Published in final edited form as:

Brain Cogn. 2014 August ; 89: 39–50. doi:10.1016/j.bandc.2013.12.004.

Social Anhedonia and Medial Prefrontal Response to Mutual Liking in Late Adolescents

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Abstract

Anhedonia, a cardinal symptom of depression defined as difficulty experiencing pleasure, is also a possible endophenotype and prognostic factor for the development of depression. The onset of depression typically occurs during adolescence, a period in which social status and affiliation are especially salient. The medial prefrontal cortex (mPFC), a region implicated in reward, self-relevant processing, and social cognition, exhibits altered function in adults with anhedonia, but its association with adolescent anhedonia has yet to be investigated. We examined neural response to social reward in 27 late adolescents, 18–21 years old, who varied in social anhedonia. Participants reported their social anhedonia, completed ratings of photos of unfamiliar peers, and underwent a functional magnetic resonance imaging task involving feedback about being liked. Adolescents with higher social anhedonia exhibited greater mPFC activation in response to mutual liking (i.e., being liked by someone they also liked) relative to received liking (i.e., being liked by someone whom they did not like). This association held after controlling for severity of current depressive symptoms, although depressive severity was also associated with greater mPFC response. Adolescents with higher levels of social anhedonia also had stronger positive connectivity between the nucleus accumbens and the mPFC during mutual versus received liking. These results, the first on the pathophysiology of adolescent anhedonia, support altered neural reward-circuit response to social reward in young people with social anhedonia.

Keywords

Anhedonia; Reward; Social Cognition; Adolescence; Medial Prefrontal Cortex; Depression

1. Introduction

Anhedonia, or difficulty experiencing pleasure in anticipation or response to rewarding stimuli, is a cardinal feature of depression. Across the lifespan, depression is a leading cause of disability and suffering (World Health Organization, 2011). In addition to characterizing

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depression, anhedonia is associated with the onset, course, and outcome of the disease. Low levels of anhedonia in people with depression are protective, presaging better outcomes (Joiner et al., 2002) and a lower chance of recurrence (Kasch et al., 2002). The clinical relevance of anhedonia is particularly important in young people, as anhedonia predicts the onset of clinical-level depression in children and adolescents (Pine et al., 1999; Wilcox & Anthony, 2004) and resistance to standard depression treatment in adolescents (McMakin et al., 2012). Despite anhedonia's associations with the development of depression, a disorder that most commonly begins during adolescence (Lewinsohn et al., 1994), relatively little work has been done to examine the neural correlates of anhedonia in adolescence.

Anhedonia is relevant to appetitive and consummatory aspects of reward function, which reflect the motivation to pursue rewarding experiences and the enjoyment of rewarding experiences once obtained, respectively. Frontostriatal circuits, including dopamine-targeted regions such as the ventral striatum (VS) and medial prefrontal cortex (mPFC), play critical roles in reward function. Specifically, the striatum contributes to the motivation to approach rewarding stimuli and the enjoyment of those stimuli, and a subregion of the mPFC (i.e., Brodmann Areas 24, 32, and medial 10) contributes to the regulation of reward function, partly through its input to the striatum (Haber & Knutson, 2010). Broadly, meta-analytic evidence indicates that depression involves low striatal response to monetary reward for youth and adults (Zhang et al., 2013). More specifically, Wacker et al. (2009) found that self-reported anhedonia—but not other symptoms of depression—were associated with nucleus accumbens activation to reward receipt during a monetary incentive delay task. In that study, anhedonia was negatively correlated with self-reported positive affect, indicating that affective aspects of anhedonia are related to neural response to reward.

Consistent with anhedonia's subjective, behavioral, and neural aspects, adolescents with depression experience lower subjective positive affect (Lonigan et al., 2003; Silk et al., 2011), express shorter-duration, lower-intensity positive affect (Sheeber et al., 2009), and exhibit low striatal response to reward (see Forbes & Dahl, 2012). Specific associations between anhedonia and neural response to reward have yet to be reported in adolescents, but the literature on clinical-developmental neuroscience suggest that adolescence is an important developmental period for investigating anhedonia. Reward-related behavior and affect change markedly during adolescence, with increased risky, reward-seeking activities (see Somerville et al., 2010), more sensation-seeking (Steinberg et al., 2008), and stronger experience of rewards (Ernst et al., 2005; Steinberg et al., 2008). Strikingly, these changes occur in tandem with apparent decreases in reward responding, including low levels of subjective positive affect (e.g., Larson et al., 2002), and increasing levels of depressive symptoms (Sawyer et al., 2009). Developmental neuroimaging studies indicate that adolescents show altered response to reward in the striatum (Bjork et al., 2004; Ernst et al., 2005; Forbes et al., 2010; Galván et al., 2006) and mPFC (Bjork et al., 2004; Forbes et al., 2010).

Response in the mPFC may be particularly relevant to adolescent anhedonia. In addition to its role in reward processing as the destination of the mesocortical dopamine pathway, the mPFC is a key region in the brain's default-mode network and is implicated in affect regulation and in processing social and self-relevant stimuli (Amodio & Frith, 2006; Denny

et al., 2012). In responding to rewarding events, mPFC response could therefore indicate how relevant the reward is to one's preferences and whether the reward enhances one's status among others. Depression is associated with greater mPFC response to reward, which could reflect processes such as difficulty shifting out of a negative, self-focused pattern of thought or over-regulation of more basic, striatal response to reward (Forbes & Dahl, 2012). Notably, anhedonia itself is associated with greater mPFC response to positive autobiographical memories but less mPFC response to negative stimuli (Keedwell et al., 2005b). This pattern is similar to that observed in adults with depression but the opposite of that exhibited by healthy adults (Keedwell et al., 2005a). This suggests that neural function underlying anhedonia, especially in the context of depression, is disrupted in response to what are generally highly valued, self-defining experiences. Furthermore, this disruption in the mPFC could reflect a pattern of responding to such typically pleasant, poignant stimuli as somehow aversive.

In addition to specific regional responding, anhedonia is postulated to involve altered connectivity between the mPFC and VS, such that the mPFC might serve to dampen VS responses to reward (Forbes & Dahl, 2012). The disruption of functional connectivity between the mPFC and VS during response to monetary reward in adolescents with a history of depression (Morgan et al., under review) suggests that such functional connectivity—likely via altered input to the VS from the ventral tegmental area—could be a mechanism for the development of anhedonia. Neural response to reward and functional connectivity between regions in rewarding contexts answer different questions: the first, about response in specific regions in isolation, and the second, about coordination between regions during specific contexts. Both of these can address function in reward circuitry, but they provide different information. Given that previous conceptual models have postulated that both neural response and frontostriatal connectivity are disrupted in anhedonia and in those who develop depression, investigations with anhedonia in adolescents are crucial to critically test developmental hypotheses.

Although functional connectivity techniques such as psychophysiological interaction (PPI) have been traditionally used to examine how regions coordinate in response to task context, there is a burgeoning mental health literature in which investigations of brain circuitry in psychopathology include examining whether psychopathology is related to functional connectivity within the circuitry of interest. For example, studies of affective disorders have reported differences between subgroups of patients or between patients and healthy comparison participants in functional connectivity between the amygdala and orbitofrontal or prefrontal cortex during the processing of affective faces (e.g., Almeida et al., 2009; Almeida et al., 2011; Kong et al., 2013; Versace et al., 2010; Wang et al., 2012). Similarly, in schizophrenia, another disorder that includes the symptom of anhedonia, group differences in functional connectivity have been reported during experiences such as working memory and social processing (e.g., Eack et al., 2013; Mukherjee et al., 2013; Straube et al., 2013). Aside from categorical group differences, studies of mental health have also employed functional connectivity to examine function in neural circuitry that varies with a dimensional characteristic, such as neuroticism or symptom severity (Cremers et al., 2010; Davey et al., 2012; Doucet et al., 2013; Servaas et al., 2013; Yue et al., 2013). Several studies have now used both approaches, describing functional connectivity as a correlate of

both between-group differences and continuous, within-sample variability (e.g., Davey et al., 2012). Most relevant to our questions in the current study, a study of adults recently reported that trait anhedonia is associated with altered response *and* altered functional connectivity in contexts involving pleasant musical stimuli (Keller et al., 2013).

