tech who have influenced and inspired me as a clinician and researcher including, Drs. Thomas Ollendick, Rosanna Breaux, George Clum, Pearl Chui, and Jungmeen Kim-Spoon. Specifically, I'd like to thank Drs. Thomas Ollendick and Rosanna Breaux for the unyielding support and kindness that they have given me across my entire graduate career – I absolutely would not be the person I am today without them and cannot put into words how thankful I am to have them as mentors. Lastly, but certainly not least, I'd like to specially thank Dr. John Richey, my committee chair and mentor throughout my graduate career, who has fundamentally shaped my development as a clinical scientist and has taught me to approach scientific questions with a strong theoretical lens and carry out science with rigorous methodology.

Finally, I would like to thank the adolescents who participated in this project, as well as the funding sources for this project including the Thomas H. Ollendick PhD and Mary Catherine Haley Ollendick Graduate Fellowship in Clinical Child and Adolescent Psychology, the Virginia Tech Office of the Vice President for Research and Innovation Grant, the Graduate Research Development Program Dissertation Grant, and the Society for a Science of Clinical Psychology Dissertation Grant, without which this project could not have come to fruition.

Table of Contents

Introduction

Adolescence coincides with normative increases in fears of negative social evaluation (Westenberg et al., 2007), as well as clinically significant forms of social anxiety including social anxiety disorder (SAD; American Psychiatric Association, 2013; Farrell et al., 2019; Solmi et al., 2021). During the adolescent developmental period, SAD ranks among the most prevalent anxiety disorders (at roughly 10-15% prevalence rate; Kessler et al., 2005; Merikangas et al., 2010), and is linked to significant functional impairment across educational and occupational domains (e.g., Moitra et al., 2011; Vilaplana-Pérez et al., 2021). SAD has been further associated with lower self-reported quality of life in both adolescent and adult samples and follows a chronic course if left untreated (Albano & Hayward, 2004; Ollendick et al., 2014; Park et al., 2021). Social anxiety during adolescence also causes significant impairment within interpersonal domains. For example, in a recent systematic review, de Lijster and colleagues (2018) concluded that adolescents with SAD experience more peer victimization, less peer acceptance, and increased levels of loneliness on average as compared to those without a social anxiety diagnosis. Although prior work has explored mechanisms of SAD maintenance in adults (e.g., fear- and threat-based mechanisms), considerably less is known about the affective vulnerabilities that may potentiate and maintain social anxiety symptomatology during adolescence. Accordingly, the purpose of the present study is to evaluate a novel, theory-driven, mechanism of social anxiety maintenance focusing on reward processing in socially anxious adolescents.

General Theoretical Model

Broadly, adolescence is characterized by heightened sensitivity to social rewards (Somerville, 2013). Prior work has also illustrated that acute psychological stress suppresses reward processing (Lincoln et al., 2019). This stress-induced suppression of reward processing may decelerate motivational drive and therefore represent a risk factor for the development of anhedonia (i.e., diminished interest or pleasure in previously rewarding stimuli), which may in turn maintain social anxiety symptoms by diminishing motivation to engage in social behaviors. Investigation of this potential linkage is crucial, as anhedonia ranks as one of the most treatment-resistant symptoms and as one of the strongest negative predictors of treatment outcomes (Craske et al., 2016). Although not an official DSM-5 symptom, anhedonia figures prominently among adults with SAD. Indeed, it has been appreciated for some time now that in *adults*, stress suppresses reward circuitry function and has been linked to the development of anhedonia (Bogdan & Pizzagalli, 2006; Pizzagalli, 2014). However, what is unknown is whether this same risk pattern is seen in *adolescents*. Consequently, this potential mechanism of anhedonia development has been largely unexplored as a method of prevention or intervention, which may further explain why treatment outcomes for this population remain among the poorest in the affective disorders (e.g., Ginsburg et al., 2011). In light of prior work illustrating that neurobiologically-based motivational systems are centrally involved in anhedonia and are susceptible to suppression by psychological stress, the theory motivating the research outlined here is as follows: during the developmental period where social rewards are most impactful (i.e., adolescence; Somerville, 2013) these biologically-based motivational systems for perceiving and encoding rewards should be at particular risk for suppression if social outcomes are negative. That is, social reinforcement history (acceptance and rejection feedback) should proximally influence patterns of activation in regions of the brain involved in encoding expected future value during anticipation of social feedback, particularly in the ventral striatum (VS), which is involved in anticipation of normally rewarding stimuli and scales linearly in its pattern of activation with reward magnitude and probability.

Social Anxiety and Fear- and Threat-Processing

Most prior work aimed at identifying neurobiological mechanisms of social anxiety etiopathogenesis has focused on fear- and threat-based arousal systems in adult samples. Specifically, prior neuroimaging work in adults with SAD has largely focused on patterns of activation within the amygdala – a region of the brain implicated in threat and arousal and is also part of an extended "fear circuit" (Davis & Whalen, 2001). Among other theorized roles, the amygdala appears to be involved in negative-valenced tasks such as looking at harsh faces or threatening words (for reviews, see Etkin & Wager, 2007; Klumpp & Fitzgerald, 2018; Schulz et al., 2013). For example, a study by Simon and colleagues (2017) demonstrated that socially anxious adults show heightened amygdala activation following aversive loud voice cues as compared to non-anxious control participants. Moreover, this same pattern of amygdala activation has been consistently exhibited in adults with SAD as compared to healthy controls in the presence of threat-relevant words (e.g., Blair et al., 2008; Schmidt et al., 2010), speech anticipation (e.g., Davies et al., 2017), and threatening facial expressions (for meta-analysis, see Gentili et al., 2016). Further, heightened amygdala reactivity in SAD has been demonstrated in both social and non-social aversive situations (Kraus et al., 2018). Although less explored in adolescent samples, this pattern of hyperactivation in the amygdala during the processing of threatening cues such as fearful faces and social threat (e.g., Beesdo et al., 2009; Caouette & Guyer, 2014; Hahn et al., 2011). Moreover, this pattern of amygdala hyperactivation has been demonstrated to be co-segregated with social anxiety within families (Bas-Hoogendam et al., 2020). However, it should be noted that these elevations in "fear-circuit" activation in regions such as the amygdala in adults with SAD share significant overlap with other anxiety disorders such as generalized anxiety disorder (GAD; see Buff et al., 2016); thus, potentially suggesting a more global sensitivity to fear- and threat-based arousal as a function of anxiety rather than being implicated in maintaining social anxiety specifically. In line with this notion, when considering current "gold-standard" treatment programs that target these fear- and threat-based mechanisms (e.g., Cognitive Behavioral Therapy), efficacy rates for SAD are significantly worse than those of other anxiety and affective disorders (e.g., GAD, specific phobia, depression; Higa-McMillan et al., 2016; James et al., 2020)– producing only moderate efficacy rates (Ginsburg et al., 2011; Herbert et al., 2009). Collectively, this suggests that although recent neuroimaging work has plausibly implicated the functional neurobiology of fear and arousal in SAD, treatment outcome research has not supported the notion that symptom reduction tracks with changes in the fear and arousal system. Taken together, these lines of reasoning imply that social anxiety symptom maintenance and change are linked to neurobiological systems separate from negatively-valenced fear and arousal. This gap in knowledge has motivated a recent shift toward evaluating positively-valenced motivational systems as potentially influential mechanisms in social anxiety maintenance.

Social Anxiety and Reward Processing

Reward Processing in Adults

Most work evaluating reward neurocircuitry in humans and nonhuman primates has focused on the meso-limbic dopamine (DA) pathway. This pathway consists of several interconnected brain regions including the ventral tegmental area, VS, orbitofrontal cortex, ventromedial prefrontal cortex, and the anterior cingulate cortex (Haber & Knutson, 2010). Collectively, these areas have been shown to be sensitive to both the magnitude and probability of non-social (i.e., monetary) as well as social rewards (Rademacher et al., 2010; Saddoris et al., 2015; Schultz, 1998, 2000). Moreover, reward network activation is also distinguishable according to the temporal phase of processing, involving both anticipatory and consummatory periods

(Rademacher et al., 2010). The mesolimbic-DA pathway is segregated into distinct regions that hold specific functional roles in detecting and sustaining reward-related signals as well as translating anticipatory reward-value into approach-related action (Haber & Knutson, 2010). For example, the VS has been widely implicated as being pivotal in decision-making, for movement of motivation into approach, as well as anticipation of both non-social and social rewards (Balleine et al., 2007; FitzGerald et al., 2014; O'Doherty, 2004). Functionally, the VS shows significant activity while processing social incentives, reflecting its role in detection of social rewards and perhaps it's role in motivation to avoid reward loss in social contexts, or social punishment (e.g., Kohls et al., 2013). While prior empirical studies have broadly demonstrated that socially anxious adults show blunted neural activity across multiple reward regions – suggesting that adults with SAD may demonstrate a relative lack of motivational preference for social reward (e.g., Cremers et al., 2015) – the VS is of particular interest in the present study, as it has been consistently implicated as a marker of aberrant reward processing in individuals with SAD. For example, recent empirical work has indicated that socially anxious adults exhibit blunted VS activation during the anticipation of social contexts that is independent of neural systems of negative valence (Richey et al., 2017). Moreover, this study further demonstrated a significant blunting in VS activation during anticipation of positive social incentives in adults with SAD as compared to outcome; suggesting unique blunting of the VS to the anticipatory phase of reward feedback in socially anxious samples (Richey et al., 2017). Further, an additional study demonstrated that socially anxious adults show diminished social-context-dependent variation during feedback processing, which was specifically evidenced by blunted activation of the VS during social contexts (Becker et al., 2017). Taken together, the empirical base has pointed towards the VS as a key area for reward processing dysfunction in socially anxious samples.

Reward Processing in Adolescents

Whereas empirical work among adults with SAD has consistently supported the notion of blunted reward processing in key reward regions of the brain, similar work in adolescents has paradoxically revealed heightened sensitivity to reward among adolescents with or at risk for social anxiety symptoms (for review see Richey et al., 2019). Adolescence is characterized by heightened sensitivity to reward in general (see Casey et al., 2015; Schreuders et al., 2018), and social evaluative reward in particular (Somerville, 2013). Recent work has indicated that adolescents at risk for SAD (i.e., exhibited heightened behavioral inhibition in early childhood) demonstrate heightened activation in the VS as compared to controls (Bar-Haim et al., 2009; Guyer et al., 2012, 2014). For example, in the study by Bar-Haim and colleagues (2009), neural activation in striatal regions was examined during a reward-contingency task in adolescents between the ages of 14 and 18 (N = 35). Results from this study indicated that adolescents who were at risk for developing SAD demonstrated increased activation in the VS when they believed their choices would affect reward outcomes. In an additional study examining striatal response in behaviorally inhibited adolescents (N = 39; 18 behaviorally inhibited, 18 controls), Guyer et al. (2014) provided additional evidence that adolescents who are at risk for developing SAD demonstrate heightened VS response in the presence of rewards. Moreover, Guyer and colleagues (2012) conducted the only known study to investigate striatal responses in response to monetary rewards in adolescents who met diagnostic criteria for SAD. Specifically, they compared striatal responses in adolescents with SAD (N = 14) as compared to adolescents with GAD (N = 18) and “healthy” adolescents (N = 26) during a monetary incentive delay task. Results from this study indicated that adolescents with SAD exhibited heightened VS activation in response to monetary rewards relative to the healthy comparison and GAD group. Taken together, these studies suggest that aberrant reward processing is occurring in response to non-social rewards in adolescents with or at risk for SAD.

Impact of Social Stress on Reward Function

Recent theoretical work has posited that adolescence is a critical period for the development of normative patterns of reward reinforcement patterns. In typical development, adolescents have been shown to recruit significantly greater VS activity in response to rewards as compared to adults, and more broadly demonstrate a higher sensitivity to rewards than adults (e.g., Ernst et al., 2009; Galván et al., 2006; see Galván, 2010 for review). This sensitivity to rewards, and social rewards in particular, provides a generally adaptive role in normative development (see Somerville, 2013). On the other hand, enhanced neurobiological sensitivity to reward, combined with potentially adverse environmental factors (e.g., social stress, peer victimization) may maladaptively lead to negative future expectations about social reward by potentiating the impact of failed coping outcomes (i.e., suppressing motivated action to resolve future aversive emotions). It has been further theorized that this pattern of frustrative non-reward may further lead to the development of clinically significant anhedonia, with adolescence serving as a distinct risk period (Carlton et al., 2020; Richey et al., 2019). Specifically, this theoretical work suggests that this early hypersensitivity to socially salient contexts during adolescence interacts with negative learning experiences to produce a coping pattern which is similar in principle to 'learned helplessness' during transient periods of stress, ultimately culminating in anhedonia symptoms. This stress-induced suppression of reward processing could serve as a specific and pernicious combination of factors that explain the development of anhedonia among socially anxious adolescents.

