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The neural correlates of emotional face-processing in adolescent depression: a dimensional approach focusing on anhedonia and illness severity

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Abstract

Deficits in emotional processing, a known clinical feature of major depression (MDD), have been widely investigated using emotional face paradigms and neuroimaging. However, most studies have not accounted for the high inter-subject variability of symptom severity. Similarly, only sparse research has focused on MDD in adolescence, early in the course of the illness. Here we sought to investigate neural responses to emotional faces using both categorical and dimensional analyses with a focus on anhedonia, a core symptom of MDD associated with poor outcomes. Nineteen medication-free depressed adolescents and eighteen healthy controls were scanned during presentation of happy, sad, fearful, and neutral faces. ANCOVAs and regressions assessed group differences and relationships with illness and anhedonia severity, respectively. Findings included a group by valence interaction with depressed adolescents exhibiting decreased activity in the superior temporal gyrus (STG), putamen and premotor cortex. Post-hoc analyses confirmed decreased STG activity in MDD adolescents. Dimensional analyses revealed associations between illness severity and altered responses to negative faces in prefrontal, cingulate, striatal, and limbic regions. However, anhedonia severity was uniquely correlated with responses to happy faces in the prefrontal, cingulate, and insular regions. Our work highlights the need for studying specific symptoms dimensionally in psychiatric research.

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Keywords

adolescents; depression; anhedonia; emotion perception; fMRI; faces

1. Introduction

Major depressive disorder (MDD) is a devastating illness that often develops during adolescence; however, most research has examined adults with a long-standing illness. Thus, more research is needed in adolescence to identify neurobiological changes early in the course of disease, and in a population free of psychotropic medication. Similarly, there has been an increasing emphasis on studying specific MDD symptoms dimensionally to address the heterogeneous nature of the disorder, as well as high inter-individual variability of symptom severity (Insel et al., 2010). Anhedonia, a core symptom of MDD, has been proposed as a promising target for such an approach. This is especially relevant for depressed adolescents, as anhedonia severity is highly variable in this population, often results in contrasting phenotypes. Of clinical significance, anhedonia was identified as a predictor for adult MDD (Pine et al., 1999; Wilcox & Anthony, 2002), treatment non-response (McMakin et al., 2012), and suicidality (Fawcett et al., 1983; Fawcett et al., 1990; Spijker et al., 2010). In our prior research, we were able to identify specific neuroimmunological alterations associated with anhedonia severity in adolescents with MDD (Gabbay et al., 2012a; Gabbay et al., 2012b; Gabbay et al., 2013). Extending this work, here we sought to examine group differences in brain activity in response to emotional faces, as well as relationships with overall illness and anhedonia severity.

There is a consensus among clinicians that deficits in emotion processing are a key clinical feature of MDD. Reflecting this, functional magnetic resonance imaging (fMRI) paradigms in which subjects view emotional faces have been widely used to examine the neural circuitry underlying such deficits in both adults and youths with MDD (Fitzgerald et al., 2008; Stuhmann et al., 2011; Barch et al., 2012; Mingtian et al., 2012). Across age groups, much of this research has focused on altered amygdala responses to emotional faces (Sheline et al., 2001; Peluso et al., 2009; Yang et al., 2010; Suslow et al., 2010); however, whole-brain approaches have also found disruptions in fronto-limbic circuitry. Specifically, depressed adults show decreased prefrontal and increased striatal/amygdala activity in response to negative emotional faces (e.g., sad, angry, fearful), and the opposite pattern of responses for happy faces (Lawrence et al., 2004; Surguladze et al., 2005; Fu et al., 2007; Fitzgerald et al., 2008; Sturhmann et al., 2011). Findings have been similar in adolescent MDD, with reports of heightened amygdala activation to negative faces but no group differences for positive faces (Yang et al., 2010; Barch et al., 2012; Mingtian et al., 2012; Hall et al., 2014).