Research with adolescents introduces important considerations. One is the definition of adolescence itself, which has been debated in the fields of psychology, anthropology, and pediatrics, among others. Adolescence is defined as the period between the end of puberty and the attainment of adult-level status and competence. Specifying an age range for this developmental period requires consideration of a variety of factors (e.g., psychological and biological processes), as well as consideration of the ongoing developmental tasks. For research purposes, it is particularly important to consider the ongoing developmental tasks that are relevant to a research question when defining an adolescent population. Given that the developmental tasks of adolescence are postulated to include impulse control, accurate assessment of risk vs. reward, and affect regulation during challenges (Hazen et al., 2008) and that the neural circuitry underlying these cognitive and behavioral functions continues development throughout the teen years and into the 20s (Lenroot & Giedd, 2006), we defined adolescence as occurring through the early 20s. That is, our deliberate focus on a population in which the processes of interest (i.e., function in reward circuitry, social processing) have not yet reached adult levels led us to consider this a study of *adolescent* development. Other approaches might classify participants over age 18 as adults based on legal or cultural changes in status at that age (e.g., attaining the right to vote or perform military service). It is also notable that many psychology studies conducted with undergraduate samples describe their participants as adults rather than late adolescents, and this practice has been identified as a key limitation for interpreting findings on constructs that involve self and social cognition (Sears, 1987). Other terms have also been used for the late adolescent developmental period, such as “emerging adulthood” (Conger & Little, 2010). Based upon our focus on neural reward circuitry and the emergence of a symptom relevant to several forms of psychopathology that have onset during the later stages of brain development, we studied a population from age 18–21 years, termed hereafter as *late adolescents*.

In addition, investigating function in reward circuitry during adolescence requires sufficient context. First, reward circuitry is undergoing substantial development during adolescence (Spear, 2000). The function of the striatum and mPFC in response to reward changes with puberty (Forbes, 2009) and with adolescent development (Bjork et al., 2004; Ernst et al., 2005; Galván et al., 2007). Thus, these brain regions are especially malleable and, consequently, potentially vulnerable to developing dysfunction during this period (Davey et al., 2008). Second, the value and salience of social contexts increases as adolescents spend more time with peers, experience more intense emotions in peer contexts, and pursue newly valued abstract social rewards (e.g., initiating a romantic relationship; Furman & Simon, 1999; Larson et al., 1999; Steinberg, 2008). Hence, a class of rewards that is perhaps most important to anhedonia, to the function of frontostriatal reward circuitry, and to adolescent development is social reward. In particular, adolescents’ reward circuitry and decision-making behavior are sensitive to peer context (Albert et al., 2013; Chein et al., 2011), and

peer experiences are postulated to influence the development of reward circuitry (Albert et al., 2013). Thus, peer social reward is likely to be salient during this developmental period.

The model presented by Davey et al. (2008) may be further elaborated to emphasize the role of being accepted by peers when peers' opinions are highly valued, as opposed to being minimally valued or ambiguous. Accordingly, Davey and colleagues (2010) developed a social reward paradigm in which participants view images of unfamiliar peers and rate how much they thought they would like the peer. Participants are led to believe that their own images will also be evaluated by these unfamiliar peers. In a separate fMRI assessment session, participants receive feedback about whether these unfamiliar peers liked them (i.e., social reward) or whether unfamiliar peers were unable to provide ratings (i.e., ambiguous outcome). A key feature of this paradigm is the participants' own ratings of the unfamiliar peers, which allows the neural response to both acceptance in general and to mutual acceptance to be investigated. Indeed, Davey et al. (2010) found that being liked activates primary reward regions, such as the nucleus accumbens and vmPFC, for 15- to 24-year-old adolescents and young adults. Furthermore, mutual acceptance, or being liked by highly regarded peers, activated the mPFC more strongly in that study than being liked by less-liked peers. Response to social reward could be particularly relevant to *social anhedonia*, or difficulty experiencing pleasure from social contact (Blanchard et al., 2000). Whereas previous studies have focused on anhedonia as broadly related to *hedonic capacity*—a construct that can include physical, affective, and social components—the importance of social reward to adolescents and the disruption of social functioning in depression together point to the importance of understanding neural response to social reward in relation to social anhedonia.

Using an fMRI paradigm involving feedback about peer social acceptance—specifically, presenting whether unfamiliar peers the participant had rated for their likeability also rated the participant as likeable—we examined the association of social anhedonia with adolescents' mPFC response and functional connectivity during social reward contexts. Specifically, we examined functional connectivity between the ventral striatum and the mPFC, two key regions in reward circuitry that are also relevant to processing social reward and likely to respond in tandem to social reward. We hypothesized that late adolescents' social anhedonia would be associated with higher mPFC response during the social reward of mutual acceptance, as opposed to acceptance from peers whom participants liked less. In addition, to confirm that mutual liking—rather than all positive feedback—was particularly associated with altered mPFC response, we examined whether mPFC response to social reward in general was associated with social anhedonia.

2. Method

2.1 Participants

Participants were 27 late adolescents, aged 18–21 ($M=20.4$, $SD=.80$; 51.9% female; 78% European American, 7% African American, 4% Asian and 11% other). An additional 7 participants took part in the study but were excluded from analyses (and, therefore, did not contribute data to the current paper) for the following reasons: not completing the questionnaires ($n=1$), not completing the fMRI task ($n=5$), or excessive movement during

fMRI data acquisition ($n=1$). These 7 participants had higher severity of both anhedonia and depression than the 27 participants in the final data set ($F = 5.81, p = .02$ and $F = 5.65, p = .02$, respectively). Sample characteristics and results described below all refer to the sample of 27 participants.

The sample was recruited in the Pittsburgh metropolitan area by flyers, online ads, and from a previous large, psychometric study of depression and temperament in young adults ($n = 6$) (Olino et al., 2013). To obtain variability in anhedonia, recruitment materials targeted both healthy adolescents and adolescents with depression. Participants were allowed to have current Major Depressive Disorder ($n=9$) and anxiety disorders other than Obsessive-Compulsive Disorder (Generalized Anxiety Disorder (GAD) $n=2$, Social Phobia $n=1$). Participants were excluded if they met criteria for Bipolar Disorder or lifetime Substance Dependence because of those disorders' association with altered reward function (Koob & Le Moal, 2008; Nusslock et al., 2012). Diagnoses were made by interview with the KSADS-PL (Kaufman et al., 2000). All participants were free of lifetime psychotropic medications and free of illicit drugs on the day of the scan. Written informed consent was obtained after a complete description of the study and study procedures according to the guidelines of the University of Pittsburgh Institutional Review Board.

2.2 Measures

2.2.1 Anhedonia—Participants completed the Revised Chapman Social Anhedonia Scale (RSAS; Eckblad et al., 1983), a widely used, 40-item true/false questionnaire that focuses on anhedonia experienced in social contexts (e.g., “having close friends is not as important as many people say”). We used the total score of the RSAS measure ($M=7.17, SD=7.22$, Range 0–26), for which internal consistency was high in this sample ($\alpha=.91$). Anhedonia was sufficiently normally distributed, as indicated by its acceptable level of skewness (1.49, $SE=.45, p>.001$).

2.2.2 Depression—The Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) is a 20-item questionnaire that assesses depressive symptom severity, and contains 4 items related to anhedonia (e.g., “I felt I was just as good as other people”). We used the total score of the CES-D ($M=12.63, SD=14.52$, Range 0–45), for which internal consistency was high in this sample ($\alpha=.97$). Depression severity was sufficiently normally distributed, as indicated by its acceptable level of skewness (.94, $SE=.45, p>.001$).

2.2.3 Social reward task—We adapted the likeability task developed by Davey and colleagues (Davey et al., 2010). Participants were asked to rate photos of other late adolescents (40 photos; 50% female) based on how much they thought that they would like the people in the photos. They were told that they would, in turn, be rated by other participants. Approximately 3 weeks before the scan, participants had their photo taken and rated the photo stimuli. Ratings were made on a 1–9 scale, with 1 being “not at all” liked and 9 being “very much” liked. Photo stimuli were drawn from a database of face stimuli (Martinez & Benavente, 1998; <http://www.ece.osu.edu/~aleix/ARdatabase.html>). As ratings of likeability may have been influenced by sexual attraction, participants were asked about their sexual orientation. One participant reported being “100% homosexual,” and the

remaining participants reported being either “mostly heterosexual” or “100% heterosexual.” As a result, we did not include sexual identity in our analyses (Corliss et al., 2009).

Ratings of the photo stimuli were classified into 3 sets of stimuli for each participant: *most-liked* stimuli (participant’s 8 highest-rated faces, 4 of each sex), *least-liked* stimuli (participant’s 8 lowest-rated faces, 4 of each sex), and *neutral* stimuli (16 faces per participant, based on rank order 7–14 of each sex). These classifications were used to create the stimulus sets for the 3 types of blocks in the task: *mutual liking* blocks contained favorable feedback from the 8 stimuli rated by the participant as most highly liked, *received liking* blocks contained favorable feedback from the 8 stimuli rated by the participant as least liked, and *ambiguous* blocks contained no feedback from the neutral stimuli. Stimuli ranked 5, 6, 15, and 16 for each sex (i.e., 8 total stimulus faces) were discarded to increase the differential value between mutual liking, received liking, and ambiguous stimuli. For both mutual and received-liking blocks, the participant was told that the individuals in the photos had selected the participant as a highly liked peer. As a comparison, the participant was told that individuals in the ambiguous block did not have a chance to rate them. We term this type of feedback *ambiguous* because participants could interpret the no-feedback information in several possible ways.