With regard to the impact of stress on reward processing, in adult samples, prior empirical work has indicated that the presence of stress suppresses reward circuitry function and that repeated exposure to stress is indeed related to the development of anhedonia (e.g., Bogdan & Pizzagalli, 2006; Pizzagalli, 2014). However, little work has investigated this relation in socially anxious adolescent samples. Recent work has shown that following acute social stress, healthy adolescents demonstrate blunted VS response (Lincoln et al., 2019)—a marked shift from the hypersensitivity generally displayed by adolescents in rewarding contexts (see Somerville, 2013). In fact, younger children who are at risk for developing SAD (based on temperamental factors such as elevated behavioral inhibition and heightened wariness) have shown impacted neural processing to threats in the presence of social stressors (Jarcho et al., 2019). Although this study did not examine regions of reward, this provides initial evidence in youth samples that exposure to a social stressor may potentiate brain-based sensitivity. Collectively, this work in combination with the heightened fear of negative evaluation and rejection that is central to SAD, suggests that in the presence of social stress (which tends to significantly increase during adolescence; Eiland & Romeo, 2013) exposure to the potential for social rejection, as a form of acute stress, may have a blunting effect on reward processing in socially anxious adolescents.

Anhedonia and Social Anxiety

According to a recent study, the prevalence of anhedonia within socially anxious youth is up to 14%; representing a significant subset (Carlton et al., in preparation). Recent work has demonstrated that in adults, anhedonia (but not general distress or anxious arousal) is associated with slower reward learning in SAD samples (Reilly et al., 2020). Moreover, prior work has consistently established that adults with SAD report diminished positive affect – a central component of anhedonia – that is not explained by depression (Brown et al., 1998; Eisner et al., 2009; Gilboa-Schechtman et al., 2000; Kashdan, 2007). Additionally, socially anxious adults often indicate lower enjoyment of and desire to pursue social interactions, as well as expressions and experiences of positive affectivity more broadly (Trew & Alden, 2012). Further, recent work has also assessed neural connectivity of key reward regions as they relate to positive affectivity in adults with SAD. Finding from this study demonstrated that hypoconnectivity (i.e., diminished strength of connections) in key reward regions is related to low positive affect in adults with SAD (Carlton et al., 2023). Despite work in adults with SAD that suggests a marked decrease in motivation to pursue social interaction, and work indicating that adolescence is a critical period for reward sensitivity to social context, research within the adolescent period regarding anhedonia within heightened social anxiety presentations remains unexplored. The investigation of the potential linkage between blunted reward and anhedonia in socially anxious adolescents remains critical, as anhedonia ranks as one of the most treatment resistant symptoms, and as one of the strongest negative predictors of treatment outcomes (Craske et al., 2016). Therefore, the development of anhedonia may itself be a modifiable maintenance factor for high social anxiety in adolescent populations. Precursors and maintenance factors of anhedonia, such as exposure to social stress are also of importance when considering the social landscape during adolescence. Moreover, it is unknown if baseline factors such as peer victimization play a role in the stress to anhedonia pipeline during adolescence given their significant impact on reward processing (e.g., Rappaport et al., 2019). Consequently, the stress induced altered reward processing-to-anhedonia development pipeline has been largely unexplored as a window for prevention or intervention, which may further explain why treatment outcomes for this population remain among the poorest in the affective disorders.

Indexing of Reward Signal: Utility of the Island Getaway Task

A core component of the present study is the use of the Island Getaway task (see full description in the Methods section below) to replicate social interactive situations whereby social feedback is both elicited from the participant and provided by a fictive counterpart. The task also allows both anticipatory (awaiting partner feedback) and consummatory (observing partner feedback) phases of reward processing to be evaluated. Most prior work using the Island Getaway task has evaluated reward responses via electroencephalogram (EEG). Through this work, the Island Getaway task has consistently, and reliably, elicited event-related potentials (ERP) modulated by social reward in large community samples of children (Kujawa et al., 2014, 2017). Additionally, the Island Getaway task has shown moderate stability over the course of 3 years with the reward-related positivity– an ERP that indexes reward activation – being reliably enhanced for social feedback (Kujawa et al., 2018). This suggests that with additional adjustment for adolescent samples and magnetic resonance imaging (MRI) use, the functional MRI (fMRI) version of the Island Getaway task should reliably index reward systems of interest in the present study. Moreover, in addition to the Island Getaway task eliciting reward response across adolescent samples, confederate peer "co-players" are generally perceived as realistic (Kujawa et al., 2017, 2018); thus, adding an additional layer of ecologically valid social context to the present study.

Current Study

In summary, prior work suggests that altered reward circuitry function may act as a mechanism by which anhedonia develops when social stress is high and may be of particular risk for vulnerable adolescent samples. However, this mechanistic risk-chain has yet to be evaluated in socially anxious adolescent samples. As such, it is unknown if this mechanism represents a targetable pathway for future intervention approaches for socially anxious adolescents. Collectively, the overarching hypothesis of this study is that acute social stress suppresses reward-related signals in the VS, a core reward-related region of the brain.

Aims & Hypotheses

Accordingly, the present study aimed to accomplish the following within a sample of socially anxious adolescents (ages 13-17):

AIM 1: Characterize markers of reward sensitivity during periods of social feedback using a well validated social feedback paradigm.

Hypothesis 1. The VS will demonstrate blunted patterns of activation during the anticipatory phase of social feedback stress (as evidenced by aggregate blood-oxygen-level-dependent (BOLD) levels during the built-in delay period of the task that occurs immediately prior to social feedback receipt) as compared to outcome phases (1a), and that the degree of VS suppression during anticipation of social feedback will correlate with social anxiety symptoms (1b).

AIM 2: Evaluate clinical relations between fMRI reward markers and anhedonia.

Hypothesis 2. Suppressed anticipatory VS activation will predict increased anhedonia symptoms.

AIM 3: Investigate if elevated levels prior exposure to stress (i.e., peer victimization) are associated with the degree of VS suppression and anhedonia symptoms in a social feedback context.

Hypothesis 3. Higher levels of peer victimization will predict anticipatory VS suppression and anhedonia presentation.

Method

The present study utilized self-report assessments of behavioral and psychological functioning, diagnostic information resulting from a clinical interview, and a social interaction task modified for use in the fMRI scanner in order to accomplish the central aims.

Participants

Using Fmripower (Mumford & Nichols, 2008) – a power analysis tool specifically designed for calculating power in neuroimaging contexts – with previously collected data, we found that for a within-subjects design with a type 1 error rate of 0.05 and a power of 80%, we would need to recruit about 25 participants. Moreover, previous work involving task-based studies using a similar within-group design have recruited between 20-30 participants (e.g., Bayard et al., 2020; Calderon et al., 2021; Robinson et al., 2013). To be eligible to participate in the proposed study, all individuals had to be between the ages of 13 and 17 years old, meet cutoff scores of at least 29.5 on the Liebowitz Social Anxiety Scale for Children and Adolescents (Masia-Warner et al., 2003), had to indicate the presence of moderate stress by scoring at least a 14 on the Perceived Stress Scale-10 (Cohen & Williamson, 1988), and had to be right-handed (see Jang et al., 2017). Adolescents who were actively suicidal and/or who experience restrictions barring fMRI (e.g., metal in the body, history of seizures, claustrophobia) were excluded from the study.

A total of 29 adolescents between the ages of 13 and 17 years old (M_{age} = 15.31; SD = 1.51) participated in the present study. Regarding gender, 55.2% of participants identified as cisgender girls, 24.1% as cisgendered boys, 13.8% as non-binary, and 6.9% as transgender boys; thus, approximately 21% of the present sample represent gender-diverse youth. Participants also reported their sexual orientation, with 41.4% of participants identifying as heterosexual, 20.7% as bisexual, 13.8% as queer, 10.3% as pansexual, 10.3% as homosexual, and 3.5% as "other"; demonstrating that approximately 62% of the sample represent sexuality-diverse youth. The racial breakdown of the sample is 86.2% White, 6.9% Black, and 6.9% Asian/Pacific Islander. No participants identified as Latine in the present study. Regarding proxies for socioeconomic status, the mean family income of participants in the present sample ranged from $65,000-$100,000 and

75.9% of families had at least one parent working a full-time job, 13.8% working a part-time job, and 6.9% were considered unemployed. All participant demographics are also presented in Table 1 below.

Table 1

Demographic Information for All Participants

Age (Mean (*SD*))	15.31 (1.51)
Family Income (mean range)	$65,000-$100,000
Family Employment	
Full-time	75.9%
Part-time	13.8%
Unemployed	6.9%
Gender	
Cisgender Girl	55.2%
Cisgender Boy	24.1%
Non-Binary	13.8%
Transgender Boy	6.9%
Race	
White	86.2%
Black	6.9%
Asian/Pacific Islander	6.9%
Sexual Orientation	
Heterosexual	41.4%
Homosexual	10.3%
Bisexual	20.7%
Pansexual	10.3%
Queer	13.8%
"Other"	3.5%

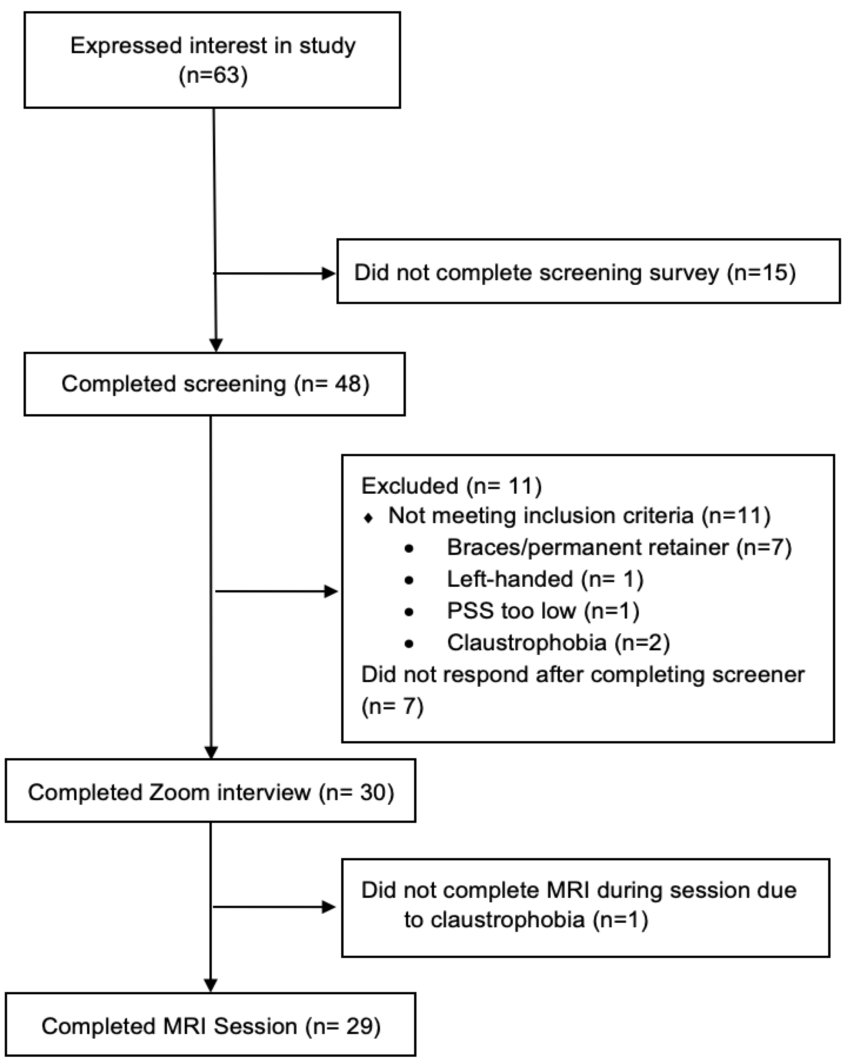
Procedures

See Figure 1 for recruitment diagram. Inclusion and exclusion criteria were established remotely prior to inviting the adolescent and parent to the in-person session in the lab. Specifically, the adolescent completed a screening questionnaire via Virginia Tech's REDCap platform to assess for eligibility. Upon completion of screening measures and being determined eligible to participate, the adolescent and their parent were asked to schedule a Zoom call. During this call, the potential participant and their parent were provided additional information about the study and asked if they would like to provide consent/assent. Once consent/assent was received, the participant underwent the semi-structured interview. At the end of the semi-structured interview, the participant was scheduled for their in-person session.