A few studies have utilized a dimensional analysis approach to examine relationships between MDD severity and brain activity during emotional processing in children and adolescents. These have reported that greater illness severity correlates with increased responses to negative emotional faces in the amygdala (Yang et al., 2010; Gaffrey et al., 2011; Mingtian et al., 2012; Barch et al., 2012), as well as the prefrontal and cingulate cortices (Killgore et al., 2005; Barch et al., 2012). However, studies examining the neural

correlates of specific depressive symptoms are lacking. Only one group has investigated the relationships between MDD symptoms, including anhedonia, and neural responses in adults during a task involving emotional faces and autobiographical recall (Keedwell et al., 2005). For anhedonia, they reported increased prefrontal and decreased limbic activity in response to happy faces, and the opposite pattern for sad faces. It is important to note that these analyses did not control for illness severity; however, the reported alterations in reward circuitry for happy faces support the notion that anhedonia reflects deficits in reward processing, as happy faces may act as a cue for social rewards (Barbour et al., 2012; Lin et al., 2012; Rademacher et al., 2013).

Addressing the need for a more detailed investigation of emotion processing in MDD during development, this study aimed to examine neural responses to emotional faces in adolescents with MDD both categorically and dimensionally. Based on these observations, we hypothesized that compared to healthy controls (HC), adolescents with MDD would exhibit: 1) decreased activity in the striatum and increased medial prefrontal cortex (PFC) and anterior cingulate cortex (ACC) activity while viewing happy faces, and 2) greater activity in the striatum and reduced activity in fronto-cingulate regions while viewing negative faces. We further predicted that activity in the medial PFC, ACC, and striatum would show unique relationships with anhedonia severity independent of illness severity. Finally, we predicted that relationships between anhedonia severity and brain activity would be detected only in response to socially rewarding happy faces, and not broadly to any category of emotional faces.

2. Methods

2.1 Subjects

The sample consisted of 19 adolescents with MDD and 18 HC, group matched for age and sex, all right-handed. Nine additional adolescents were scanned but excluded from all analyses; four due to excessive head movement during scanning and five due to missing task data. There were no differences in illness severity or any other metric between our excluded and included subjects. Adolescents with MDD were recruited through the New York University (NYU) Child Study Center, the Bellevue Hospital Center Department of Psychiatry, and local advertisements in the NY metropolitan area. HC were recruited through local advertisements and families of NYU staff. The study was approved by the NYU School of Medicine Institutional Review Board (IRB) and the Icahn School of Medicine at Mount Sinai IRB. Prior to enrollment, study procedures were explained to the subjects and parents. Written informed consent was provided by participants age 18 and older; those under age 18 provided signed assent and a parent provided signed informed consent.

Inclusion and Exclusion Criteria—All subjects were 12–20 years old and did not present with any significant medical or neurological disorders. Other exclusion criteria consisted of an IQ < 80, MRI contraindications, a positive urine toxicology test, or a positive pregnancy test.

All MDD subjects met the DSM-IV-TR diagnosis of MDD with a current episode eight weeks duration, raw severity score 39 (i.e., T score 63) on the Children's Depression Rating Scale-Revised (CDRS-R), and were psychotropic medication-free for at least seven half-lives of the medication. Exclusionary criteria for the MDD group included current/past DSM-IV-TR diagnoses of bipolar disorder, schizophrenia, pervasive developmental disorder, panic disorder, obsessive-compulsive disorder, conduct disorder, or Tourette's disorder; or a substance-related disorder in the past 12 months. Current diagnoses of post-traumatic stress disorder or an eating disorder were also exclusionary. HC subjects did not meet criteria for any major current/past DSM-IV-TR diagnoses and had never received psychotropic medication.

2.2 Clinical Assessments

All subjects were assessed by a board-certified child/adolescent psychiatrist or a clinical psychologist. Clinical diagnoses were established using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997), a semi-structured interview performed with both the subjects and their parents. Depression severity was assessed by the CDRS-R and the Beck Depression Inventory, Second Edition (BDI-II; Beck et al., 1997). Additionally, suicidality and IQ were assessed using the Beck Scale for Suicidal Ideation (BSSI; Beck et al., 1979) and the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990), respectively. Urine toxicology and pregnancy tests were administered the day of scanning.