The fMRI portion of the task was administered in a block design. Stimuli for positive-feedback blocks were displayed on a green background, and stimuli for ambiguous blocks were displayed on a white background (Fig 1). The task contained positive-feedback blocks and ambiguous-feedback blocks. Each of the 32 stimulus photographs included in the final fMRI paradigm (16 positive-feedback faces [8 high-rated and 8 low-rated] and 16 ambiguous-feedback faces) were presented 3 times over 8 blocks. Each block consisted of 12 stimuli for a total of 84s, for a total task time of 12 minutes and 8 seconds. Of the 8 blocks, 2 were primarily mutual liking, 2 were primarily received liking, and 4 were primarily ambiguous feedback. Each block also contained 2 stimuli of the other type (e.g., an ambiguous block contained 2 positive-feedback faces). A proportion (16.67%) of non-block-category stimuli was included within each block in order to reduce the predictability and habituation that can accompany the repeated viewing of stimuli from a single stimulus category within a block. Each stimulus photograph was presented for 3s, with a jittered inter-trial fixation screen between stimuli (1, 3, 5, or 7 s). The inter-block interval (IBI) was 8 seconds. The instructions for each block were presented with either a green (positive feedback) or white (ambiguous feedback) background to signal the block type.

During the scan, the participants were instructed to pay attention to the faces in the photos and try to remember who liked them and who had not rated them. Participants were instructed to press any button when they saw a face, to confirm that they were awake and attending to the task. After the scan, participants completed ratings in which they recalled how good they felt when they saw each of the stimulus photos; the order of stimuli shown (faces from ambiguous blocks vs. faces from positive-feedback blocks) was counterbalanced across participants. At the end of the scan session, participants were debriefed on the deception in the task and informed that their photo had not been rated by others.

2.3 fMRI acquisition and preprocessing

Each participant was scanned using a Siemens 3T Trio scanner. BOLD functional images were acquired with a gradient echo planar imaging (EPI) sequence and covered 39 axial slices, 3.1 mm thick, beginning at the cerebral vertex and encompassing the entire cerebrum and the majority of the cerebellum (TR/TE=2000/25ms, FOV=20cm, matrix=64×64, flip angle=90°). All scanning parameters were selected to optimize the quality of the BOLD signal while maintaining a sufficient number of slices to acquire whole-brain data. Before the collection of fMRI data for each participant, we acquired a reference EPI scan that we visually inspected for artifacts (e.g., ghosting) and for good signal across the entire volume of acquisition. The fMRI data from all included participants were cleared of such problems.

Preprocessing and image analysis were completed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). For every scan, images for each participant were segmented and then realigned to correct for head motion. Data sets were then selected for quality based on our standard small-motion correction (<3mm). Realigned images were spatially normalized into standard stereotactic space (Montreal Neurological Institute template) using a 12-parameter affine model. Normalized images were smoothed with a 6mm full-width at half-maximum Gaussian filter. Voxel-wise signal intensities were ratio normalized to the whole-brain global mean. Voxels were resampled during preprocessing to be 2mm³.

2.4 Data Analytic Strategy

We conducted two sets of analyses: one testing mPFC response to social reward and the other testing functional connectivity between the nucleus accumbens and the mPFC. The first set of analyses addressed whether mPFC response to reward varied with anhedonia. The second set of analyses addressed whether anhedonia was associated with the coordination of two important regions in reward circuitry during the processing of social reward. For both sets of analyses, we used widely applied, conventional strategies as implemented through SPM8: general linear models for mPFC response, and psychophysiological interaction for functional connectivity.

In preparation for both sets of analyses, for each participant and scan, first-level predetermined condition effects (i.e., main effects of task) at each voxel were calculated using a *t*-statistic, producing a statistical image for the 2 contrasts of interest: (a) *mutual liking* > *received liking* and (b) *all positive feedback* (i.e., mutual liking + received liking) > *ambiguous feedback*. We were primarily interested in neural response to mutual liking > received liking, as this contrast reflects being reciprocally liked by an unfamiliar peer vs. being liked by an unfamiliar peer whom you had not rated as highly likeable. This contrast is proposed to capture both receiving social reward and weighing one's own preferences in social stimuli. We included the *all positive feedback* > *ambiguous feedback* contrast to examine whether social anhedonia was also associated with disrupted response to social reward in general, regardless of the participant's own preferences.

2.4.1 Analyses of mPFC Response to social reward—To test the association of social anhedonia with mPFC response to social reward, preprocessed data sets were analyzed using second-level random effect models that account for both scan-to-scan and

participant-to-participant variability to determine task-specific regional responses. Individual contrast images were then included in the group-level (i.e., second-level) mPFC region of interest (ROI) analysis to test our hypotheses. The ROI was constructed using the WFU PickAtlas Tool (v2.4) and defined as a 25 mm-radius sphere including medial Brodmann Area (BA) 10 and BA32, which are part of the anterior rostral mPFC region implicated in social cognition and self-systems (Forbes et al., 2010; Forbes et al., 2012). Regression analyses were used to test associations between task-related mPFC reactivity and social anhedonia using the RSAS total score as a regressor in SPM. We also conducted exploratory, whole-brain analyses for these same models to confirm that the mPFC was one of the main regions engaged. To test whether social anhedonia was related to mPFC response on its own or because of its relation to depression, we then conducted regression analyses with RSAS but included CES-D score as a covariate to adjust for the influence of depressive severity.

2.4.2. Functional connectivity analyses—To test whether mPFC response detected in our first set of analyses might reflect the disruption of coordination of reward-circuit regions in relation to social anhedonia, we then conducted functional connectivity analysis. We conducted a single, fairly popular type of functional connectivity analysis: task-based PPI. The purpose of PPI analyses was to examine task-specific changes in the association between mPFC and ventral striatum connectivity in relation to level of social anhedonia. Functional connectivity allows the testing of functional interaction of separate regions within neural circuitry (Friston, 1994, 2011; O'Reilly et al., 2012). In the case of PPI, this functional interaction is related to a specific context (see O'Reilly et al., 2012 for an excellent tutorial on PPI). In PPI, a region is selected as a seed – in the current study, the bilateral nucleus accumbens – and the strength of its association to other regions is examined during a psychological context – in the current study, the receipt of mutual vs. received liking. Specifically, the time course of the seed region's response to the contrast of interest is modeled, entered into a GLM regression, and then used to create an interaction term between task-related time course and seed-region time course. This interaction is then used to identify voxels whose activity is associated with the task-seed interaction. Because of our focus on the potential role of the mPFC in social reward and anhedonia, we masked our PPI analyses using the same mPFC ROI described above.

Since we were interested not only in whether mPFC and VS had associated responses to social reward but whether this association was related to individual differences in social anhedonia, we conducted second-level regression analyses with social anhedonia score predicting PPI. We masked these results for mPFC response and also conducted exploratory whole-brain analyses to confirm that mPFC was among the areas whose functional connectivity with VS varied with level of social anhedonia. This approach has now been used in many studies to investigate whether psychopathology is related to functional coordination among regions in affective circuitry (e.g., Keller et al., 2013). In fact, given that neural response and PPI-based functional connectivity address different research questions—that is, task responding in specific brain regions vs. functional coordination between regions during a task context – it is now often the case that studies include both techniques in a single paper (e.g., Eack et al., 2013).

PPI analyses included 26 participants because one participant was removed from analyses due to incorrect file format. Given our hypotheses, the bilateral nucleus accumbens was selected as our seed region of interest and we evaluated correlations of activation between the nucleus accumbens and the mPFC. We examined whether social anhedonia was associated with fronto-striatal connectivity by regressing PPI on social anhedonia. We also conducted exploratory whole-brain analyses for our PPI hypothesis tests, to confirm that the mPFC was one of the main regions interacting with the accumbens during social reward.

For analyses testing our hypotheses, simulations in the AlphaSim program in AFNI were used to estimate the minimum number of contiguous voxels in each cluster required to avoid Type I error (corrected cluster level threshold of $p < .05$) for the ROI masks. These simulations resulted in the following minimum extent for significant clusters: 136 voxels for mPFC and 580 voxels for whole-brain findings.

3. Results

3.1 Behavior

As in previous studies using this task, female faces were rated higher than male faces ($t=3.01$, $df=2, 25$, $p < 0.01$). Reaction times did not differ significantly between male and female faces. There was no correlation between post-scan ratings and mean reaction time for all stimuli ($r = -.02$, $p = .92$). Participant sex was unrelated to reaction time ($F=0.02$, $p=.91$), stimulus ratings ($F=.737$, $p=.34$), and post-scan ratings ($F=2.60$, $p=.12$). There was no significant difference between participants' post-scan ratings of their response to positive-feedback and ambiguous-feedback stimuli. Age was associated with higher RSAS ($r=.45$, $p<.02$) and CES-D scores ($r=.52$, $p<.01$). Sex was unrelated to RSAS ($F=1.56$, $p=0.22$) or CES-D scores ($F=0.20$, $p=0.51$).