During the in-person session, the participants were provided an overview of the in-person session (e.g., would be answering some questions and then playing a game with other peers while in the MRI) and then consent/assent was re-established. Then, participants filled out self-report measures related to anhedonia, social anxiety, perceived stress, and depression to get baseline measures of these constructs. Participants also filled out an additional MRI safety screening form to assess for any changes in eligibility status prior to entering the MRI and were asked to have a photo taken of themselves by the experimenter to set up their online profile for the game. Participants were told that their peers would be viewing their profiles. Following completion of all self-report measures, participants received instructions on how to respond in the Island Getaway task (Kujawa et al., 2014, see description below) and completed a practice trial of the Island Getaway task before being placed in the MRI scanner. Once in the scanner, participants underwent a structural scan, resting state scan, and then completed the functional scan while playing the full version of the Island Getaway Task. Of note, participants practiced the task one additional time prior to playing while they were in the scanner to ensure comfort and comprehension. In total, each participant spent approximately 35 minutes in the fMRI scanner. Following the completion of the scan, participants were asked to fill out the same self-report measures of anhedonia, social anxiety, perceived stress, and depression as well as a questionnaire regarding their impression of the game. Lastly, prior to leaving the session, participants were compensated, provided a copy of their structural brain scan, and fully debriefed about the artificial nature of the social rejection they may have experienced to alleviate any potential increased stress responses.

Figure 1

Recruitment Diagram



Measures

The breakdown of the measures and the administration timeline is listed in Table A1 of the Appendix section.

Semi-Structured Interview

Anxiety Disorders Interview Schedule for DSM-5 Child Version (ADIS-C; Albano & Silverman, in press). The ADIS-C is a semi-structured interview that assesses for internalizing and externalizing disorders. For the purposes of the present study, only select modules of the ADIS-C were administered to the adolescent and parent conjointly based on recommendations from prior work (Carlton et al., under review; Radtke et al., 2023). Specifically, the SAD, GAD, and major depressive disorder (MDD) modules of the ADIS-C were administered to gain a diagnostic picture of functioning. Presence or absence of a diagnosis did not impact eligibility. However, active suicidality was an exclusionary criterion for the present study.

Self-Report Questionnaires

Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA; Masia-Warner et al., 2003). The LSAS-CA is a 24-item measure that assesses social anxiety severity in youth. Participants were asked to indicate first how anxious or fearful they would be in certain situations (e.g., "Giving a verbal report or presentation in class"; "Telling others that you disagree or that you are angry with them") on a 4-point scale ranging from 0= "*I do not fear it at all*" to 3= "*Severely fear it*". Next, they were asked to rate how often they avoid those situations on a 4-point scale ranging from 0= "*Never avoid it*" to 3= "*Usually (like 67-100% of the time)*". Participants were considered eligible if the meet a cutoff score of 29.5 on the LSAS-CA, indicating that they are experiencing significant current social anxiety. Previous work has demonstrated that the LSAS-CA has shown excellent psychometric properties (α = .83 -.95 across subscales) and that a score of 29.5 is optimal for distinguishing SAD from other anxiety disorders in adolescent samples (Masia-Warner et al., 2003). The LSAS-CA was administered during the screening, baseline, and endpoint portions of the current study. The LSAS showed excellent internal consistency in the current study across timepoints (Baseline: α = .95; Endpoint: α = .94).

Perceived Stress Scale-10 (PSS-10; Cohen & Williamson, 1988). The PSS-10 is a 10-item self-report measure that determines how much participants perceive situations in their lives to be stressful. Participants were asked to indicate how often they have felt a certain way (e.g., "How often have you felt nervous and stressed"; "How often have you felt that things were going your way?") on a 5-point scale ranging from 0 = "*Never*" to 4 = "*Very Often*". Participants were considered eligible if they meet a cutoff score of at least 14, indicating that they have been experiencing at least moderate stress over the last month. The PSS-10 has been administered among diverse populations of adolescents (e.g., Carlozzi et al., 2010) and has demonstrated good internal consistency (α = .82). The PSS-10 was administered at screening, baseline, and endpoint. Of note, for the baseline and endpoint administrations, instructions were changed from reporting on the past month, to reporting "in the moment". The PSS demonstrated good internal consistency in the present study (Baseline α = .78; Endpoint α = .79).

Patient Health Questionnaire for Adolescents (PHQ-9A; Johnson et al., 2002). The PHQ-9A is a 9-item questionnaire that measures depression symptom presentation in adolescents. Participants were asked to indicate how often they have been bothered by each symptom over the past two weeks on a scale ranging from 0 = "*Not at all"* to 3 = "*Nearly every day*". The PHQ-9A has consistently demonstrated good psychometric properties in adolescent samples (Johnson et al., 2002; Richardson et al., 2010). The PHQ-9A was administered at screening, baseline, and endpoint and showed good internal consistency (Baseline α = .83; Endpoint α = .87). It should also be noted that item 9 regarding suicidality was dropped for baseline and endpoint administrations of the PHQ-9A.

Dimensional Anhedonia Rating Scale (DARS; Rizvi et al., 2015). The DARS is a 17-item measure that assesses severity of anhedonia symptoms in 4 areas: hobbies/past-times, food/drinks, social activities, and sensory experiences. Within each area, participants were asked to provide a minimum of two examples of rewarding/pleasurable experiences that are rewarding "right now". After this, participants were asked to indicate their level of desire, motivation, effort, and pleasure for each the examples that provided on 5-point Likert-type scale ranging from 0 ("*Not at all*") to 4 ("*Very much*"). Higher scores indicate less anhedonia. The DARS has exhibited good to excellent internal consistency (α = .75 - .92 across all subscales) in previous studies (e.g., Carlton et al., 2021; Rizvi et al., 2015). The DARS was administered at baseline and endpoint and demonstrated adequate to excellent internal consistency across domains (Baseline: Hobbies/Past-times α= .84, Food/Drink α= .75, Sensory Experiences α= .93; Endpoint Hobbies/Past-times α= .87, Food/Drink α= .82, Sensory Experiences α= .94), with the exception of the Social Activities domain (Baseline α = .68; Endpoint α = .71). Thus, results concerning the DARS Social subscale should be interpreted with caution.

Anhedonia Scale for Adolescents (ASA; Watson et al., 2021). The ASA is a 14-item scale that was designed to assess facets of anhedonia in adolescent samples. Specifically, the ASA has a total score as well as three distinct factors: Enjoyment, Emotional Flattening, and Detachment; Connection, Purpose, and Enthusiasm; Effort, Motivation and Excitement. Participants were asked to report on how interesting and enjoyable they have found their lives to be over the past two weeks on a scale ranging from 0 = "*Never*" to 3= "*Always*". The ASA has shown good internal consistency (α = .77 - .95 across all subscales) and psychometric properties in adolescent samples (Watson et al., 2021). The ASA was administered at baseline and endpoint and showed excellent internal consistency across subscales (Baseline: Enjoyment α = .93, Connection α = .85, Motivation α =.95; Endpoint: Enjoyment α = .88, Connection α = .73, Motivation α =.88).

Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). The SHAPS is a 14-item measure that assesses anhedonic experiences. Participants were asked to rate how strongly they agree with each item (e.g., "I would enjoy being with my family or close friends"; "I would find pleasure in the scent of flowers or the smell of a fresh breeze or freshly baked bread") on a 4-point Likert scale from 0 = "*Strongly disagree"* to 3 = "*Strongly agree".* The SHAPS has consistently demonstrated good psychometric properties in both adult and adolescent samples (Leventhal et al., 2006, 2015; Snaith et al., 1995). The SHAPS was administered at baseline and endpoint. In the present study, the SHAPS demonstrated adequate internal consistency (Baseline α = .76; Endpoint α = .78).

Peer Experiences Scale Revised (RPEQ; De Los Reyes & Prinstein, 2004). The RPEQ is a 20-item questionnaire that measures experiences with peer victimization in the domains of Overt, Relational, Reputational, and Prosocial contexts. Participants were asked to report how frequently they have experienced certain situations (e.g., "A teen made other people not talk to me", "A teen damaged something of mine on purpose") on a 5-point scale ranging from 1= "*Not at all*" to 5 = "*A whole lot*". Higher scores on the RPEQ indicate more frequent experiences of peer victimization. The RPEQ has shown excellent psychometric properties (De Los Reyes & Prinstein, 2004). The RPEQ was administered at screening in the present study and demonstrated good internal consistency (Overt α = .91, Relational α = .82, Reputational α =.89, Prosocial α = .84).

Behavioral Task

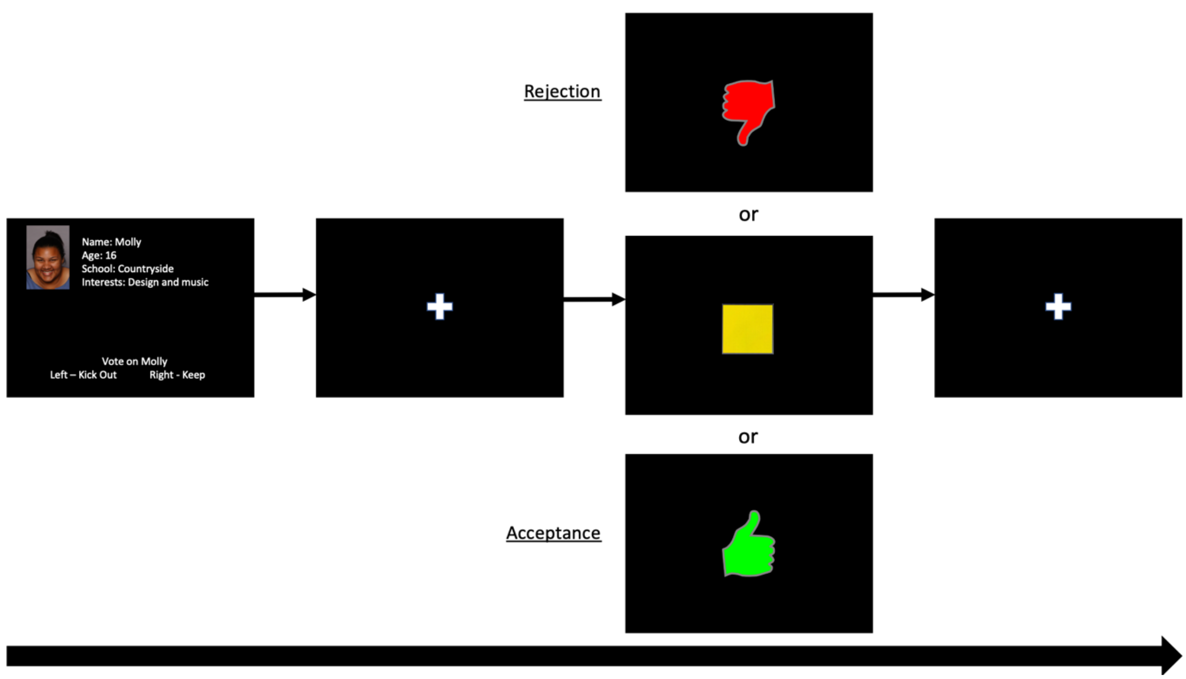
Island Getaway Task (Kujawa et al., 2014). The Island Getaway Task (see Figure 3 below) is a social feedback task where participants must vote on which people should stay or get kicked off of a virtual island, like the television show "Survivor". Participants were told that they would be playing a game with 13 age-matched peers that are participating at the same time in other labs. Participants were first asked to enter information about themselves (e.g., name, age, gender, interests, etc.) to compile a profile for themselves, including a photo of them taken by the experimenter. Following completion of their profile, they were presented with all of the co-player's profiles and asked to rate how much they "liked" each person based solely on the co-player's profile.

Once participants were placed in the MRI and were ready to being the game, participants began the game in round 1. Across all rounds, participants were asked to vote on whether each co-player should "stay" or be "voted off" the island. There is a built-in delay prior to receiving feedback to increase believability. Following this delay, participants were be shown the co-player's votes on them as to whether the co-players thought that the participant should stay in the game (i.e., the outcome phase of the task). They can receive either positive feedback (i.e., co-player voted for them to stay), negative feedback (i.e., co-player voted for them to be kicked off), or neutral feedback (i.e., no feedback). The neutral condition is explained to participants as "no feedback was received due to a computer network error" or "due to a co-player not voting in time" so that neutral feedback is not perceived as either rejection or acceptance. All participants "survived" the game by making it to the "Big Island" with a group of peers, but acceptance, rejection, and neutral feedback were presented in equal proportions across the task (21 trials per condition). Participants completed 6 rounds of the task. In this task, we were specifically interested in looking at VS activation during the anticipation of feedback phase to evaluate reward response to the potential for social rejection.

The Island Getaway task used in the present study was modified from the original EEG version to be compatible with MRI systems. Notable changes from the original task include the removal of continuous liking ratings in between rounds based on free responses, the lengthening of anticipation and outcome phase blocks to 7 seconds to allow enough time to capture the hemodynamic response, and the adjustment of adding standardized co-player adolescent images from the NIMH-ChEFS Picture Set (Egger et al., 2011). All adjustments were made in collaboration with the author of the original task. Task code and data cleaning scripts for the MRI version of the Island Getaway task can be found at https://github.com/corinnecarlton/ARSA.