Anhedonia—As in our previous studies (Gabbay et al., 2012a; Gabbay et al., 2012b; Gabbay et al., 2013), anhedonia scores were computed by summing the responses to three items associated with anhedonia from the clinician-rated CDRS-R (“difficulty having fun;” scale of 1–7) and the self-rated BDI-II (“loss of pleasure,” “loss of interest;” scale of 0–3), with the total score ranging from 1–13. Our rationale for using a combined score from two scales was to account for both the clinician-rated score (that takes into account parent's perspective) and the adolescent self-rated score. This approach fits current diagnostic standards for MDD in adolescents requiring collateral information from both the adolescent and the parent to allow for an accurate assessment of clinical presentation.

Illness Severity was determined from CDRS-R scores. However, when both anhedonia and illness severity were used in a model, illness severity was determined from CDRS-R scores computed without the anhedonia-related item since it is used to calculate anhedonia scores.

2.3 Face Task

Similar to past research investigating responses to emotional faces (Pine et al., 2004; Roberson-Nay et al., 2006; Guyer et al., 2011), subjects were presented with a series of emotional faces (i.e., happy, sad, fearful, neutral) from the NimStim Set of Facial Expressions (Tottenham et al., 2009), in black and white versions. Subjects were asked to judge either how sad the faces were (i.e., emotional judgment), or how wide the noses were (i.e., physical judgment), on a scale from 1 (*very*) to 4 (*not at all*). Each trial began with 500 ms of fixation, followed by an emotional face for 2500 ms, and then a 500 ms inter-trial-interval. Subjects made emotional or physical judgments about the faces during the 2500 ms

presentation. Faces were presented over two pseudo-randomized runs. The study was designed to show eight alternating blocks of 20 trials (i.e., four emotional judgment blocks, four physical judgment blocks), which were preceded by a 3500 ms presentation of instructions for that block. However, several responses were not recorded due to technical issues with the scanner pulse being recorded instead of the subject's response. Additionally, instruction screens were occasionally skipped when a scanner pulse or subject response occurred during the preloading period for the instructions. As such, there were unequal numbers of physical and emotional judgment blocks, with far more emotional judgments ($M = 196.21$, $SD = 33.61$, range 140–260) than physical judgments ($M = 125.37$, $SD = 36.06$, range 60–180). Therefore, all analyses were limited to the emotional judgment trials, which did not significantly differ between the MDD ($M = 187.37$, $SD = 29.97$) and HC ($M = 205.55$, $SD = 35.51$) groups [$t(35) = 1.68$, $p = 0.10$]. Within each block, there were four randomly selected presentations of happy, sad, fearful, or neutral faces as well as four catch-trials. Catch-trials consisted of a black screen presented for the same duration as face trials and were included to increase jitter.

2.4 Data Acquisition & Processing

Imaging data were acquired on a Siemens Allegra 3.0 T scanner at the NYU Center for Brain Imaging. High-resolution T_1 -weighted anatomical images were acquired using a magnetization prepared gradient echo sequence (TR = 2500 ms; TE = 3.93 ms; TI = 600 ms; flip angle = 8°; 176 slices; FOV = 256 mm; acquisition voxel size = 1×1×1 mm). Functional T_2^* -weighted gradient echo images were acquired over 2 runs with 40 contiguous 3.0 mm axial interleaved slices (TR = 2000 ms; TE = 25 ms; flip angle = 80°; FOV = 192; 64×64 matrix size; inter-slice gap = 0 mm).

All preprocessing and analyses were performed using AFNI (<http://afni.nimh.nih.gov/afni>). Preprocessing included despiking, slice-timing correction, and volume registration. Data were smoothed with a 6 mm FWHM Gaussian kernel, and subjects with motion exceeding 2 mm were excluded. In order to estimate task-related changes in blood-oxygen-level dependent signal at each voxel at the onset of each stimulus, a general linear model (GLM) was performed which included four regressors of interest for the four emotional faces, one regressor for the instruction screens/physical judgment trials, six regressors for motion, and five regressors for linear trends. Responses were modeled with general additive model (GAM) functions and convolved with a hemodynamic response. Responses to each category of faces were contrasted with an implicit baseline estimate, and beta values were used for all analyses. Finally, subject maps were co-registered to in-plane anatomical images, resampled to 1×1×1 mm³ voxels, and normalized to standard Talairach space (TTN27 template).