3.2 Neural response

3.2.1 Effects of task—Analyses with a within-sample t -test indicated that, as expected, participants exhibited mPFC response to mutual liking > received liking. ROI analysis yielded 2 clusters (dorsal anterior cingulate, 132 voxels, [peak voxel (Talairach): $-14, 35, 31$], $t=2.47$, $p<.05$; pregenual anterior cingulate; 60 voxels, $[-14, 40, 20]$, $t=2.35$, $p<.05$), both of which also emerged in whole-brain analyses for the effects of this contrast (Table 1). Whole-brain analyses for mutual liking > received liking also yielded response in several other mPFC clusters, as well as in reward processing regions such as the caudate, social processing areas such as the precuneus, and affective regions such as the insula. As expected, participants also exhibited mPFC response to all positive > ambiguous feedback. ROI analyses yielded 4 clusters (perigenual anterior cingulate, 206 voxels, $[-8, 41, 10]$, $t=2.72$, $p_{\text{corrected}} < .05$; rostral mPFC/dorsal mPFC/perigenual anterior cingulate, 161 voxels, $[6, 52, 15]$, $t=2.37$, $p_{\text{corrected}} < .05$). Whole brain analyses for all positive > ambiguous feedback also yielded response in several mPFC clusters, as well as in social/self-processing regions (e.g., temporoparietal junction, precuneus, posterior cingulate), reward regions (e.g., caudate, putamen, globus pallidus), and affective regions (e.g., insula, ventrolateral PFC). As participants varied in anhedonia and depressive symptoms, however, these findings do not represent the typical adolescent response to this task and thus are not suitable as a mask

for hypothesis tests (see Davey et al., 2010, for a thorough exploration of the effects of this task in a healthy sample).

3.2.2 Social anhedonia and neural response to social reward—Higher social anhedonia was associated with heightened response to mutual liking > received liking in a large cluster in the mPFC (4826 voxels, [1,44,41], $t=4.01$, $p_{\text{corrected}} < .05$; Fig. 2). This cluster included the following subregions of mPFC, as described by Etkin et al. (2011): dorsal mPFC, pregenual anterior cingulate, and rostral mPFC.

Whole-brain analyses yielded a large cluster with a peak in the mPFC (see Table 2 for all whole-brain results), confirming that the mPFC was one of the key brain regions associated with social anhedonia. Whole-brain analyses also indicated that the striatum (ventral and dorsal), precuneus, dorsolateral prefrontal cortex, and insula were among the other regions whose response to mutual liking was associated with level of social anhedonia (see Table 2 for all whole-brain results for hypothesis tests). Social anhedonia was unrelated to mPFC response to all positive > ambiguous feedback.

3.2.3 Specificity of association between social anhedonia and neural response to social reward—To examine whether the association between social anhedonia and response in reward-circuit regions is evident after adjusting for depression, we re-computed regressions of brain function on social anhedonia, including CES-D score as a covariate. The association of social anhedonia remained in two somewhat smaller clusters of activation in the mPFC (peak in BA8, 814 voxels, [15,36,42], $t=3.29$, $p_{\text{corrected}} < .05$; peak in BA9, 908 voxels, [6,46,18], $t=2.97$, $p_{\text{corrected}} < .05$) in response to mutual liking > received liking. These clusters included the following regions: dorsal mPFC, pregenual anterior cingulate, and anterodorsal anterior cingulate.

3.2.4 Depression and neural response to social reward—Higher depression severity was associated with heightened response to mutual liking > received liking in a very large cluster centered in dorsal mPFC (peak in BA9, 2971 voxels, [14,1,44], $t=3.36$, $p_{\text{corrected}} < .05$). This cluster included the following subregions: dorsal mPFC and anterodorsal anterior cingulate. Whole-brain analyses confirmed the association of the mPFC with depression, and they also indicated that function in the dorsolateral prefrontal cortex and precuneus was greater in late adolescents with higher depressive symptoms (Table 2). Depression was unrelated to mPFC response to all positive > ambiguous feedback.

3.2.5 Social anhedonia and frontostriatal connectivity—Higher social anhedonia was associated with greater positive connectivity between the bilateral nucleus accumbens and the mPFC (peak in BA9, 1110 voxels, [-12,41,33], $t=3.44$, $p_{\text{corrected}} < .05$; peak in BA32, 292 voxels, [-12,29,36], $t=3.26$, $p_{\text{corrected}} < .05$) in response to mutual liking > received liking. This large cluster contained the following subregions: dorsal mPFC, pregenual anterior cingulate, rostral mPFC, and anterodorsal anterior cingulate. Whole brain analyses confirmed that the mPFC was a primary region whose function varied positively with that of the nucleus accumbens in late adolescents with higher social anhedonia. The large cluster

containing the mPFC in our whole-brain findings also included the VS, orbitofrontal cortex, temporoparietal junction, and insula (Table 1).

3.2.6 Specificity of association between social anhedonia and frontostriatal connectivity—As with analyses to examine neural response above, we examined the contribution of social anhedonia over and above that of depression severity by re-computing regressions of frontostriatal connectivity on social anhedonia, including CES-D score as a covariate and masking with the results of the original regression. The association of social anhedonia with greater positive connectivity between the bilateral nucleus accumbens and the mPFC remained (peak in BA9, 656 voxels, [6,54,32], $t=3.90$, $p_{\text{corrected}} < .05$; Figure 3) in response to mutual liking > received liking. This large cluster was located in the dorsal subregion of the mPFC.

4. Discussion

In a sample of late adolescents with varying levels of anhedonia, we found that neural response and frontostriatal connectivity to social reward were related to anhedonia and depression. Specifically, late adolescents with higher levels of social anhedonia and depression showed greater mPFC response and stronger positive connectivity between the mPFC and the nucleus accumbens to receiving positive peer social feedback. Notably, anhedonia and depression were associated with altered reward-circuit function to feedback about *mutual liking*, in which late adolescents learned that peers whom they liked also liked them. The mPFC response to social reward was specific to anhedonia, as it remained even when depressive symptoms were covaried. Thus, anhedonia itself, above the effects of depression, was associated with disrupted neural responding to peer social feedback. These findings are among the first to focus on the neural substrates of adolescent anhedonia and to investigate social anhedonia in relation to social reward.

Interestingly, depression and social anhedonia were only associated with neural response to *mutual liking* relative to received (non-mutual) liking, not simply to all positive peer social feedback. Both mutual liking relative to received liking and positive feedback relative to ambiguous feedback elicited response in mPFC and other reward- and social-processing regions in this sample, but only the former was related to social anhedonia. Late adolescents higher in social anhedonia did not respond differently to positive feedback in general, but they showed greater mPFC response and greater positive functional connectivity between the nucleus accumbens and mPFC in response to mutual compared to received feedback about being liked. Because fMRI analyses rely on difference scores (i.e., contrasts of conditions), this pattern could reflect greater mPFC response (or VS-mPFC functional connectivity) to mutual liking, less mPFC response to received liking, or both. Given the putative functions of dorsal mPFC, these results could reflect altered social processing involving judgments of others (Denny et al., 2012) or over-regulation of response to mutual liking (Ochsner et al., 2012; Phillips et al., 2008). Our results for functional connectivity indicate that the mPFC might engage more intensely when the VS responds in pleasant social contexts, potentially dampening the VS response and resulting in a positive correlation of function between these two regions during mutual liking. Alternatively, the mPFC could be signaling to elicit greater or more sustained response from the VS, which is

not responding with typical magnitude or duration. Results for dorsal mPFC response could also indicate that late adolescents with anhedonia might respond to mutual liking as if it were aversive or, alternatively, to received liking as if it were less salient. The former possibility is consistent with previous findings on greater mPFC response to pleasant self-relevant stimuli in people with depression or anhedonia, which is the opposite pattern found in healthy adults, who exhibit greater mPFC response to unpleasant stimuli (Keedwell et al., 2005a, 2005b).

Given the location of our findings in the mPFC in relation to meta-analytic findings about self-relevant judgments (Denny et al., 2012), our results suggest that late adolescents with higher levels of anhedonia could possibly experience mutual liking as reflecting negatively on their identity or self, or, alternatively, could experience received liking as less meaningful for their identity or self. These late adolescents might thus be less motivated by mutual liking or less sensitive to its value. A possible cognitive consequence for such a response in reward circuitry could be that late adolescents with anhedonia second-guess or discount their own preferences. Then, instead of being more drawn to people they like, they could defer to others' preferences, potentially allowing others to make decisions about social behavior for them. Thus, they might have weaker social preferences or might be less guided by their social preferences, so that they may not distinguish between liking and not liking others. Another possibility is that late adolescents with high levels of anhedonia respond to mutual liking with a kind of dread, in which they expect the other person to end up disliking or rejecting them, thereby dealing a blow to their identity and social status. These speculative interpretations are based upon the putative functions of the mPFC and the content of our task condition, and it will be compelling for future studies to examine the nuances of anhedonia's influence on late adolescents' social experience and behavior.