Figure 2

Island Getaway Task Voting and Feedback Screens for fMRI Version



Data Analytic Plan

Neuroimaging Data Acquisition

Neuroimaging data was collected using a 3.0T Siemens Magentom Trio scanner. To reduce head movement in the scanner, foam cushions were placed around the participant's head. Structural scans were obtained using a rapid gradient echo sequence (repetition time (TR)/ echo time (TE): 2000ms/3.02ms; FOV: 22 cm; Image matrix: 184 x 256 x 192; voxel size = .82 mm x 1.00 mm x 1.00 mm). Functional runs utilized a hyperscan EPI sequence (TR = 2000 ms, TE = 25 ms, flip angle = 90°, 220 mm field of view (FOV), 64 × 64 matrix). Standard orientation of functional slices occurred (i.e., 30° superior-caudal to the anterior and posterior (AC/PC) commissures). Functional images were obtained via an interleaved approach. Axial slices for the functional BOLD signal were 37.4 mm and yielded 3.4 mm × 3.4 mm × 4.0 mm voxels.

fMRI Preprocessing

Skull-stripping was run via the brain extraction tool for structural images in FSL (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford University, U.K.). All functional data was preprocessed via Statistical Parametric Mapping software (SPM12) leveraged by Nipype, a python-based framework for handling neuroimaging data (Gorgolewski et al., 2011; http://nipy.org/nipype). Preprocessing of functional data included slice timing correction. The middle functional image was then corrected using a six-parameter rigid-body transformation. Next, functional images were co-registered to structural images in native space. Structural images were normalized into a standard space (i.e., MNI space; Montreal Neurological Institute) via the use of Advanced Normalization Tools (ANTS; Avants et al., 2011). Via statistical analyses drawn upon in Nipype we estimated the general linear model (GLM) for BOLD responses in SPM12. All code involved in the fMRI preprocessing and analysis of the present study is included on Github in addition to original task code as cleaning scripts at: https://github.com/corinnecarlton/ARSA. The cleaning script is written in SAS, and all task scripts, preprocessing, and imaging processing scripts are written in Python version 3.11.0.

Data Analytic Plan by Aim

Aim 1 Analytic Plan. Beta weights for bilateral VS were extracted via the use of an anatomical region of interest (ROI)-driven approach based on the Harvard-Oxford subcortical atlas. The anticipation phase (i.e., all phases of anticipation) versus outcome phase (i.e., all phases of outcome) beta weights in the VS were compared statistically via paired-samples *t*-tests. Then, through the use of Nipype as described above, average functional BOLD contrasts were statistically compared between anticipatory (i.e., all times when the participant was anticipating feedbacks) and outcome (i.e., all times when the participants received feedback) phases via a one sample *t*-test to determine whether the activation patterns of the VS were diminished during social feedback anticipation as compared to social feedback outcomes.

Aim 2 Analytic Plan. Change scores were computed for any significant changes in anhedonia from baseline to endpoint as demonstrated by paired samples *t*-tests. Next, we performed a regression with anticipatory VS BOLD activation as the independent variable and change in anhedonia levels (across domains if relevant) as the dependent variable(s) while controlling for age and gender. Moreover, we also ran the same analyses for VS activation during outcome, to examine differences between anticipatory activation as it relates to anhedonia as compared to outcome VS activation as it relates to anhedonia. Lastly, we ran exploratory regressions for baseline measures of anhedonia in all reported measures to assess for dimensional and domain-specific relations with VS activation across anticipatory and outcome phases.

Aim 3 Analytic Plan. Additional regression analyses were performed, such that levels of peer victimization across domains were inputted as independent variables and VS activation across phases (i.e., anticipatory, outcome, anticipation > outcome, anticipation following rejection feedback, and anticipation following acceptance feedback) were the dependent variables while controlling for age and gender. Additionally, exploratory regressions were run with the same variables as listed above but also included baseline stress, baseline depression, and baseline anhedonia as control variables. Regression analyses were also performed to evaluate peer victimization as a predictor of anhedonia. As such, levels of peer victimization across domains were inputted as independent variables and baseline anhedonia level was inputted as the dependent variable while controlling for age and gender.

Results

Descriptive Statistics

Descriptive statistics for all variables of interest are included in Table 2. Of note, one participant was excluded from subsequent analyses due to being an outlier (>3SD) with respect to observed parameter estimates in the VS; resulting in a total sample of 28. Overall, the sample presented as significantly socially anxious, with a mean total score on the LSAS of 68.59, well above the cutoff of the LSAS-CA of 29.5 as suggested by Masia-Warner and colleagues (2003). Additionally, the sample was also in the high stress range per cutoffs on the PSS-10 (Cohen & Williamson, 1988) and demonstrated less anhedonia as compared to depressed adult samples (e.g., depressed adults DARS mean total score = 36.3, Rizvi et al., 2015).

Paired samples *t*-tests were utilized to determine whether self-report variables significantly changed from baseline to endpoint. These significant changes are also displayed in Table 2 below. Correlations among study measures are presented in Table A2 of the Appendix.

Table 2

Descriptive Statistics for All Study Measures of Interest

Measure	Screening	
	Mean (SD)	**Met Clinical CSR Cutoff**
ADIS CSRs		
SAD	4.28 (1.99)	*N* = 24
GAD	3.13 (1.96)	*N* = 14
MDD	2.17 (2.33)	*N* = 9
RPEQ		
Overt	1.33 (0.45)	
Relational	2.17 (0.91)	
Reputational	1.94 (1.20)	
Prosocial	2.71 (0.96)	
	Baseline Mean (SD)	**Endpoint Mean (SD)**
LSAS Total	68.59 (26.3)	68.00 (26.39)
PSS-10	23.17 (5.65)**	21.69 (6.56)**
PHQ-9A	11.34 (4.99)**	10.07 (5.29)**
DARS		
Total	68.00 (9.20)	69.31 (9.51)
Hobbies	17.48 (2.59)	17.97 (2.35)
Food/Drink	17.38 (2.78)	17.07 (3.06)
Sensory	14.97 (4.61)*	16.03 (4.28)*
Social	14.65 (2.71)	14.55 (2.63)
ASA		
Total	16.59 (7.41)*	15.58 (7.80)*
Enjoyment	6.76 (3.91)*	6.03 (4.44)*
Motivation	5.31 (2.69)	5.07 (2.87)
Connection	4.52 (1.64)	4.41 (1.55)
SHAPS	1.83 (2.21)	1.93 (2.02)

Note: * = significantly different at $p < 0.05$; ** = significantly different at $p < 0.01$. RPEQ = Peer Experiences Scale Revised; LSAS-CA = Liebowitz Social Anxiety Scale for Children and Adolescents; PSS-10 = Perceived Stress Scale-10; PHQ-9A = Patient Health Questionnaire for Adolescents; ADIS C = Anxiety Disorders Interview Schedule for DSM-5 Child Version; CSR = Clinician Severity Rating; DARS = Dimensional Anhedonia Rating Scale; SHAPS = Snaith–Hamilton Pleasure Scale; ASA = Anhedonia Scale for Adolescents.

Reward Sensitivity During Periods of Social Feedback

A paired samples *t*-test was performed to determine whether the VS BOLD signal during the anticipatory phase of the task was significantly blunted as compared to the outcome phase. Results demonstrated that there were significant differences in the left VS during anticipation versus outcome phases of the task ($t(27) = -1.84$, $p < 0.05$) such that the VS was significantly less active during anticipation as compared to outcomes phases of the task. However, when considering right VS, there was no significant difference between anticipation and outcome activation. ($p = 0.19$). Results from functional data derived from in the Nipype in second-level analyses are shown in Figure 3 below indicating significant activation patterns in the VS during both phases (FDR corrected at $p < 0.05$; anticipatory phase: left $k = 457$, peak voxel [x, y, z]: 101, 134, 68, $t = 4.58$, right $k = 480$, peak voxel [x, y, z]: 77, 132, 67, $t = 24.15$; outcome phase left $k = 1{,}858$, peak voxel [x, y, z]: 100, 135, 70, $t = 4.55$, right $k =$ $k = 1{,}315$, peak voxel [x, y, z]: 79, 135, 71, $t = 4.40$);[1] thus, supporting the notion that the fMRI version of the Island Getaway task evokes BOLD signal patterns in the VS. The full cluster tables are provided in listed in Tables A3 and A4 of the Appendix.

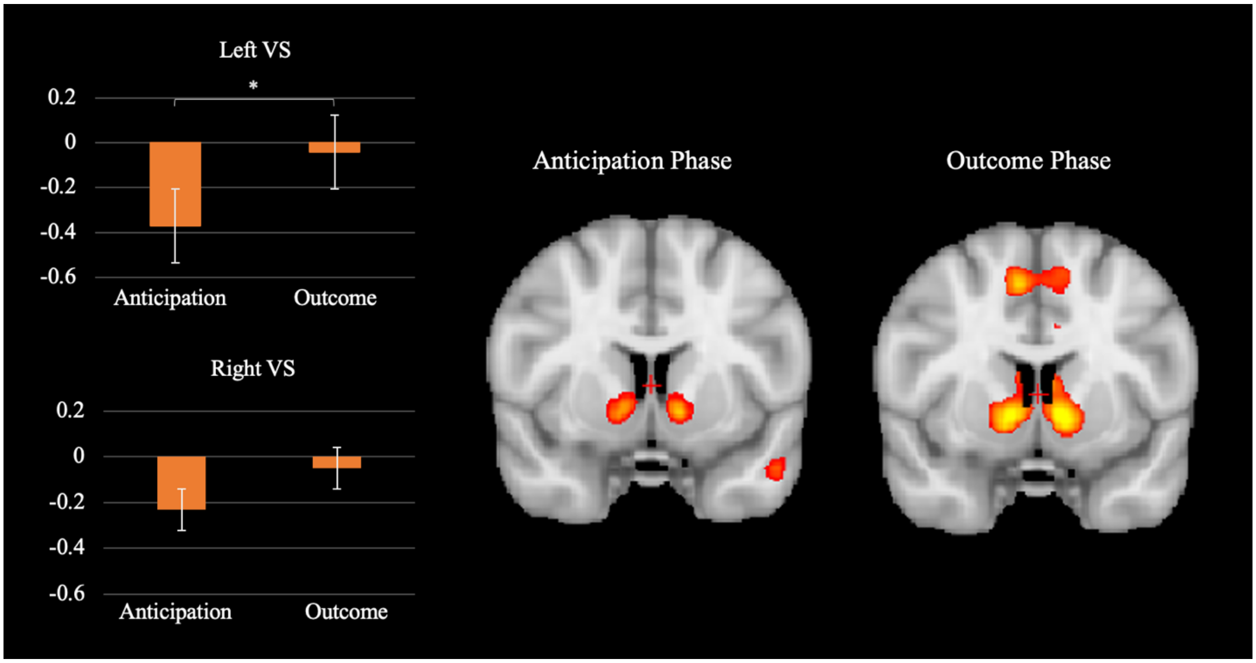
Correlations were also carried out to assess the association between baseline social anxiety severity and average beta weight VS activation during anticipation as well as outcome phases. Results indicated that left VS activation during the anticipatory phase was not significantly correlated with social anxiety severity ($r(27) = -0.27$, $p = 0.17$); however left VS activation during the outcome phase demonstrated a trend-level association with social anxiety severity ($r(27) = -0.36$, $p = 0.06$). These patterns are consistent when evaluating the right VS, such that activation during the anticipatory phase was not significantly correlated with social anxiety severity ($r(27)=$

[1] FSL cluster coordinates are displayed in voxel space rather the MNI space.

-0.28, $p = 0.15$), but right VS activation during the outcome phase, while not significant, showed trend-level associations with social anxiety severity ($r(27) = -0.34$, $p = 0.08$).

Figure 3

Average VS BOLD Activation During General Anticipatory and Outcome Phases.



Note ps < 0.05 for BOLD Signal

Clinical Relations Between VS Activation and Anhedonia

As is demonstrated above, only the DARS Sensory subscale, ASA Total scale, and ASA Enjoyment subscale were significantly different from baseline to endpoint, as such, change scores for these variables were calculated and entered into a regression equation as the dependent variable with the anticipatory phase VS BOLD activation as the independent variable while controlling for age and gender. Results indicated that neither left nor right VS during anticipation nor outcome were significantly associated with ΔDARS Sensory anhedonia (*ps* > 0.05). Results also indicated that the left VS activation during the anticipatory phase demonstrated trend level significance in predicting Δtotal anhedonia via the ASA ($t(27) = -1.78$, $p = 0.09$), however this pattern did not hold during the outcome phase ($p = 0.56$). Results further indicated that the right VS activation during the anticipatory phase and during the outcome phase were not significantly associated with Δtotal anhedonia ($p = 0.19$ and $p = 0.20$, respectively). With regard to the ΔASA Enjoyment subscale, the left VS activation during the anticipatory phase demonstrated trend level significance ($t(27) = -1.99$, $p = 0.06$). However, no relations among the VS were significantly predictive of the ΔASA Enjoyment subscale (all *p*s > 0.05). Taken together, although not statistically significant, *left* VS activation during anticipatory phases may be associated with total heightened anhedonia symptoms, but not the specific enjoyment domain, following exposure to acute social stress.