2.5 Group-Level Behavioral, fMRI, and Brain-Behavior Analyses

Face ratings, response times, and neural responses for emotional judgment trials were submitted to a series of 2 (group: MDD, HC) × 4 (face valence: happy, neutral, fearful, sad) mixed model analyses of covariance (ANCOVA) controlling for age and gender. Average beta values were extracted from significant clusters to examine relationships emerging from the whole-brain ANCOVA. Group-by-face-valence interaction effects were assessed via a series of two-tailed, equal-variance independent-samples t-tests. To assess dimensional

relationships between illness severity and neural responses to happy, sad, fearful, and neutral faces, four voxel-wise regressions using beta values from the emotional face (happy, sad, fearful, neutral) > baseline contrasts were carried out in the MDD group, with illness severity, age, and gender entered as covariates. Four additional regressions were performed using anhedonia severity instead of illness severity. Additionally, because illness severity was significantly correlated with anhedonia severity ($r = 0.55, p < 0.03$), we performed four additional regressions with both anhedonia and illness severity entered as covariates, along with age and gender. The HC group was excluded from these analyses due to the limited range of anhedonia scores (as expected).

To correct for multiple comparisons for whole-brain analyses, a Monte Carlo simulation was run using AFNI's 3dClustSim on an averaged group mask with 10,000 iterations, assuming 6 mm of interdependence. Using an individual voxel-wise threshold of $p = 0.005$, a cluster of 607 voxels resulted in a whole-brain correction to $p < 0.05$.

3. Results

3.1 Subjects

Demographic and clinical characteristics are summarized in Table 1. One subject with MDD had been treated with escitalopram for six months but was medication-free for nine months prior to scanning. One MDD subject had been taking amphetamine mixed salts as needed for school, but had not taken it for several weeks prior to scanning. All other subjects were psychotropic medication-naïve. Sixteen subjects with MDD had experienced only one episode of depression, with length of episode ranging from 4–48 months, and three patients reported having two distinct episodes.

Within the MDD group, anhedonia severity ranged from 1–10 ($M = 6.50, SD = 2.80$). Importantly, the anhedonia specific scores from the self-rated BDI and the clinician-rated CDRS-R were positively correlated ($r = 0.57, p = 0.01$). Anhedonia severity was also positively correlated with illness severity (with the anhedonia item removed; $r = 0.55, p < 0.03$). Therefore, all correlational analyses with anhedonia severity were repeated while controlling for illness severity.

3.2 Face Ratings & Response Times

As expected, sadness ratings differed for the four emotional faces [$F(3,30) = 3.29, p = 0.03$]. Sad faces were rated the most sad ($M = 1.67, SD = 0.35$), then fearful faces ($M = 2.39, SD = 0.81$), neutral faces ($M = 2.85, SD = 0.50$), and happy faces ($M = 3.77, SD = 0.33$; all post-hoc pairwise p 's < 0.005). The groups did not differ on overall sadness ratings [$F(1,32) = 0.84, p = 0.77$], or ratings for any specific category of faces [$F(3,30) = 0.89, p = 0.45$]. Response times did not significantly differ for the four categories of faces [$F(3,30) = 1.14, p = 0.35$], between the two groups [$F(1,32) = 2.35, p = 0.14$], or for any specific category of faces [$F(3,30) = 0.71, p = 0.55$].

3.3 Group Comparisons: Neural Responses to Emotional Faces

The 2×4 ANCOVA controlling for age and gender revealed no main effect of group but a robust main effect of face valence which included activations across the brain in bilateral medial PFC (MPFC), precuneus, posterior cingulate cortex (PCC), visual cortex, inferior temporal cortex, right dorsolateral PFC (DLPFC), and left anterior insula (Table 2). Additionally, three regions emerged demonstrating a group by face valence interaction involving the left STG, right putamen, and left premotor cortex (Table 3). Average beta values were extracted from each significant cluster and independent sample t-tests were carried out comparing responses between the groups for each category of face to understand what drove each interaction (Table 3). MDD adolescents had larger deactivation to sad and neutral faces compared to HC in the STG (p 's = 0.01, 0.04, respectively). There were no other significant differences between MDD and HC groups for any category of face for the putamen and premotor clusters. However, there was a trending difference between the two groups in the putamen for sad faces, $p = 0.07$.