The pattern of greater mPFC response we found could be related specifically to social anhedonia or to the context of social reward. Notably, Wacker et al. (2009), despite hypothesizing that mPFC function would be related to anhedonia, did not find such an association in adults. That study used a monetary reward fMRI task, however, and defined anhedonia more generally. The recent study by Keller et al. (2013) reported findings in a set of affect-related regions that did not include mPFC, but they employed musical stimuli and focused on psychiatrically healthy adults. However, as with that study, we also found that anhedonia was associated with altered functional connectivity of VS and other reward-related regions. In the current study, although we focused specifically on the mPFC, we also found that VS response—occurring as part of two large clusters, one of which also contained the mPFC and OFC, and one of which also contained dorsal striatum and thalamus—was related to higher social anhedonia. The positive correlation between response in this large cluster and social anhedonia could reflect the role of reward-circuit regions in processing both rewarding and potentially aversive stimuli. Whole-brain results also indicated that late adolescents' social anhedonia was associated with greater response or greater functional connectivity with the nucleus accumbens in regions implicated in social processing (i.e., the precuneus and temporoparietal junction; Mar, 2011; Van Overwalle et al., 2009), affective processing (i.e., insula, orbitofrontal cortex; Phan et al., 2002; Phillips et al., 2008), and effortful affect regulation (dorsolateral prefrontal cortex; Phillips et al., 2008). In addition, the dorsolateral prefrontal cortex and precuneus exhibited greater response in those with

higher depression. Together, these findings support the role of the mPFC and suggest that other regions in reward and affective circuitry also contribute to social anhedonia.

Similar to our results with social anhedonia, we found that depression severity was related to greater mPFC response to mutual liking relative to received liking. This is consistent with our previous findings on the association between adolescent depression and neural response to monetary reward (Forbes et al., 2009; Morgan et al., 2013), as well as with some other researchers' findings on mPFC function in adult anhedonia and depression (Keedwell et al., 2005a, 2005b; Knutson et al., 2008). However, unlike other previous findings in adolescent depression (Forbes et al., 2009; Forbes et al., 2006), our whole-brain findings did not indicate that depressive severity was related to response in the VS. One possibility related to our choice of fMRI task is that the mPFC is especially sensitive to social rewards, and depression particularly disrupts responding to a social reward in that region rather than in the VS. Also, unlike a previous study using this social reward task with late adolescents (Davey et al., 2011), we did not find that depression was related to amygdala response to social reward. That study took a group-differences approach, however, comparing a group of clinically depressed young people with a group of healthy young people. In addition, that study used an event-related version of the social reward task.

Our study is the first to examine reward-circuit response to social reward in relation to adolescent anhedonia. In contrast, most extant findings on reward in adolescents with depression or at risk for depression have used monetary or other non-social classes of reward (e.g., Forbes et al., 2009; Gotlib et al., 2010; McCabe et al., 2012; Monk et al., 2008; Olino et al., 2011). Despite the importance of the social context to adolescent depression and to adolescents' reward processing (e.g., Chein et al., 2011), the study of social reward and its association with affective disorders has been minimal in adolescent research. In addition, much of the research on personally relevant stimuli has focused on social loss or exclusion rather than social reward. Social stimuli are especially salient if they are self-relevant, and previous studies either have used stimuli such as images, videos, or audio clips of loved ones (e.g., Hooley et al., 2005; Leibenluft et al., 2004; Whittle et al., 2012) or have employed paradigms that mimic situations participants encounter in the real world (e.g., playing a computer game with peers, as in Eisenberger et al., 2003). Thus, it is valuable to note that our mPFC results echo findings for adolescents' response to social evaluation paradigms, such as those reported with the social-exclusion cyberball task (Bolling et al., 2011) and with a simulated chat room task (Silk et al., 2012). It is not surprising that mPFC function is sensitive to social reward in various forms, such as being liked, being included, and being selected for interaction.

Furthermore, this is the first study to link late adolescents' social anhedonia to functional connectivity in reward circuitry, with greater coordination between the nucleus accumbens and mPFC during the experience of mutual relative to received liking. Thus, it appears that the mPFC is not simply responding differently to social reward but is also coordinating its response more closely with the nucleus accumbens in those with higher levels of social anhedonia. Admittedly, the application of functional connectivity to answer questions about whether the coordination among regions in affective or social circuitry varies with psychopathology is a somewhat new approach. Nonetheless, this approach is also becoming

widely applied in clinical neuroscience (e.g., Almeida et al., 2009; Davey et al., 2012; Mukherjee et al., 2013). The current findings thus build on an important emerging literature in the neural bases of affective and schizophrenia-spectrum disorders.

In terms of adolescent brain development, our findings indicate that low subjective response to social reward is associated with disrupted function in reward circuitry. This association might be especially pronounced during late adolescence, given the dramatic changes in social context, the pursuit of high-intensity rewarding experiences, and the enhanced intensity of social goals during this developmental period (Davey et al., 2008). In addition, disrupted function in reward-relevant regions or in frontostriatal connectivity could be particularly evident in response to acceptance from peers, rather than to feedback involving people of other ages. One question we are now investigating is whether personally relevant peer social reward—for example, video stimuli of a close friend displaying positive affect during a conversation with the adolescent in the scanner—is particularly evocative of differences in neural circuitry that are linked to reward-related problems.

Clinically, the implications of our findings are that disrupted function of neural reward circuitry could play a role in the development of depression. Anhedonia is a strong prognostic factor for the onset and clinical course of depression in adolescents (McMakin et al. 2012; Pine et al., 1999; Spijker et al., 2001; Wilcox & Anthony, 2004) and its association with depression could be mediated by neural response to reward. Social anhedonia, which was the focus of the current study, might be addressed by preventive interventions that target adolescents who experience that symptom. In adolescents who are experiencing high levels of anhedonia in the context of depression, encouraging the pursuit and experience of social rewards in treatments such as behavioral activation therapy (Dimidjian et al., 2011) or savoring (McMakin et al., 2011) could be fruitful. Given that late adolescents with high social anhedonia were less responsive to mutual liking in the current study, adolescents with depression might be taught to be aware of or enhance their own responses to others. For example, mindfulness exercises could strengthen their experience of their social preferences and possibly facilitate a more intense response to feedback from people who are important to them.

While the present study represents an important step forward, it has limitations worth noting, including its relatively small sample, cross-sectional design, and focus on late adolescents. To fully address the range of variability in a continuous characteristic such as anhedonia, it will be valuable for future studies to include larger samples. We acknowledge that our data might reflect a restricted range of anhedonia severity, as the participants who could not be included in fMRI analyses tended to have higher severity of anhedonia than those who were included. Thus, it will be important to include broad range of anhedonia in future studies. If anything, this difference might have led to Type II error, as restricted range attenuates statistical power to detect associations. In addition, our strict adjustment for multiple comparisons resulted in very large clusters of BOLD response that encompassed many regions, a challenge that commonly occurs when using extent-based thresholds. This approach can also increase the risk of Type II error, since it can limit the ability to detect response in small regions. As a result of our cross-sectional design, we are unable to address anhedonia as a precursor to depression or the role of neural reward circuitry in the

development of depression in late adolescents who are high in anhedonia. We describe our participants as *late adolescents*, which is consistent with evidence of continued development in reward- and affect-related neural circuitry into the early 20s (Lenroot & Giedd, 2006). We chose this developmental focus because of the importance of social reward and the ability to pursue that reward more freely during this period. While people in this developmental period may be assuming some adult-like status and roles in their lives, leading some researchers to describe this period as *emerging adulthood* (e.g., Conger & Little, 2010), they are likely to have quite a bit in common with younger adolescents in terms of their reward-related behavior and anhedonia. In addition, because our participants are past the typical age of onset of depression (Kessler et al., 2001; Lewinsohn et al., 1994), and many have already developed depression, our focus on neural response to reward in this age group could capture some effects of depression.

It is critical to examine the role of anhedonia across the range of development, and thus the inclusion of children, younger adolescents, and adults in future studies will be valuable for addressing potential developmental influence in the association between anhedonia and neural response to social reward. In addition, we focused on social reward and social anhedonia, which is only one type of anhedonia. It will be important to investigate other types of anhedonia in relation to neural response to various classes of reward stimuli. Furthermore, the instrument we used, the RSAS, assesses trait-like rather than state-like anhedonia, and it will be worthwhile for future work to consider episode-relevant anhedonia as a symptom. Finally, the examination of other types of psychopathology (e.g., substance use, psychosis, eating disorders) in future studies will also allow the examination of the role of anhedonia across other types of reward-related behaviors.

5. Conclusion

The current study is the first to focus on the neural correlates of adolescent anhedonia. This characteristic, which is a cardinal symptom in depression, a prognostic factor for the development of depression, and a potential endophenotype of depression, is an important dimension of psychopathology that reflects alterations in positive valence systems. In addition, this study is one of few to examine neural response to social reward, a class of reward that is especially salient to adolescents and may have meaning for the development of depression (Forbes, 2009). Our findings of high responding in neural regions implicated in the regulation of reward responding, in combination with our finding of heightened positive connectivity between the VS and mPFC, provide preliminary evidence on the pathophysiology of adolescent anhedonia. These findings could thus contribute to our understanding of the role of anhedonia in the developmental psychopathology of reward-related problems.