To assess for dimensional and domain-specific of fMRI markers with regard to anhedonia prior to exposure to acute social stress, we also ran exploratory correlational analyses among all self-reported baseline measures of anhedonia with VS activation during the anticipatory and outcome phases. Correlational results indicated that there were no significant association between any measures of anhedonia at baseline or endpoint for both the left and right VS during the anticipatory phase (all *p*s > 0.05). However, for the outcome phase, both left and right VS demonstrate significant relations with baseline anhedonia (left VS: $r(27) = -0.39$, $p < 0.05$, right VS: $r(27) = -0.39$, $p < 0.05$) via the SHAPS, suggesting that anhedonia prior to exposure to social stress may correlate with the strength of reward signal during socially-valenced outcomes.

Association of Peer Victimization with VS Activation and Anhedonia

VS Activation

Additional regression analyses were performed to assess for the association of peer victimization and VS responses. Step 1 variables included age and gender, and step 2 variables included baseline levels of peer victimization across domains; VS activation added as the dependent variable across phases. Results indicated that overt peer victimization significantly predicted left VS activation during the anticipatory phase (step 1 $R^2 = 0.06$; step 2 $R^2 = 0.60$, $t(27) = -3.81$, $p < 0.001$) and in the right VS activation during the anticipatory phase (step 1 $R^2 = 0.06$; step 2 $R^2 = 0.64$, $t(27) = -4.26$, $p < 0.001$) above and beyond age or gender. This pattern of results is demonstrated also in the anticipation > outcome VS activation contrast (step 1 $R^2 = 0.07$; step 2 $R^2 = 0.59$, $t(27) = -3.80$, $p < 0.001$). This pattern appears to be specific to the anticipatory phases, as no domain of peer victimization was significantly predictive of VS activation during outcome (all *ps* > 0.05).

Additionally, exploratory analyses were run to assess this effect within the main effect of anticipatory and outcome domains while incorporating other theoretically linked variables. Specifically, in these analyses, step 1 included age, gender, baseline anhedonia (per the ASA), baseline stress, and baseline depression, and step 2 included domains of peer victimization. In these exploratory results, the same pattern emerges such that overt peer victimization significantly predicted left VS activation during the anticipatory phase (step 1 $R^2 = 0.13$; step 2 $R^2 = 0.62$, $t\,(27) = -3.55$, $p < 0.01$) and in the right VS activation during the anticipatory phase (step 1 $R^2 = 0.13$; step 2 $R^2 = 0.66$, $t(27) = -3.96$ $p < 0.001$) above and beyond age, gender, depression, stress, or anhedonia. Moreover, these same analyses were run as predictors of the contrast of anticipation phase > outcome phases. Again, results suggest that overt peer victimization predict left and right VS activation above and beyond the effect of age, gender, stress, depression, or anhedonia in the contrast of anticipation phase > outcome phase (left VS: step 1 $R^2 = 0.14$; step 2 $R^2 = 0.62$, $t(27) = -3.54$, $p < 0.01$; right VS: step 1 $R^2 = 0.14$; step 2 $R^2 = 0.66$, $t(27) = -3.98$, $p < 0.001$).

Anhedonia

Regression analyses were similarly run with change in anhedonia and baseline anhedonia as separate dependent variables while controlling for age and gender. These results indicated that only reputational peer victimization was significantly associated with motivational anhedonia at baseline via the ASA (step 1 $R^2 = 0.05$; step 2 $R^2 = 0.23$, $t(27) = 2.40$, $p < 0.01$), but no other measure of anhedonia (all *ps* > 0.05).

Recap of Aims Summary of Results by Aim

AIM 1. Characterize markers of reward sensitivity during periods of social feedback using a well validated social feedback paradigm.

Hypothesis 1. The VS will demonstrate blunted patterns of activation during the anticipatory phase of social feedback stress (as evidenced by aggregate blood-oxygen-level-dependent (BOLD) levels during the built-in delay period of the task that occurs immediately prior to social feedback receipt) as compared to outcome phases (1a), and that the degree of VS suppression during anticipation of social feedback will correlate with social anxiety severity (1b).

Narrative Summary of Results. Hypothesis 1a was somewhat supported such that, consistent with predictions, the VS did indeed demonstrate significantly diminished BOLD signal during the anticipatory phase of social feedback as compared to the outcome phase. However, this was specific to the left VS only. Regarding hypothesis 1b, VS activation was not significantly associated with social anxiety severity during either anticipation or outcome phases, thus hypothesis 1b was not supported. Although it should be noted that VS activation during the outcome phase demonstrated a trend-level negative association with social anxiety severity.

AIM 2. Evaluate clinical relations between fMRI reward markers and anhedonia.

Hypothesis 2. Suppressed anticipatory VS activation will predict increased anhedonia symptoms.

Narrative Summary of Results. Hypothesis 2 was partially supported. Specifically, no significant associations were demonstrated among change in anhedonia and VS BOLD signal in either the anticipation or outcome phases. However, results indicated that the left VS activation during the anticipatory phase demonstrated trend level significance in negatively predicting Δtotal anhedonia via the ASA and ΔASA Enjoyment subscale, such that lower VS activation during anticipation indicated higher anhedonia. Additionally, exploratory analyses demonstrated that for the outcome phase, both left and right VS demonstrate significant relations with baseline anhedonia via the SHAPS. Indicating that higher baseline levels of anhedonia were associated with lower VS activation during outcome phases of the task.

AIM 3. Investigate if elevated levels prior exposure to stress (i.e., peer victimization) are associated with the degree of VS suppression and anhedonia symptoms in a social feedback context.

Hypothesis 3. Higher levels of peer victimization will predict anticipatory VS suppression and anhedonia presentation.

Narrative Summary of Results. Hypothesis 3 was supported regarding peer victimization predicting diminished VS activation, such that overt peer victimization, but *not* other forms of peer victimization, significantly predicted suppressed VS activation during the anticipatory phase of the task, above and beyond age, gender, depression, stress, or anhedonia. However, regarding the hypothesis that peer victimization would predict anhedonia presentation at baseline (i.e., prior to the task), only reputational peer victimization, not other forms of peer victimization, was significantly associated with motivational anhedonia at baseline via the ASA (step 1 $R^2 = 0.05$; step 2 $R^2 = 0.23$, $t(27) = 2.40$, $p < 0.01$), but no other measure of anhedonia ($ps > 0.05$).

Discussion

The overall purpose of this study was to characterize reward processing and associations with anhedonia in socially anxious adolescents when under the condition of acute social stress.

The work presented here was collectively motivated by gaps in the literature regarding reward processing in the context of peer social feedback and how stress-induced suppression of neural responses in the ventral striatum may be related to the development of anhedonia within socially anxious adolescents. As such, the present study had three primary aims within a sample of socially anxious adolescents: (1) to characterize markers of reward during social feedback; (2) to evaluate clinical relations between fMRI markers of reward sensitivity and anhedonia; and (3) to determine whether prior exposure to adverse social stress (i.e., peer victimization) tracked with both reward activation and anhedonia.

First, regarding characterizing reward activation during social feedback contexts, it was hypothesized that the VS would demonstrate blunted patterns of activation during the anticipatory phase of social feedback stress as compared to outcome phases based on prior work suggesting that exposure to acute stress blunts anticipatory VS response in adolescents (Lincoln et al., 2019) as well as the idea that socially anxious adolescents view social rejection as a form of stress. Results from the present study indicated that this hypothesis was partially supported, such that left VS activation during anticipation of social feedback was significantly lower as compared to left VS activation during the outcome phase. Moreover, functional analyses also support these findings with an identical pattern of blunted left VS activation during the anticipatory phase. Thus, these results are the first to demonstrate diminished expectancy of reward in social stress contexts for socially anxious youth, supporting prior theoretical work positing this pattern (Richey et al., 2019). It should be noted that this pattern was not significant in the right VS; indicating potential laterality specificity in anticipatory reward processing. Prior work in adults has demonstrated unique lateralization by reward stimulus and phase (see meta-analysis by Arsalidou et al., 2020); however, this work has yet to be evaluated in adolescent samples during social contexts. Results from the current study add to this line of scientific inquiry by suggesting that there may be specific reward-related left lateralization of striatal responses during the processing of social stimuli in socially anxious adolescents.

Based on prior work indicating that adolescents with high social anxiety tend to demonstrate heightened striatal activation (e.g., Bar-Haim et al., 2009; Guyer et al., 2012, 2014) as compared to typically developing peers, it was hypothesized that the degree VS activation during anticipation of social feedback would be significantly related to social anxiety severity. Results demonstrated that VS activation during the anticipatory phase was not significantly correlated with social anxiety severity in either left or right VS. Similar analyses were also scrutinized during the outcome phase. Results in that case indicated that VS activation during the outcome phase demonstrated trend-level association with social anxiety severity, such that blunted VS during outcome was associated with higher social anxiety severity. While not statistically significant, this pattern of results is consistent with the model mentioned above suggesting that adolescents with high social anxiety when exposed to acute stress (i.e., exposed to the potential of social rejection) may experience a blunting effect on normally elevated VS response (Lincoln et al., 2019; Richey et al., 2019). This pattern of results was somewhat surprising given prior work; however, this pattern could be attributed to the sample itself consisting of solely highly socially anxious participants, thus limiting potential variability of social anxiety severity. Future work should assess striatal activation during social anticipatory contexts within adolescent samples consisting of high and low social anxiety levels.

Recent work has theorized that socially anxious adolescents may be particularly vulnerable to the development of anhedonia due to a pernicious combination of blunted reward processing in social contexts leading to diminished approach-related behaviors and exposure to significant social adversity (e.g., peer victimization) during development (Carlton et al., 2020; Richey et al., 2019). However, limited empirical work has been developed in the area of reward processing, social adversity, and anhedonia development in socially anxious adolescents. As such, the second aim of the present study was to evaluate relations between fMRI markers of reward and anhedonia and the third aim of the present study was to determine whether prior exposure to peer victimization was significantly associated with both reward activation and anhedonia. Regarding the second aim, it was hypothesized that suppressed anticipatory VS activation would predict increased anhedonia given that prior work has suggested that blunted VS during anticipatory contexts is significantly correlated with anhedonia in both adult (Borsini et al., 2020; Wang et al., 2021) and adolescent samples (Stringaris et al., 2015). However, results were mixed, such that decreases in anhedonia from baseline to endpoint showed trend-level associations with heightened VS activation during anticipation but not outcome phases. When evaluating exploratory associations of baseline anhedonia and VS activation, anhedonia was not significantly associated with anticipatory VS activation but was significantly associated with outcome VS activation. Overall, these results are consistent with the possibility that only in the presence of social stress does anhedonia correlate with striatal activation during anticipation of feedback, while in non-stressful situations, anhedonia may correlate with striatal outcome responses. Future studies should assess this pattern in a longitudinal framework, so that anhedonia can be assessed over time instead of in a state-like manner as was done in the present study.

Regarding the final aim to determine whether prior exposure to peer victimization was significantly associated with both reward activation and anhedonia, it was hypothesized that higher baseline levels of peer victimization would predict anticipatory VS suppression and anhedonia severity. These hypotheses were grounded in prior empirical work linking the exposure to early adverse experiences (including peer victimization) to altered reward processing (e.g., Rappaport et al., 2019) as well as prior theoretical work proposing the stress-to-anhedonia pipeline (Richey et al., 2019) in socially anxious youth. The hypothesis positing that peer victimization would predict anhedonia was largely unsupported, such that only reputational peer victimization predicted the motivational subscale of anhedonia, but not other domains. However, results largely supported the hypothesis that peer victimization was associated with VS activation during anticipation. Specifically, findings revealed that overt peer victimization was significantly associated with blunted VS activation during the main effect of anticipation and contrast anticipatory > outcome phases above and beyond age, gender, baseline depression, baseline anhedonia, or baseline stress. This pattern of results did not hold for VS activation during the outcome phases, suggesting a potentially key link between overt peer victimization and anticipatory reward processing. These results suggest that peer victimization may specifically act on anticipatory systems of reward processing by suppressing anticipated reward value, which may in turn reduce future approach-related behaviors. Diminished anticipation of reward has been proposed as a central mechanism in the development of anhedonia over time, thus supporting theoretical work by Richey and colleagues (2019).