3.4 Associations of Neural Responses with Overall Illness Severity

Within the MDD group, there were no correlations between illness severity and neural activity to happy faces (Table 4). For sad faces, positive correlations were found in the thalamus, putamen, amygdala, anterior insula, ventromedial PFC (VMPFC), STG, fusiform gyrus, and postcentral gyrus (Figure 1A). Positive correlations were also found for fearful faces in the dorsal ACC (DACC) thalamus, and anterior insula (Figure 1B). Two clusters emerged for neutral faces demonstrating negative relationships in the ventrolateral PFC (VLPFC) and precentral gyrus.

3.5 Associations of Neural Responses with Anhedonia Severity

Neural responses to happy faces were negatively correlated with anhedonia severity in the anterior insula, a cluster encompassing the medial frontal gyrus (MFG; BA 8) and DACC (BA 32), the premotor cortex (BA 6), and the cerebellum (Table 4; Figure 1B–C). For sad faces, there were positive correlations with anhedonia in the anterior insula, thalamus, caudate, putamen, and amygdala (Figure 2A–B). There were no correlations with anhedonia for fearful or neutral faces.

3.6 Associations of Neural Responses with Anhedonia Severity Controlling for Illness Severity

When both anhedonia and illness severity (quantified with CDRS-R minus the anhedonia question) were entered into our model (along with age and gender), the correlations between anhedonia and neural responses to happy faces remained significant in the anterior insula, MFG/DACC, and cerebellum. For sad, fearful, and neutral faces, there were no clusters that remained significant for either anhedonia severity or illness severity when both were included in the model. Thus, we confirmed our prediction that significant relationships would only be detected between anhedonia and happy faces.

4. Discussion

In keeping with our hypothesis, three regions emerged as demonstrating a group $\times$ valence interaction involving the left STG, right putamen, and left premotor cortex with depressed adolescents exhibiting decreased activity in these regions. Yet, our hypothesis that adolescents with MDD would exhibit widespread alterations in prefrontal, cingulate, and striatal regions in response happy and negative faces viewing was not fully supported. Nonetheless, as expected, when utilizing a dimensional investigative approach, we were able to identify distinct relationships within MDD subjects between illness severity and anhedonia severity in the MPFC, ACC, and striatum. Moreover, we confirmed our prediction that anhedonia would be most strongly related with responses to happy faces, and would not strongly correlate with responses to sad, fearful, or neutral faces after controlling for illness severity.

4.1 Group Differences

We identified an interaction of diagnostic group by valence with adolescents with MDD exhibiting greater deactivation in the left STG, right putamen and left premotor cortex. Post-hoc analyses revealed greater deactivation in left STG in the MDD group for sad and neutral faces. There was also a trend for happy and fearful faces. Involvement of the STG in our sample is likely to be due to the region's key role in facial emotional processing (Adolphs, 2002). Similar findings were reported recently by in adolescents with MDD using similar face task (Hall et al., 2014). Indeed a meta-analysis of emotional face processing in MDD also concluded reduced activity in the left STG for MDD patients compared to HC when exposed to negative emotional stimuli (Fitzgerald et al., 2008). Fitzgerald and colleagues suggest that the STG, prefrontal, insular, and cingulate regions comprise an emotion-processing network that demonstrates reduced activity both at rest and in response to negative affect in MDD. Structurally, reduced gray matter in the STG was also reported in adolescents with MDD (Shad et al., 2012). These data suggest that alterations in the STG occur early in the course of illness in MDD.

While reduced activity in the right dorsal putamen and left premotor cortex were also associated with the diagnosis of MDD based on group by valence interaction post-hoc analyses were not significant. The finding in the putamen was unexpected, as most research has found increased activity in striatal regions in MDD to negative emotional stimuli (Fitzgerald et al., 2008). However, given that the dorsal caudal putamen and premotor cortex are both involved with motor control and responses (Di Martino et al., 2008; Hardwick et al., 2013), and that the study task was to judge the sadness of the faces, one possible explanation is that the sad faces acted as a target for HC and a distraction for the MDD group. In this way, the HC would have increased motor-related responses to the target sadder faces relative to the MDD group, whereas the sad content may have distracted depressed adolescents. Similar findings have been reported when using emotional Stroop tasks in depressed populations (Epp et al., 2012). Additionally, although we found reduced activity in the MDD group in the dorsal caudal putamen, we found the expected increase in activity in response to sad faces in our dimensional analyses in a more ventral putamen cluster, implicated in conflict monitoring and emotional processes (Di Martino et al., 2008).