References

- Albert D, Chein J, Steinberg L. The teenage brain: Peer influences on adolescent decision making. *Current Directions in Psychological Science*. 2013; 22(2):114–120.
- Almeida JR, Kronhaus DM, Sibille EL, Langenecker SA, Versace A, Labarbara EJ, et al. Abnormal left-sided orbitomedial prefrontal cortical-amygdala connectivity during happy and fear face

processing: a potential neural mechanism of female MDD. *Front Psychiatry*. 2011; 2:69. [PubMed: 22163223]

- Almeida JR, Versace A, Mechelli A, Hassel S, Quevedo K, Kupfer DJ, et al. Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. *Biological Psychiatry*. 2009; 66(5):451–459. [PubMed: 19450794]
- Amodio DM, Frith CD. Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews Neuroscience*. 2006; 7(4):268–277.
- Bjork JM, Knutson B, Fong GW, Caggiano DM, Bennett SM, Hommer DW. Incentive-elicited brain activation in adolescents: Similarities and differences from young adults. *Journal of Neuroscience*. 2004; 24(8):1793–1802. [PubMed: 14985419]
- Blanchard JJ, Gangestad SW, Brown SA, Horan WP. Hedonic capacity and schizotypy revisited: a taxometric analysis of social anhedonia. *Journal of Abnormal Psychology*. 2000; 109(1):87–95. [PubMed: 10740939]
- Bolling DZ, Pitskel NB, Deen B, Crowley MJ, Mayes LC, Pelphrey KA. Development of neural systems for processing social exclusion from childhood to adolescence. *Developmental Science*. 2011; 14(6):1431–1444. [PubMed: 22010901]
- Chein J, Albert D, O'Brien L, Uckert K, Steinberg L. Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. *Developmental Science*. 2011; 14(2):F1–10. [PubMed: 21499511]
- Conger KJ, Little WM. Sibling Relationships during the transition to adulthood. *Child Development Perspectives*. 2010; 4(2):87–94. [PubMed: 20700389]
- Corliss HL, Austin SB, Roberts AL, Molnar BE. Sexual risk in “mostly heterosexual” young women: influence of social support and caregiver mental health. *Journal of Women's Health*. 2009; 18(12):2005–2010.
- Cremers HR, Demenescu LR, Aleman A, Renken R, van Tol MJ, van der Wee NJ, et al. Neuroticism modulates amygdala-prefrontal connectivity in response to negative emotional facial expressions. *Neuroimage*. 2010; 49(1):963–970. [PubMed: 19683585]
- Davey CG, Allen NB, Harrison BJ, Dwyer DB, Yücel M. Being liked activates primary reward and midline self-related brain regions. *Human Brain Mapping*. 2010; 31(4):660–668. [PubMed: 19823984]
- Davey CG, Allen NB, Harrison BJ, Yücel M. Increased amygdala response to positive social feedback in young people with major depressive disorder. *Biological Psychiatry*. 2011; 69(8):734–741. [PubMed: 21257158]
- Davey CG, Harrison BJ, Yücel M, Allen NB. Regionally specific alterations in functional connectivity of the anterior cingulate cortex in major depressive disorder. *Psychological Medicine*. 2012; 42(10):2071–2081.
- Davey CG, Yücel M, Allen NB. The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. *Neuroscience & Biobehavioral Reviews*. 2008; 32(1):1–19. [PubMed: 17570526]
- Denny BT, Kober H, Wager TD, Ochsner KN. A meta-analysis of functional neuroimaging studies of self- and other judgements reveals a spatial gradient for mentalizing in medial prefrontal cortex. *Journal of Cognitive Neuroscience*. 2012; 24(8):1742–52. [PubMed: 22452556]
- Dimidjian S, Barrera M Jr, Martell C, Muñoz RF, Lewinsohn PM. The origins and current status of behavioral activation treatments for depression. *Annual Review of Clinical Psychology*. 2011; 7:1–38.
- Doucet GE, Skidmore C, Sharan AD, Sperling MR, Tracy JJ. Functional connectivity abnormalities vary by amygdala subdivision and are associated with psychiatric symptoms in unilateral temporal epilepsy. *Brain and Cognition*. 2013; 83(2):171–182. [PubMed: 24036129]
- Eack SM, Wojtalik JA, Newhill CE, Keshavan MS, Phillips ML. Prefrontal cortical dysfunction during visual perspective-taking in schizophrenia. *Schizophrenia Research*. 2013
- Eckblad, ML.; Chapman, LJ.; Chapman, JP.; Mishlove, M. Unpublished test. T.R. Kwapil, Department of Psychology, University of North Carolina; Greensboro, P.O. Box 26170, Greensboro, NC, 27402–6170: 1983. The revised social anhedonia scales. copies available from

- Eisenberger NI, Lieberman MD, Williams KD. Does rejection hurt? An fMRI study of social exclusion. *Science*. 2003; 302:290–292. [PubMed: 14551436]
- Ernst M, Nelson EE, Jazbec S, McClure EB, Monk CS, Leibenluft E, et al. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *Neuroimage*. 2005; 25(4):1279–1291. [PubMed: 15850746]
- Forbes EE. Where's the fun in that? Broadening the focus on reward function in depression. *Biological Psychiatry*. 2009; 66(3):199–200. [PubMed: 19577042]
- Forbes EE, Dahl RE. Research Review: Altered reward function in adolescent depression: what, when and how? *Journal of Child Psychology and Psychiatry*. 2012; 53(1):3–15. [PubMed: 22117893]
- Forbes EE, May JC, Siegle GJ, Ladouceur CD, Ryan ND, Carter CS, et al. Reward-related decision-making in pediatric major depressive disorder: an fMRI study. *Journal of Child Psychology and Psychiatry*. 2006; 47(10):1031–1040. [PubMed: 17073982]
- Forbes EE, Ryan ND, Phillips ML, Manuck SB, Worthman CM, Moyles DL, et al. Healthy adolescents' neural response to reward: associations with puberty, positive affect, and depressive symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49(2):162–172. e161–165. [PubMed: 20215938]
- Forbes EE, Stepp SD, Dahl RE, Ryan ND, Whalen D, Axelson DA, et al. Real-world affect and social context as predictors of treatment response in child and adolescent depression and anxiety: an ecological momentary assessment study. *Journal of Child and Adolescent Psychopharmacology*. 2012; 22(1):37–47. [PubMed: 22339611]
- Friston KJ. Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping*. 1994; 2:56–78.
- Friston KJ. Functional and effective connectivity: A review. *Brain Connectivity*. 2011; 1(1):13–36. [PubMed: 22432952]
- Furman, W.; Simon, VA. Cognitive representations of adolescent romantic relationships. In: Furman, W.; Brown, BB.; Feiring, C., editors. *The Development of Romantic Relationships in Adolescence*. Cambridge, UK: Cambridge University Press; 1999. p. 75–98.
- Galván A, Hare TA, Parra CE, Penn J, Voss H, Glover G, Casey BJ. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience*. 2006; 26(25):6885–6892. [PubMed: 16793895]
- Galván A, Hare TA, Voss H, Glover G, Casey BJ. Risk-taking and the adolescent brain: who is at risk? *Developmental Science*. 2007; 10(2):F8–F14. [PubMed: 17286837]
- Gotlib IH, Hamilton JP, Cooney RE, Singh MK, Henry ML, Joormann J. Neural processing of reward and loss in girls at risk for major depression. *Archives of General Psychiatry*. 2010; 67(4):380–387. [PubMed: 20368513]
- Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*. 2010; 35(1):4–26. [PubMed: 19812543]
- Hazen E, Schlozman S, Beresin E. Adolescent psychological development: a review. *Pediatrics in Review*. 2008; 29(5):161–167. [PubMed: 18450837]
- Hooley JM, Gruber SA, Scott LA, Hiller JB, Yurgelun-Todd DA. Activation in dorsolateral prefrontal cortex in response to maternal criticism and praise in recovered depressed and healthy control participants. *Biological Psychiatry*. 2005; 57(7):809–812. [PubMed: 15820239]
- Joiner TE Jr, Lewinsohn PM, Seeley JR. The core of loneliness: lack of pleasurable engagement--more so than painful disconnection--predicts social impairment, depression onset, and recovery from depressive disorders among adolescents. *Journal of Personality Assessment*. 2002; 79(3):472–491. [PubMed: 12511016]
- Kasch KL, Rottenberg J, Arnow BA, Gotlib IH. Behavioral activation and inhibition systems and the severity and course of depression. *Journal of Abnormal Psychology*. 2002; 111(4):589–597. [PubMed: 12428772]
- Kaufman J, Birmaher B, Brent DA, Ryan ND, Rao U. K-SADS-PL. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2000; 39(10):1208. [PubMed: 11026169]
- Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. *Biological Psychiatry*. 2005a; 58(6):495–503. [PubMed: 15993859]

- Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. The neural correlates of anhedonia in Major Depressive Disorder. *Biological Psychiatry*. 2005b; 58:843–853. [PubMed: 16043128]
- Keller J, Young CB, Kelley E, Prater K, Levitin DJ, Menon V. Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. *Journal of Psychiatric Research*. 2013; 47(10):1319–1328. [PubMed: 23791396]
- Kessler RC, Avenevoli S, Merikangas K. Mood disorders in children and adolescents: An epidemiologic perspective. *Biological Psychiatry*. 2001; 49(12):1002–1014. [PubMed: 11430842]
- Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH. Neural responses to monetary incentives in major depression. *Biological Psychiatry*. 2008; 63(7):686–692. [PubMed: 17916330]
- Kong L, Chen K, Tang Y, Wu F, Driesen N, Womer F, et al. Functional connectivity between the amygdala and prefrontal cortex in medication-naïve individuals with major depressive disorder. *Journal of Psychiatry and Neuroscience*. 2013; 38(5):120117. [PubMed: 23953680]
- Koob GF, Le Moal M. Addiction and the brain antireward system. *Annual Review of Psychology*. 2008; 59:29–53.
- Larson, RW.; Clore, GL.; Wood, GA. The emotions of romantic relationships: Do they wreak havoc on adolescents?. In: Furman, W.; Brown, BB.; Feiring, C., editors. *The Development of Romantic Relationships in Adolescence*. Cambridge, UK: Cambridge University Press; 1999. p. 19-49.
- Larson RW, Moneta G, Richards MH, Wilson S. Continuity, stability, and change in daily emotional experience across adolescence. *Child Development*. 2002; 73(4):1151–1165. [PubMed: 12146740]
- Leibenluft E, Gobbi MI, Harrison T, Haxby JV. Mothers' neural activation in response to pictures of their children and other children. *Biological Psychiatry*. 2004; 56(4):225–232. [PubMed: 15312809]
- Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews*. 2006; 30(6):718–729. [PubMed: 16887188]
- Lewinsohn PM, Clarke GN, Seeley JR, Rohde P. Major depression in community adolescents: Age at onset, episode duration, and time to recurrence. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1994; 33(6):809–818. [PubMed: 7598758]
- Lonigan CJ, Phillips BM, Hooe ES. Relations of positive and negative affectivity to anxiety and depression in children: Evidence from a latent variable longitudinal study. *Journal of Consulting and Clinical Psychology*. 2003; 71(3):465–481. [PubMed: 12795571]
- Mar RA. The neural bases of social cognition and story comprehension. *Annual Review of Psychology*. 2011; 62:103–134.
- Martinez, AM.; Benavente, R. CVC Technical Report #24. 1998. The AR-face database.
- McCabe C, Woffindale C, Harmer CJ, Cowen PJ. Neural processing of reward and punishment in young people at increased familial risk of depression. *Biological Psychiatry*. 2012; 72(7):588–594. [PubMed: 22704059]
- McMakin DL, Siegle GJ, Shirk SR. Positive Affect Stimulation and Sustainment (PASS) module for depressed mood: A preliminary investigation of treatment-related effects. *Cognitive Therapy and Research*. 2011; 35(3):217–226. [PubMed: 22140287]
- McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G, et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2012; 51(4):404–411. [PubMed: 22449646]
- Monk CS, Klein RG, Telzer EH, Schroth EA, Mannuzza S, Moulton JL 3rd, et al. Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. *The American Journal of Psychiatry*. 2008; 165(1):90–98. [PubMed: 17986682]
- Morgan, JK.; Shaw, DS.; Musselman, SC.; Kurapati, N.; Olino, TM.; Forbes, EE. Frontostriatal functional connectivity during reward processing in adolescent boys with a history of depression. (under review) Unpublished manuscript
- Morgan JK, Olino TM, McMakin DL, Ryan ND, Forbes EE. Neural response to reward as a predictor of increases in depressive symptoms in adolescence. *Neurobiology of Disease*. 2013; 52:66–74. [PubMed: 22521464]

- Mukherjee P, Whalley HC, McKirdy JW, Sprengelmeyer R, Young AW, McIntosh AM, et al. Altered Amygdala Connectivity Within the Social Brain in Schizophrenia. *Schizophrenia Bulletin*. 2013
- Nusslock R, Almeida JR, Forbes EE, Versace A, Labarbara EJ, Klein CR, et al. Waiting to win: elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults. *Bipolar Disorders*. 2012; 14(3):249–260. [PubMed: 22548898]
- O'Reilly JX, Woolrich MW, Behrens TE, Smith SM, Johansen-Berg H. Tools of the trade: Psychophysiological interactions and functional connectivity. *Social Cognitive Affective Neuroscience*. 2012; 7(5):604–609. [PubMed: 22569188]
- Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*. 2012; 1251(1):E1–E24. [PubMed: 23025352]
- Olino TM, McMakin DL, Dahl RE, Ryan ND, Silk JS, Birmaher B, et al. “I won, but I’m not getting my hopes up”: Depression moderates the relationship of outcomes and reward anticipation. *Psychiatry Research*. 2011; 194(3):393–395. [PubMed: 22079656]
- Olino TM, Yu L, McMakin DL, Forbes EE, Seeley JR, Lewinsohn PM, et al. Comparisons across depression assessment instruments in adolescence: An IRT study using two linking methods. *Journal of Abnormal Child Psychiatry*. 2013; 41(8):1267–1277.
- Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*. 2002; 16(2):331–348. [PubMed: 12030820]
- Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry*. 2008; 13(9):829, 833–857. [PubMed: 18574483]
- Pine DS, Cohen E, Cohen P, Brook J. Adolescent depressive symptoms as predictors of adult depression: Moodiness or mood disorder? *American Journal of Psychiatry*. 1999; 156(1):133–135. [PubMed: 9892310]
- Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977; 1:385–401.
- Sawyer MG, Pfeiffer S, Spence SH. Life events, coping and depressive symptoms among young adolescents: a one-year prospective study. *Journal of Affective Disorders*. 2009; 117(1–2):48–54. [PubMed: 19168224]
- Sears, DO. Implications of the life-span approach for research on attitudes and social cognition. In: Abeles, RP., editor. *Life-span Perspectives and Social Psychology*. Hillsdale, NJ: Lawrence Erlbaum; 1987. p. 17–60.
- Servaas MN, Riese H, Renken RJ, Marsman JB, Lambregts J, Ormel J, et al. The effect of criticism on functional brain connectivity and associations with neuroticism. *PLoS One*. 2013; 8(7):e69606. [PubMed: 23922755]
- Sheeber LB, Allen NB, Leve C, Davis B, Shortt JW, Katz LF. Dynamics of affective experience and behavior in depressed adolescents. *Journal of Child Psychology and Psychiatry*. 2009; 50(11):1419–1427. [PubMed: 19702661]
- Silk JS, Forbes EE, Whalen DJ, Jakubcak JL, Thompson WK, Ryan ND, et al. Daily emotional dynamics in depressed youth: a cell phone ecological momentary assessment study. *Journal of Experimental Child Psychology*. 2011; 110(2):241–257. [PubMed: 21112595]
- Silk JS, Stroud LR, Siegle GJ, Dahl RE, Lee KH, Nelson EE. Peer acceptance and rejection through the eyes of youth: pupillary, eyetracking and ecological data from the Chatroom Interact task. *Social Cognitive and Affective Neuroscience*. 2012; 7(1):93–105. [PubMed: 21775386]
- Somerville LH, Jones RM, Casey BJ. A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain and Cognition*. 2010; 72(1):124–133. [PubMed: 19695759]
- Spear LP. The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews*. 2000; 24(4):417–463. [PubMed: 10817843]
- Spijker J, Bijl RV, de Graaf R, Nolen WA. Determinants of poor 1-year outcome of DSM-III-R major depression in the general population: results of the Netherlands Mental Health Survey and