Taken together, findings from the present study identify potential targets for intervention and prevention in socially anxious adolescents that could be modifiable, although that issue awaits future investigation. Specifically, it may be possible that preventing or buffering against the effects of peer victimization through extant interventions may have the indirect effect of modifying reward processing. The findings reported here are particularly important in that context, given that current "gold-standard" interventions that focus primarily on negative-valence systems demonstrate low rates of positive treatment outcomes in socially anxious youth (e.g., Ginsburg et al., 2011).

Recently, there has been an emphasis on the development of treatments that target positive valence systems in therapeutic treatments, such as the Positive Affect Treatment (PAT; Craske et al., 2016) and the Amplification of Positivity Treatment (AMP; Taylor et al., 2020). Individuals who have participated in PAT or AMP trials have demonstrated significant enhancements in reward processing following administration of the intervention (Craske et al., 2023; Kryza-Lacombe et al., 2021). Thus, these treatment approaches may also represent productive avenues for intervention among for socially anxious youth. Future work should assess the effectiveness of these interventions in socially anxious adolescent samples, perhaps also in combination with peer victimization prevention-based programs, such as UTalk (La Greca et al., 2016).

Overall, the present study answers key preliminary questions about reward processing in socially anxious adolescents when under the condition of perceived social peer evaluation stress. Prior foundational work has consistently noted significantly heightened anticipatory VS signal in the presence of reward in adolescent samples in general as compared to adults (see Galván, 2010 and Somerville, 2013 for reviews), in youth at risk for developing SAD as compared to youth not at risk (Guyer et al., 2014), and in socially anxious youth samples as compared to other psychiatric groups (e.g., Guyer et al., 2012). However, the present study demonstrated a strikingly different pattern of reward processing within socially anxious adolescents, such that VS signal was actually significantly blunted during anticipation of social reward as compared to outcome. While those prior studies set the stage for the current study, these studies did not assess reward processing in socially anxious adolescents within the context of socially valenced peer stress. Thus, the present study extends the literature in this area by adding additional study design elements to the underlying framework of prior work. First, the present work added a social valence to the study design to assess patterns of reward processing in a social context such as prior adult work utilizing the social incentive delay task (e.g., Richey et al., 2017). Second, the present study added an additional layer onto this broader social valence context – a peer salience context – and evaluated whether the presence of social stress that tapped into peer salience (vis-à-vis the potential for *peer* rejection) demonstrated consistent patterns with prior work in adults. These distinctions in study design may be critical to understanding the opposite pattern of reward responsiveness demonstrated in the present study because during the adolescent developmental period, peer relationships and peer acceptance are particularly salient (e.g., Somerville, 2013) and of central concern for socially anxious adolescents due to the core fear of negative evaluation. Consistent with prior models of acute stress induced blunting of VS signal (e.g., Jarcho et al., 2019; Lincoln et al., 2019); the present study may represent a proof of concept of this stress-reward blunting model within socially valenced peer contexts within socially anxious youth. Additionally, it should be highlighted that the findings from the present study fit squarely within a high-risk profile for anhedonia development based on theoretical work positing this pattern of reward dysfunction in the context of early adversity (Richey et al., 2019) and thus may represent the "pre-anhedonic" phase of development for this population whereby this vulnerability to social stress is exhibited. Taken together, the present study leads to additional lines of inquiry that should be evaluated. Specifically, future research in this area should consider assessing stress-reward processing pipelines longitudinally within socially valenced tasks that tap into core contributors of SAD and anhedonia to further characterize reward processing patterns in this population under ecologically valid and ecologically relevant conditions.

Limitations & Future Directions

As with all studies, the results presented here should be taken in light of study limitations. First, while recruitment of a relatively robust sexuality- and gender-diverse sample from a rural community was possible, this sample largely consisted of white individuals who also fell within a relatively high family income range. As such, the present study may not generalize to individuals of different racial backgrounds or lower socioeconomic status. This is not trivial, as children who live in under-resourced areas tend to experience higher rates of adversity during development (Brendgen et al., 2021; Cicchetti & Lynch, 1993; Sedlak et al., 2010). Thus, it is critical that future work intentionally recruit these samples to increase generalizability of the present study to samples who these variables may impact most. Next, while the present study was able to modify the EEG version of the Island Getaway task to an MRI format, not all portions of the task could be carried over without compromising data collection. First, free response items in the task were limited solely to the profile creation phase due to difficulty starting and stopping functional runs in between each round. Next, likability ratings were also limited to the profile creation phase, such that participants only reported on how much they liked a co-player prior to beginning the game. This limitation is due to concerns of movement, as well as available button options programmed to the scanner via the button box. Thus, continuous ratings of likability of co-players were not able to be collected. Lastly, with regard to the task, although standardized pictures of adolescents (via the NIMH-ChEFS picture set) were included, these pictures only had a single positive valence (i.e., smiling faces) to remain consistent. Future work should consider switching out mixed valence images to assess voting preferences and reward signal in the presence of negative or neutral peer facial expressions. Additionally, future work should consider the possibility of adding in photos of peers that the participant may actually recognize (e.g., friends and/or peers at school). This approach is recently being utilized in certain labs via pictures of peers from school yearbooks in the local community, although it was not possible in this study due to differing IRB regulations. Additionally, while participants found the task to be realistic as in prior studies (e.g., Kujawa et al., 2014), the ecological validity of the task could be increased by having confederate families/peers sit in the waiting room prior to experimental sessions. Future work should consider incorporating this as an additional layer of task realism particularly since other aspects of the original task (e.g., text box responses) were not able to be incorporated into the present MRI version.

The present study intentionally recruited a sample of socially anxious adolescents to test within-subjects effects of reward processing within the context of social peer stress. Given that adolescents enrolled in the present study could also demonstrate significant generalized anxiety and depression, it may be beneficial to recruit adolescents who solely have SAD (i.e., have SAD in the absence of other psychiatric conditions) and those who solely have GAD or MDD to further disentangle mechanisms of anhedonia development that are *specific* to SAD. This additional investigation of singular comparator groups may be particularly fruitful, given recent work showing the development of anhedonia in youth with GAD as having potentially distinct reward-based predictors as compared to youth with GAD (Carlton et al., in preparation). Additionally, the present study's inclusion criteria included high social anxiety and moderate stress based on theoretical work positing that stress within the context of elevated social anxiety may represent a vulnerable combination for the development of anhedonia during adolescence (Richey et al., 2019). When evaluating self-reported anhedonia from participants, anhedonia levels were relatively low (as compared to depressed adult samples); which may indicate that this study did indeed "catch" this sample during a potentially vulnerable period (i.e., where significant anhedonia has not yet occurred). However, to further delineate the developmental trajectory of anhedonia within socially anxious youth, future work should utilize a longitudinal study design to track and identify “dosage effects” of accumulated stress as well as optimal timing for intervention and prevention efforts within this population of youth.

Conclusion

In sum, findings from the present study suggest that when in the presence of social stress (i.e., the potential for negative feedback), socially anxious adolescents demonstrate significantly blunted VS activation when anticipating feedback. Additionally, results indicate that there are some associations among VS activation and anhedonia severity. Lastly, it was shown that peer victimization is one of the most robust predictors of blunted striatal activation during anticipation of social feedback. The results identify potentially modifiable mechanisms associated with anhedonia severity and blunted reward processing in socially anxious youth.

References

Albano, A. M., & Hayward, C. (2004). Social anxiety disorder In J.S. March & T. H. Ollendick (Eds.), *Phobic and anxiety disorders in children and adolescents: A clinician's guide to effective psychosocial and pharmacological interventions* (pp. 198–235). New York: Oxford University Press.

Albano, A. M. & Silverman WK (in press). *The Anxiety and Related Disorders Interview Schedule for DSM-5, Child Interview Schedule*. Oxford University Press.

Arsalidou, M., Vijayarajah, S., & Sharaev, M. (2020). Basal ganglia lateralization in different types of reward. *Brain Imaging and Behavior*, *14*, 2618-2646.

Association, A. P. (2013). Diagnostic and statistical manual of mental health disorders, (DSM-5).

Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., & Gee, J. C. (2011). A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage*, *54*(3), 2033-2044.

Balleine, B. W., Delgado, M. R., & Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision-making. *Journal of Neuroscience, 27*(31), 8161-8165.

Bar-Haim, Y., Fox, N. A., Benson, B., Guyer, A. E., Williams, A., Nelson, E. E., Perez-Edgar, K., Pine, D. S., & Ernst, M. (2009). Neural Correlates of Reward Processing in Adolescents with a History of Inhibited Temperament. *Psychological Science, 20*(8), 1009–1018.

Bas-Hoogendam, J. M., van Steenbergen, H., van der Wee, N. J., & Westenberg, P. M. (2020). Amygdala hyperreactivity to faces conditioned with a social-evaluative meaning–a multiplex, multigenerational fMRI study on social anxiety endophenotypes. *NeuroImage: Clinical, 26,* 102247.

Bayard, F., Abé, C., Wrobel, N., Ingvar, M., Henje, E., & Petrovic, P. (2020). Emotional Instability Relates to Ventral Striatum Activity During Reward Anticipation in Females*. Frontiers in Behavioral Neuroscience, 14*, 76.

Becker, M. P. I., Simon, D., Miltner, W. H. R., & Straube, T. (2017). Altered activation of the ventral striatum under performance-related observation in social anxiety disorder. *Psychological medicine*, *47*(14), 2502-2512.

Beesdo, K., Lau, J. Y. F., Guyer, A. E., McClure-Tone, E. B., Monk, C. S., Nelson, E. E., Fromm, S. J., Goldwin, M. A., Wittchen, H.-U., Leibenluft, E., Ernst, M., & Pine, D. S. (2009). Common and Distinct Amygdala-Function Perturbations in Depressed vs Anxious Adolescents. *Archives of General Psychiatry, 66*(3), 275–285.

Blair, K., Shaywitz, J., Smith, B. W., Rhodes, R., Geraci, M., Jones, M., McCaffrey, D., Vythilingam, M., Finger, E., Mondillo, K., Jacobs, M., Charney, D. S., Blair, R. j. r., Drevets, W. C., & Pine, D. S. (2008). Response to emotional expressions in generalized social phobia and generalized anxiety disorder: Evidence for separate disorders. *American Journal of Psychiatry, 165*(9), 1193–1202.

Bogdan, R., & Pizzagalli, D. A. (2006). Acute stress reduces reward responsiveness: implications for depression. *Biological Psychiatry, 60*(10), 1147–1154.

Borsini, A., Wallis, A. S. J., Zunszain, P., Pariante, C. M., & Kempton, M. J. (2020). Characterizing anhedonia: a systematic review of neuroimaging across the subtypes of reward processing deficits in depression. *Cognitive, Affective, & Behavioral Neuroscience*, *20*, 816-841.

Brendgen, M., Vitaro, F., Ouellet-Morin, I., Dionne, G., & Boivin, M. (2021). Links between early personal characteristics, longitudinal profiles of peer victimization in school and victimization in college or at work. *Research on Child and Adolescent Psychopathology*, *49*, 905-918.

Brown, T. A., Chorpita, B. F., & Barlow, D. H. (1998). Structural relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. *Journal of Abnormal Psychology, 107*(2), 179.

Buff, C., Brinkmann, L., Neumeister, P., Feldker, K., Heitmann, C., Gathmann, B., Andor, T., & Straube, T. (2016). Specifically altered brain responses to threat in generalized anxiety disorder relative to social anxiety disorder and panic disorder. *NeuroImage: Clinical, 12*, 698–706.

Calderon, C. B., De Loof, E., Ergo, K., Snoeck, A., Boehler, C. N., & Verguts, T. (2021). Signed reward prediction errors in the ventral striatum drive episodic memory. *The Journal of Neuroscience, 41*(8), 1716–1726.

Caouette, J. D., & Guyer, A. E. (2014). Gaining insight into adolescent vulnerability for social anxiety from developmental cognitive neuroscience. *Developmental Cognitive Neuroscience, 8*, 65–76.

Carlozzi, B. L., Winterowd, C., Steven Harrist, R., Thomason, N., Bratkovich, K., & Worth, S. (2010). Spirituality, anger, and stress in early adolescents. *Journal of Religion and Health, 49*(4), 445–459.

Carlton, C. N., Antezana, L., Garcia, K. M., Sullivan-Toole, H., & Richey, J. A. (2021). Mindfulness-Based Stress Reduction Specifically Improves Social Anhedonia among Adults with Chronic Stress. *Affective Science*, 1-15.

Carlton, C. N., Antezana, L., Lindenmuth, M, Kim-Spoon, J, Ollendick, T. H., & Richey, J.A. (In preparation). Prevalence of anhedonia in socially anxious youth: Leveraging the adolescent brain cognitive development study.

Carlton, C. N., Antezana, L., & Richey, J. A. (2023) Associations between resting-state neural connectivity and positive affect in social anxiety disorder. *Brain and Behavior*, 00, e3006.

Carlton, C. N., Larkin, E., Sloss, J., & Ollendick, T.H. (Under review) Parent-adolescent informant discrepancies and clinician agreement: Implications for the assessment of adolescent social anxiety disorder.