- Incidence Study (NEMESIS). *Acta Psychiatrica Scandinavica*. 2001; 103(2):122–30. [PubMed: 11167315]
- Steinberg L. A social neuroscience perspective on adolescent risk-taking. *Developmental Review*. 2008; 28(1):78–106. [PubMed: 18509515]
- Steinberg L, Albert D, Cauffman E, Banich M, Graham S, Woolard J. Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: Evidence for a dual systems model. *Developmental Psychology*. 2008; 44(6):1764–1778. [PubMed: 18999337]
- Straube B, Green A, Sass K, Kircher T. Superior Temporal Sulcus Disconnectivity During Processing of Metaphoric Gestures in Schizophrenia. *Schizophrenia Bulletin*. 2013
- Van Overwalle F, Baetens K. Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. *Neuroimage*. 2009; 48(3):564–584. [PubMed: 19524046]
- Versace A, Thompson WK, Zhou D, Almeida JR, Hassel S, Klein CR, et al. Abnormal left and right amygdala-orbitofrontal cortical functional connectivity to emotional faces: state versus trait vulnerability markers of depression in bipolar disorder. *Biological Psychiatry*. 2010; 67(5):422–431. [PubMed: 20159144]
- Wacker J, Dillon DG, Pizzagalli DA. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. *Neuroimage*. 2009; 46(1):327–337. [PubMed: 19457367]
- Wang F, Bobrow L, Liu J, Spencer L, Blumberg HP. Corticolimbic functional connectivity in adolescents with bipolar disorder. *PLoS One*. 2012; 7(11):e50177. [PubMed: 23185566]
- Whittle S, Yücel M, Forbes EE, Davey CG, Harding IH, Sheeber L, et al. Adolescents' depressive symptoms moderate neural responses to their mothers' positive behavior. *Social Cognitive and Affective Neuroscience*. 2012; 7(1):23–34. [PubMed: 21917846]
- Wilcox HC, Anthony JC. Child and adolescent clinical features as forerunners of adult-onset major depressive disorder: retrospective evidence from an epidemiological sample. *Journal of Affective Disorders*. 2004; 82:9–20. [PubMed: 15465572]
- World Health Organization. Depression. 2011. Retrieved December, 2011, from http://www.who.int/mental_health/management/depression/definition/en/index.html
- Yue Y, Yuan Y, Hou Z, Jiang W, Bai F, Zhang Z. Abnormal functional connectivity of amygdala in late-onset depression was associated with cognitive deficits. *PLoS One*. 2013; 8(9):e75058. [PubMed: 24040385]
- Zhang WN, Chang SH, Guo LY, Zhang KL, Wang J. The neural correlates of reward-related processing in major depressive disorder: A meta-analysis of functional magnetic resonance imaging studies. *Journal of Affective Disorders*. 2013; 151(2):531–539. [PubMed: 23856280]

- Higher social anhedonia in adolescents was associated with greater medial prefrontal cortex (mPFC) response to social reward.
- Adolescents' social anhedonia was associated with stronger positive functional connectivity between the nucleus accumbens and the mPFC during social reward.
- Anhedonia was related to brain function independently of the influence of depression.
- Anhedonia was associated with disrupted response to mutual liking rather than social reward in general.

Figure 1.

Block-design social reward fMRI task included in the current study. The task was adapted from the work of Davey et al. (2010). Participants rated 20 female and 20 male face stimuli on how much they imagined that they would like each person. Ratings were used to create personalized stimulus sets for the 3 block types: *mutual liking* (positive feedback, from most-liked faces), *received liking* (positive feedback, from least-liked faces), and *ambiguous* (no feedback, from neutral faces).

Figure 2.

Late adolescents' social anhedonia (RSAS; Eckblad et al., 1983) in relation to medial prefrontal cortex (mPFC) response (in arbitrary units, extracted from cluster mean) to mutual liking relative to received liking. The large cluster yielded by this analysis includes the following subregions of the mPFC: dorsal mPFC, pregenual anterior cingulate cortex, and rostral mPFC. Scatterplots depict the association between social anhedonia score and mPFC response (extracted as the mean across the entire cluster), for illustration purposes.

Figure 3.

Late adolescents' social anhedonia (RSAS; Eckblad et al., 1983) in relation to positive functional connectivity between the bilateral nucleus accumbens and the mPFC during mutual liking relative to received liking. Two large clusters yielded by this analysis include the following subregions of the mPFC: (1) dorsal mPFC and (2) pregenual anterior cingulate, rostral mPFC, and anterodorsal mPFC. Scatterplots depict psychophysiological interaction (PPI) values, (extracted as the mean across the entire larger cluster), for illustration purposes. R^2 value reflects the effect size of the association between social anhedonia and the mean PPI value across the depicted cluster.

Table 1

Whole-brain Results for Neural Response to Social Reward

Region	Number of voxels in cluster	t-score at peak voxel	Talairach coordinates of peak voxel
<i>Mutual Liking > Received Liking</i>			
Superior Parietal Cortex	105	4.30	-28 -58 61
Temporoparietal Junction	125	3.18	-48 -55 16
Middle Temporal Gyrus	258	2.84	58 -53 6
Inferior Parietal Cortex	56	2.74	-41 -50 55
Precentral Gyrus	76	2.61	-29 -21 50
Inferior Parietal Cortex	372	2.61	52 -53 42
DLPFC	64	2.60	-35 20 36
mPFC	40	2.49	-17 4 60
mPFC	134	2.47	-14 35 31
Insula	31	2.38	-27 15 23
mPFC/Supplementary Motor Area	78	2.38	-33 4 38
mPFC	60	2.35	-14 40 20
Postcentral Gyrus	36	2.28	-44 -27 50
Caudate Body	35	2.25	-5 8 16
Frontal Pole	37	2.14	-30 53 5
Anterior Insula	43	2.00	31 20 -4
<i>All Positive Feedback > Ambiguous Feedback</i>			
Precentral Gyrus/mPFC/Postcentral Gyrus/Superior Parietal Cortex	2228	4.29	34 -8 44
Cuneus/Caudate/mPFC/Putamen/Insula/Cerebellum/Posterior Cingulate/Parahippocampal Gyrus/Thalamus/Globus Pallidus/Lingual Gyrus	12909	4.15	-26 -90 21
Precuneus	1466	3.31	19 -57 44
Lateral Temporal Gyrus/Temporoparietal Junction/Superior Lateral Gyrus	496	3.04	-47 -2 -13
mPFC	319	2.98	-13 27 57
Ventrolateral PFC	262	2.98	49 31 13
Precentral Gyrus/Postcentral Gyrus	580	2.93	-37 -37 60
mPFC	139	2.80	-18 41 33
Temporoparietal Junction	158	2.76	45 -36 21
Temporoparietal Junction	142	2.74	-55 -46 21

Region	Number of voxels in cluster	t-score at peak voxel	Talairach coordinates of peak voxel
Inferior Parietal Cortex	252	2.70	-31 -55 47
Precuneus	139	2.60	-16 -67 36
Ventrolateral PFC/Insula	113	2.52	-45 9 8
mPFC	291	2.41	6 52 13
Superior Temporal Gyrus	30	2.40	-59 -51 7
Precuneus	193	2.35	52 5 27
Middle Temporal Gyrus	104	2.35	-38 -55 11
mPFC	116	2.34	-3 4 26
mPFC	33	2.29	12 37 48
Insula	44	2.21	38 -19 23
mPFC	39	2.20	8 10 32
mPFC	37	2.16	-13 2 46
mPFC	37	2.11	-11 43 48
Precuneus	50	2.04	-11 -56 19
Posterior Cingulate	30	1.90	-3 -26 41

Note: Analyses were conducted within the entire sample ($n=27$, $df=26$), using the contrasts indicated. All analyses were thresholded at were $p_{uncorrected}<.05$ and cluster size>30 voxels. DLPFC: dorsolateral prefrontal cortex. mPFC: medial prefrontal cortex. PFC: prefrontal cortex.

Table 2
Whole-brain Results for the Association of Social Anhedonia with Neural Response and Functional Connectivity

Regions in Cluster	Number of voxels in cluster	t-score at peak voxel	Talairach coordinates of peak voxel
<i>Neural Response and Social Anhedonia</i>			
mPFC/VS/OFC/Substantia Nigra/Clastrum	16209	4.34	-4 20 20
Precuneus/Angular Gyrus	1380	3.99	-31 -76 36
Thalamus/Caudate Tail/Posterior Cingulate/VS	1416	3.57	-1 -13 21
Precuneus/Superior Parietal Cortex	670	3.57	28 -75 44
DLPFC/Insula	984	3.46	37 -2 41
<i>Neural Response and Depressive Symptom Severity</i>			
DLPFC	927	4.93	-46 20 31
Precuneus/Inferior Parietal Cortex	1021	4.42	-28 -77 43
mPFC	4404	3.65	-18 39 35
DLPFC	697	3.19	43 10 37
<i>Functional Connectivity and Social Anhedonia</i>			
Postcentral Gyrus/VS/mPFC/OFC/Thalamus/Insula/Dorsal Striatum/Temporoparietal Junction/Inferior Parietal Cortex	14352	4.67	-48 -12 19

Note: Analyses involved the association of (1) neural response to reward and social anhedonia ($n=27$, $df=26$); (2) neural response to social reward and depressive symptom severity ($n=27$, $df=26$); and (3) functional connectivity with the bilateral nucleus accumbens and social anhedonia ($n=26$, $df=1,24$). The contrast of interest was *mutual liking > received liking*. Social anhedonia was assessed with the Revised Social Anhedonia Scales (Eckblad et al., 1983). Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (Radloff, 1977). All analyses were thresholded at $p_{corrected}<0.05$ using extent computed with AlphaSim to adjust for Type I error. mPFC: medial prefrontal cortex. VS: ventral striatum. DLPFC: dorsolateral prefrontal cortex. The first region listed for each cluster is the location of the peak voxel.