Carlton, C. N., Sullivan-Toole, H., Ghane, M., & Richey, J. A. (2020). Reward Circuitry and Motivational Deficits in Social Anxiety Disorder: What Can Be Learned From Mouse Models? *Frontiers in Neuroscience*, *14*, 154.

Casey, B., Galván, A., & Somerville, L. H. (2015). Beyond simple models of adolescence to an integrated circuit-based account: A commentary. *Developmental Cognitive Neuroscience, 17*, 128–130.

Cicchetti, D., & Lynch, M. (1993). Toward an ecological/transactional model of community violence and child maltreatment: Consequences for children's development. *Psychiatry*, *56*(1), 96-118.

Cohen, S., & Williamson, G. (1988). *Perceived stress in a probability sample of the United States*. In S. Spacapan & S. Oskamp (Eds.), The Social Psychology of Health: Claremont Symposium on Applied Social Psychology Newbury Park, CA: Sage.

Craske, M. G., Meuret, A. E., Echiverri-Cohen, A., Rosenfield, D., & Ritz, T. (2023). Positive affect treatment targets reward sensitivity: A randomized controlled trial. *Journal of Consulting and Clinical Psychology*.

Craske, M. G., Meuret, A. E., Ritz, T., Treanor, M., & Dour, H. J. (2016). Treatment for Anhedonia: A Neuroscience Driven Approach. Depression and Anxiety, 33(10), 927–938.

Cremers, H. R., Veer, I. M., Spinhoven, P., Rombouts, S. A., & Roelofs, K. (2015). Neural sensitivity to social reward and punishment anticipation in social anxiety disorder. *Frontiers in Behavioral Neuroscience*, *8*, 439.

Davies, C. D., Young, K., Torre, J. B., Burklund, L. J., Goldin, P. R., Brown, L. A., Niles, A. N., Lieberman, M. D., & Craske, M. G. (2017). Altered time course of amygdala activation during speech anticipation in social anxiety disorder. *Journal of Affective Disorders*, *209*, 23-29.

Davis, M., & Whalen, P. J. (2001). The amygdala: Vigilance and emotion. *Molecular Psychiatry, 6*(1), 13–34.

de Lijster, J. M., Dieleman, G. C., Utens, E. M. W. J., Dierckx, B., Wierenga, M., Verhulst, F. C., & Legerstee, J. S. (2018). Social and academic functioning in adolescents with anxiety disorders: A systematic review. *Journal of Affective Disorders, 230*, 108–117.

De Los Reyes, A., & Prinstein, M. J. (2004). Applying depression-distortion hypotheses to the assessment of peer victimization in adolescents. *Journal of Clinical Child and Adolescent Psychology, 33*(2), 325-335.

Egger, H. L., Pine, D. S., Nelson, E., Leibenluft, E., Ernst, M., Towbin, K. E., & Angold, A. (2011). The NIMH Child Emotional Faces Picture Set (NIMH-ChEFS): a new set of children's facial emotion stimuli. *International Journal of Methods in Psychiatric Research, 20*(3), 145-156.

Eiland, L., & Romeo, R. D. (2013). Stress and the developing adolescent brain. *Neuroscience, 249*, 162–171.

Eisner, L. R., Johnson, S. L., & Carver, C. S. (2009). Positive affect regulation in anxiety disorders. *Journal of Anxiety Disorders, 23*(5), 645-649.

Ernst, M., Romeo, R. D., & Andersen, S. L. (2009). Neurobiology of the development of motivated behaviors in adolescence: A window into a neural systems model. *Pharmacology Biochemistry and Behavior, 93*(3), 199–211.

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in ptsd, social anxiety disorder, and specific phobia. *American Journal of Psychiatry, 164*(10), 1476–1488.

Farrell, L. J., Ollendick, T. H., & Muris, P. (2019). *Innovations in CBT for Childhood Anxiety, OCD, and PTSD: Improving Access and Outcomes*. Cambridge University Press.

FitzGerald, T. H., Schwartenbeck, P., & Dolan, R. J. (2014). Reward-related activity in ventral striatum is action contingent and modulated by behavioral relevance. *Journal of Neuroscience, 34*(4), 1271-1279.

Galván, A. (2010). Adolescent development of the reward system. *Frontiers in Human Neuroscience,* 6.

Galván, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience, 26*(25), 6885–6892.

Gentili, C., Cristea, I. A., Angstadt, M., Klumpp, H., Tozzi, L., Phan, K. L., & Pietrini, P. (2016). Beyond emotions: A meta-analysis of neural response within face processing system in social anxiety. *Experimental Biology and Medicine, 241*(3), 225–237.

Gilboa-Schechtman, E., Franklin, M. E., & Foa, E. B. (2000). Anticipated reactions to social events: Differences among individuals with generalized social phobia, obsessive compulsive disorder, and nonanxious controls. *Cognitive Therapy and Research, 24*(6), 731-746.

Ginsburg, G. S., Sakolsky, D., Piacentini, J., Walkup, J. T., Coffey, K. A., Keeton, C. P., Iyengar, S., Kendall, P. C., Compton, S. N., Albano, A. M., Sherrill, J., Rynn, M. A., McCracken, J. T., Bergman, L., Birmaher, B., & March, J. (2011). Remission after acute treatment in children and adolescents with anxiety disorders: Findings from the CAMS. *Journal of Consulting and Clinical Psychology, 79*(6), 806–813.

Gorgolewski, K., Burns, C. D., Madison, C., Clark, D., Halchenko, Y. O., Waskom, M. L., & Ghosh, S. S. (2011). Nipype: a flexible, lightweight and extensible neuroimaging data processing framework in python. *Frontiers in Neuroinformatics*, 13.

Guyer, A. E., Benson, B., Choate, V. R., Bar-Haim, Y., Perez-Edgar, K., Jarcho, J. M., Pine, D. S., Ernst, M., Fox, N. A., & Nelson, E. E. (2014). Lasting associations between early-childhood temperament and late-adolescent reward-circuitry response to peer feedback. *Development and Psychopathology, 26*(1), 229–243.

Guyer, A. E., Choate, V. R., Detloff, A., Benson, B., Nelson, E. E., Perez-Edgar, K., Fox, N. A., Pine, D. S., & Ernst, M. (2012). Striatal functional alteration during incentive anticipation in pediatric anxiety disorders. *American Journal of Psychiatry, 169*(2), 205–212.

Haber, S. N., & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology, 35*(1), 4-26.

Hahn, A., Stein, P., Windischberger, C., Weissenbacher, A., Spindelegger, C., Moser, E., Kasper, S., & Lanzenberger, R. (2011). Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. *NeuroImage, 56*(3), 881–889.

Herbert, J. D., Gaudiano, B. A., Rheingold, A. A., Moitra, E., Myers, V. H., Dalrymple, K. L., & Brandsma, L. L. (2009). Cognitive behavior therapy for generalized social anxiety disorder in adolescents: A randomized controlled trial. *Journal of Anxiety Disorders, 23*(2), 167–177.

Higa-McMillan, C. K., Francis, S. E., Rith-Najarian, L., & Chorpita, B. F. (2016). Evidence base update: 50 years of research on treatment for child and adolescent anxiety. *Journal of Clinical Child & Adolescent Psychology, 45*(2), 91–113.

James, A. C., Reardon, T., Soler, A., James, G., & Creswell, C. (2020). Cognitive behavioural therapy for anxiety disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, 2020(11).

Jang, H., Lee, J. Y., Lee, K. I., & Park, K. M. (2017). Are there differences in brain morphology according to handedness?. *Brain and behavior*, *7*(7), e00730.

Jarcho, J. M., Grossman, H. Y., Guyer, A. E., Quarmley, M., Smith, A. R., Fox, N. A., Leibenluft, E., Pine, D. S., & Nelson, E. E. (2019). Connecting childhood wariness to adolescent social anxiety through the brain and peer experiences. *Journal of Abnormal Child Psychology, 47*(7), 1153–1164.

Johnson, J. G., Harris, E. S., Spitzer, R. L., & Williams, J. B. (2002). The patient health questionnaire for adolescents: validation of an instrument for the assessment of mental disorders among adolescent primary care patients. *Journal of Adolescent Health, 30*(3), 196-204.

Kashdan, T. B. (2007). Social anxiety spectrum and diminished positive experiences: Theoretical synthesis and meta-analysis. *Clinical Psychology Review, 27*(3), 348-365.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry*, *62*(6), 593–602.

Klumpp, H., & Fitzgerald, J. M. (2018). Neuroimaging predictors and mechanisms of treatment response in social anxiety disorder: an overview of the amygdala. *Current Psychiatry Reports, 20*(10), 89.

Kohls, G., Perino, M. T., Taylor, J. M., Madva, E. N., Cayless, S. J., Troiani, V., Price, E., Faja, S., Herrington, J. D., & Schultz, R. T. (2013). The nucleus accumbens is involved in both the pursuit of social reward and the avoidance of social punishment. *Neuropsychologia, 51*(11), 2062-2069.

Kraus, J., Frick, A., Fischer, H., Howner, K., Fredrikson, M., & Furmark, T. (2018). Amygdala reactivity and connectivity during social and non-social aversive stimulation in social anxiety disorder. *Psychiatry Research: Neuroimaging, 280*, 56–61.

Kryza-Lacombe, M., Pearson, N., Lyubomirsky, S., Stein, M. B., Wiggins, J. L., & Taylor, C. T. (2021). Changes in neural reward processing following Amplification of Positivity treatment for depression and anxiety: Preliminary findings from a randomized waitlist controlled trial. *Behaviour Research and Therapy*, *142*, 103860.

Kujawa, A., Arfer, K. B., Klein, D. N., & Proudfit, G. H. (2014). Electrocortical reactivity to social feedback in youth: A pilot study of the Island Getaway task. *Developmental Cognitive Neuroscience*, *10*, 140–147.

Kujawa, A., Carroll, A., Mumper, E., Mukherjee, D., Kessel, E. M., Olino, T., Hajcak, G., & Klein, D. N. (2018). A longitudinal examination of event-related potentials sensitive to monetary reward and loss feedback from late childhood to middle adolescence. *International Journal of Psychophysiology, 132*, 323–330.

Kujawa, A., Kessel, E. M., Carroll, A., Arfer, K. B., & Klein, D. N. (2017). Social processing in early adolescence: Associations between neurophysiological, self-report, and behavioral measures. *Biological Psychology*, *128*, 55–62.

La Greca, A. M., Ehrenreich-May, J., Mufson, L., & Chan, S. (2016). *Preventing adolescent social anxiety and depression and reducing peer victimization: Intervention development and open trial.* In Child & youth care forum (Vol. 45, pp. 905-926). Springer US.

Leventhal, A. M., Chasson, G. S., Tapia, E., Miller, E. K., & Pettit, J. W. (2006). Measuring hedonic capacity in depression: a psychometric analysis of three anhedonia scales. *Journal Of Clinical Psychology, 62*(12), 1545-1558.

Leventhal, A. M., Unger, J. B., Audrain-McGovern, J., Sussman, S., Volk, H. E., & Strong, D. R. (2015). Measuring anhedonia in adolescents: a psychometric analysis. *Journal Of Personality Assessment*, *97*(5), 506-514.

Lincoln, S. H., Pisoni, A., Bondy, E., Kumar, P., Singleton, P., Hajcak, G., Pizzagalli, D. A., & Auerbach, R. P. (2019). Altered reward processing following an acute social stressor in adolescents. *PLoS ONE, 14*(1), e0209361.

Masia-Warner, P. D. C., Storch, M. S. E. A., Pincus, P. D. D. B., Klein, P. D. R. G., Heimberg, P. D. R. G., & Liebowitz, A. M. R. (2003). The liebowitz social anxiety scale for children and adolescents: An initial psychometric investigation. *The Journal of the American Academy of Child and Adolescent Psychiatry, 42*(9), 1076-1084.

Merikangas, K. R., He, J., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., Benjet, C., Georgiades, K., & Swendsen, J. (2010). Lifetime prevalence of mental disorders in u.s. adolescents: results from the national comorbidity survey replication–adolescent supplement (NCS-A). *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(10), 980–989.

Moitra, E., Beard, C., Weisberg, R. B., & Keller, M. B. (2011). Occupational impairment and social anxiety disorder in a sample of primary care patients. *Journal of Affective Disorders, 130*(1–2), 209–212.

Mumford, J. A., & Nichols, T. (2008). Power calculation for group fMRI studies accounting for arbitrary design and temporal autocorrelation. *NeuroImage, 39*(1), 261–268.

O'Doherty, J. P. (2004). Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Current Opinion In Neurobiology, 14*(6), 769-776.

Ollendick, T. H., Benoit, K. E., & Grills-Taquechel, A. E. (2014). *Social anxiety disorder in children and adolescents. In The Wiley Blackwell handbook of social anxiety disorder* (pp. 181–200). Wiley Blackwell.

Park, S. H., Song, Y. J. C., Demetriou, E. A., Pepper, K. L., Hickie, I. B., Glozier, N., Hermens, D. F., Scott, E. M., & Guastella, A. J. (2021). Distress, quality of life and disability in treatment-seeking young adults with social anxiety disorder. *Early Intervention in Psychiatry, 15*(1), 57–67.

Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annual Review Of Clinical Psychology, 10*, 393-423.

Rademacher, L., Krach, S., Kohls, G., Irmak, A., Gründer, G., & Spreckelmeyer, K. N. (2010). Dissociation of neural networks for anticipation and consumption of monetary and social rewards. *Neuroimage, 49*(4), 3276-3285.

Radtke, S., Whiteside, S. P., & Ollendick, T. H. (2023). Increasing the efficiency of diagnostic interviews for childhood anxiety disorders through joint child-parent administration. *Journal of Psychopathology and Behavioral Assessment*, 45(1), 160-169.

Rappaport, B. I., Hennefield, L., Kujawa, A., Arfer, K. B., Kelly, D., Kappenman, E. S., Luby, J. L., & Barch, D. M. (2019). Peer victimization and dysfunctional reward processing: ERP and behavioral responses to social and monetary rewards. *Frontiers In Behavioral Neuroscience, 13*, 120.

Reilly, E. E., Whitton, A. E., Pizzagalli, D. A., Rutherford, A. V., Stein, M. B., Paulus, M. P., & Taylor, C. T. (2020). Diagnostic and dimensional evaluation of implicit reward learning in social anxiety disorder and major depression. *Depression and Anxiety, 37*(12), 1221–1230.

Richardson, L. P., McCauley, E., Grossman, D. C., McCarty, C. A., Richards, J., Russo, J. E., Rockhill, C., & Katon, W. (2010). Evaluation of the Patient Health Questionnaire-9 Item for detecting major depression among adolescents. *Pediatrics, 126*(6), 1117-1123.

Richey, J., Ghane, M., Valdespino, A., Coffman, M. C., Strege, M. V., White, S. W., & Ollendick, T. H. (2017). Spatiotemporal dissociation of brain activity underlying threat and reward in social anxiety disorder. *Social Cognitive And Affective Neuroscience*, *12*(1), 81-94.

Richey, J. A., Brewer, J. A., Sullivan-Toole, H., Strege, M. V., Kim-Spoon, J., White, S. W., & Ollendick, T. H. (2019). Sensitivity shift theory: A developmental model of positive affect and motivational deficits in social anxiety disorder. *Clinical Psychology Review*, 72, 101756.

Rizvi, S., Quilty, L., Sproule, B., Cyriac, A., Bagby, R., & Kennedy, S. (2015). Development and validation of the Dimensional Anhedonia Rating Scale (DARS) in a community sample and individuals with major depression. *Psychiatry Research, 229(*1-2), 109-119.

Robinson, O. J., Overstreet, C., Charney, D. R., Vytal, K., & Grillon, C. (2013). Stress increases aversive prediction error signal in the ventral striatum. *Proceedings of the National Academy of Sciences, 110*(10), 4129–4133.

Saddoris, M. P., Sugam, J. A., Stuber, G. D., Witten, I. B., Deisseroth, K., Carelli, R.M. (2015). Mesolimbic dopamine dynamically tracks, and is causally linked to, discrete aspects of value- based decision making. *Biological Psychiatry*, *77*(10), 903–11.

Schmidt, S., Mohr, A., Miltner, W. H. R., & Straube, T. (2010). Task-dependent neural correlates of the processing of verbal threat-related stimuli in social phobia. *Biological Psychology, 84(*2), 304–312.

Schreuders, E., Braams, B. R., Blankenstein, N. E., Peper, J. S., Güroğlu, B., & Crone, E. A. (2018). Contributions of reward sensitivity to ventral striatum activity across adolescence and early adulthood. *Child Development*, 89(3), 797–810.

Schultz, W. (1998). Predictive reward signal of dopamine neurons (vol. 80, pg 1, 1998). *Journal of Neurophysiology, 80*(6), U32.

Schultz, W. (2000). Multiple reward signals in the brain. *Nature Reviews Neuroscience*, *1*(3), 199–207.

Schulz, C., Mothes-Lasch, M., & Straube, T. (2013). Automatic neural processing of disorder-related stimuli in social anxiety disorder: Faces and more. *Frontiers in Psychology*, *4*, 282.

Sedlak, A. J., Mettenburg, J., Basena, M., Peta, I., McPherson, K., Greene, A., & Li, S. (2010). Fourth national incidence study of child abuse and neglect (NIS-4). *Washington, DC: US Department of Health and Human Services*, *9*, 2010.

Simon, D., Becker, M., Mothes-Lasch, M., Miltner, W. H. R., & Straube, T. (2017). Loud and angry: Sound intensity modulates amygdala activation to angry voices in social anxiety disorder. *Social Cognitive and Affective Neuroscience*, *12*(3), 409–416.

Snaith, R. P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., & Trigwell, P. (1995). A scale for the assessment of hedonic tone the Snaith–Hamilton Pleasure Scale. *The British Journal of Psychiatry*, *167*(1), 99-103.

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J. B., Jones, P., Kim, J. H., Kim, J. Y., Carvalho, A. F., Seeman, M. V., Correll, C. U., & Fusar-Poli, P. (2021). Age at onset of mental disorders worldwide: Large-scale meta-analysis of 192 epidemiological studies. *Molecular Psychiatry*, 1–15.

Somerville, L. H. (2013). The Teenage Brain: Sensitivity to Social Evaluation. *Current Directions in Psychological Science, 22*(2), 121–127.

Stringaris, A., Vidal-Ribas Belil, P., Artiges, E., Lemaitre, H., Gollier-Briant, F., Wolke, S., Vulser, H., Miranda, R., Penttila, J., Struve, M., Fadai, T., Kapell, V., Grimmer, Y., Goodman, R., Poustka, L., Conrod, P., Cattrell, A., Banaschewski, T., Bokde, A. L. W., … & IMAGEN Consortium. (2015). The brain's response to reward anticipation and depression in adolescence: dimensionality, specificity, and longitudinal predictions in a community-based sample. *American Journal of Psychiatry*, *172*(12), 1215-1223.

Taylor, C. T., Pearlstein, S. L., Kakaria, S., Lyubomirsky, S., & Stein, M. B. (2020). Enhancing social connectedness in anxiety and depression through amplification of positivity: Preliminary treatment outcomes and process of change. *Cognitive Therapy and Research*, *44*, 788-800.

Trew, J. L., & Alden, L. E. (2012). Positive affect predicts avoidance goals in social interaction anxiety: Testing a hierarchical model of social goals. *Cognitive Behaviour Therapy*, *41*(2), 174-183.

Vilaplana-Pérez, A., Pérez-Vigil, A., Sidorchuk, A., Brander, G., Isomura, K., Hesselmark, E., Kuja-Halkola, R., Larsson, H., Mataix-Cols, D., & Fernández de la Cruz, L. (2021). Much more than just shyness: The impact of social anxiety disorder on educational performance across the lifespan. *Psychological Medicine*, *51*(5), 861–869.

Wang, S., Leri, F., & Rizvi, S. J. (2021). Anhedonia as a central factor in depression: Neural mechanisms revealed from preclinical to clinical evidence. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *110*, 110289.

Watson, R., McCabe, C., Harvey, K., & Reynolds, S. (2021). Development and validation of a new adolescent self-report scale to measure loss of interest and pleasure: The Anhedonia Scale for Adolescents. *Psychological Assessment*, *33*(3), 201.

Westenberg, P. M., Gullone, E., Bokhorst, C. L., Heyne, D. A., & King, N. J. (2007). Social evaluation fear in childhood and adolescence: Normative developmental course and continuity of individual differences. *British Journal of Developmental Psychology*, *25*(3), 471–483.

Appendix

Table A1

Breakdown of Measure Administration by Study Timepoint

	Screening	Zoom	Baseline	Endpoint
RPEQ	X			
LSAS-CA	X		X	X
PSS-10	X		X	X
PHQ-9A	X		X	X
ADIS C		X		
DARS			X	X
SHAPS			X	X
ASA			X	X

Note: RPEQ = Peer Experiences Scale Revised; LSAS-CA = Liebowitz Social Anxiety Scale for Children and Adolescents; PSS-10 = Perceived Stress Scale-10; PHQ-9A = Patient Health Questionnaire for Adolescents; ADIS C = Anxiety Disorders Interview Schedule for DSM-5 Child Version; DARS = Dimensional Anhedonia Rating Scale; SHAPS = Snaith–Hamilton Pleasure Scale; ASA = Anhedonia Scale for Adolescents.

Table A2

Correlations Among All Study Self-Report Measures.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. LSAS	-																
2. PSS-10	**.46***	-															
3. PHQ-9A	.16	**.51****	-														
4. DARS Total	.11	.20	.11	-													
5. DARS Hobbies/Past-times	.29	-.08	-.18	**.55****	-												
6. DARS Food/Drink	.09	.19	-.13	**.54****	.22	-											
7. DARS Sensory Experiences	.17	.29	.27	**.81****	.23	.20	-										
8. DARS Social	-.36	-.08	.06	**.48****	.17	.10	.19	-									
9. SHAPS	.17	**.37***	.32	**-.38***	-.22	-.34	-.25	-.10	-								
10. ASA Total	.04	.30	**.70****	-.33	**-.42***	-.31	-.18	-.06	**.50****	-							
11. ASA Enjoyment	.10	.31	**.70****	-.33	**-.37***	-.33	-.19	.07	**.51****	**.93****	-						
12. ASA Connection	-.10	.16	.35	**-.41***	**-.45***	-.30	-.26	-.01	.33	**.75****	**.50****	-					
13. ASA Motivation	.02	.29	**.70****	-.19	-.35	-.18	-.05	.06	**.43***	**.95****	**.81****	**.73****	-				
14. RPEQ Overt	-.13	-.14	.02	-.11	-.15	.29	-.29	.15	-.09	.25	.19	.21	.28	-			
15. RPEQ Relational	.22	-.03	.04	-.07	.16	-.04	-.16	.02	.01	.12	.13	.04	.16	**.38***	-		
16. RPEQ Reputational	.08	.16	.26	-.03	-.18	.32	-.16	.09	.05	.36	.28	.29	**.42***	**.46***	**.46***	-	
17. RPEQ Prosocial	-.06	**.37***	.21	-.20	**-.41***	-.25	.06	-.08	.19	.15	.26	.96	.56	.51	.09	.15	-

Note: * = significantly different at $p < 0.05$; ** = significantly different at $p < 0.01$ LSAS-CA = Liebowitz Social Anxiety Scale for Children and Adolescents; PSS-10 = Perceived Stress Scale-10; PHQ-9A = Patient Health Questionnaire for Adolescents; ADIS C = Anxiety Disorders Interview Schedule for DSM-5 Child Version; DARS = Dimensional Anhedonia Rating Scale; SHAPS = Snaith–Hamilton Pleasure Scale; ASA = Anhedonia Scale for Adolescents; RPEQ = Peer Experiences Scale Revised. All measures presented here are at baseline except the RPEQ, which was done at screening.

Table A3

Main Effect of Anticipation Clusters

Size (mm^3)	*t* max	Voxel Space Coordinates		
		X	Y	Z
11710	5.42	24	80	94
6092	5.59	153	88	115
789	4.16	122	145	67
480	4.15	77	132	67
457	4.58	101	134	68
337	4.03	140	131	45
178	4.00	159	91	58
143	4.21	104	50	19
135	3.86	64	49	16
112	3.45	96	157	73
63	3.39	106	179	98
44	3.34	57	42	34
44	3.34	38	98	64
36	3.27	92	118	68
29	3.69	38	47	79
20	3.37	150	59	69
18	3.44	95	43	28
10	3.17	89	174	101
1	3.11	58	38	39
1	3.16	47	50	116

Note: Clusters significant at $p < 0.05$.

Table A4

Main Effect of Outcome Clusters

Size (mm^3)	*t* max	Voxel Space Coordinates		
		X	Y	Z
1858	4.55	100	135	70
1354	4.65	89	117	70
1315	4.40	79	135	71
1024	4.36	37	50	85
531	4.17	82	136	122
335	3.72	118	152	75
285	4.77	34	111	127
240	4.15	99	145	114
230	3.63	114	121	121
67	3.55	64	49	16
55	3.20	98	128	125
39	3.33	116	169	67
19	3.28	150	85	122
18	3.38	105	51	19
18	3.49	140	44	87
11	3.36	20	97	96
9	3.30	60	138	41
9	3.22	96	152	67
7	3.26	96	42	27
5	3.14	59	152	80
3	3.19	41	102	136

Note: Clusters significant at $p < 0.05$.