Overall, our findings for group differences were somewhat limited. However, this is not surprising considering the highly heterogeneous nature of MDD, and fits with past research demonstrating relatively few differences between MDD and HC groups while viewing emotional faces, particularly early in the course of the illness (Cusi et al., 2012; Jappe, 2013).

4.2 Relationships with Illness Severity

As expected from previous work with children and adolescents (Yang et al., 2010; Barch et al., 2012; Mingtian et al., 2012), the most robust relationships with illness severity were for the negative emotional faces (i.e., sad, fearful), with no findings for happy faces and few for neutral faces. Specifically, we found heightened activity as illness severity increased for both sad and fearful faces in limbic regions (i.e., thalamus, amygdala), regions involved in emotion processing and reward (i.e., VMPFC, anterior insula, putamen; Hansel & Von Kanel, 2008; Krebs et al., 2011), and the DACC for fearful faces. Activation of the limbic system has been implicated in motivation, emotional salience, and attentional processes (Taylor et al., 2009; Krebs et al., 2011; Cho et al., 2012), and heightened limbic activity has been previously documented in MDD when evaluating negative emotional stimuli (Lawrence et al., 2004; Peluso et al., 2009; Mingtian et al., 2012). As such, our findings suggest that greater illness severity is related to increased salience and attention towards negative emotional stimuli (i.e., focusing on mood-congruent sad aspects in the environment). With regards to the increased activity in the DACC in response to fearful faces, this region is implicated in both cognitive and emotional processes including attention, task monitoring, decision-making, and affect regulation (Stevens et al., 2011). One possible explanation for our findings is that the more severely depressed individuals had more difficulty judging sadness for the fearful faces, and thus required more attentional and decision-making resources to complete the task.

4.3 Relationships with Anhedonia Severity

Using a symptom-specific dimensional approach, we were able to distinguish circuitry associated with anhedonia while controlling for illness severity as a potential confound. Critically, associations between neural activity and anhedonia were only found for happy faces after controlling for illness severity, suggesting a relationship between deficits in the ability to experience pleasure (i.e., anhedonia) and responses to social rewards (i.e., happy faces; Barbour et al., 2012; Lin et al., 2012; Rademacher et al., 2013). As anhedonia severity increased, there was reduced activity to happy faces in areas including the MFG/DACC, anterior insula, and cerebellum. A recent meta-analysis found the involvement of all of these regions in reward processing and decision-making (Liu et al., 2011). Specifically, the anterior insula is involved in emotional and interoceptive processes, particularly in using feedback from internally generated body states to evaluate the emotional/rewarding salience of stimuli (Critchley, 2005; Taylor et al., 2009). The areas of the brain encompassed by the MFG/DACC cluster have been implicated in a variety of higher-level processes including attention and conflict monitoring (Aarts et al., 2009; Cusi et al., 2012). Taken together, our findings suggest that greater anhedonia is related to increasingly dysfunctional monitoring of both environmental and internal cues for evaluating positive stimuli.

4.4 Limitations & Future Directions

Although our sample size is comparable to those of other clinical neuroimaging studies, our findings must be considered preliminary. Specifically, it is possible our sample did not provide enough statistical power for the mixed-model ANOVA design, but was more adequately powered for the whole-brain regressions. Another potential limitation is that subjects were asked to judge the sadness of all emotional faces (i.e., happy, sad, fearful, neutral). This framing of the task made it difficult to analyze behavioral responses to other emotional faces, particularly responses to happy faces. Additionally, the unanticipated issue of skipped instruction screens limited our ability to use the physical judgments as contrasts.

4.5 Conclusions

Our investigation of responses to emotional faces in psychotropic medication-free adolescents with MDD found that increased anhedonia severity is related to reduced activity in brain regions implicated in monitoring the environment and generating an emotional response to (typically rewarding) happy faces, but not to negative or neutral faces. Additionally, we found increased activity in neural regions involved in attention and the evaluation of emotional salience for negative faces among the more severely ill adolescents. Consistent with prior work (Gabbay et al., 2012a; Henderson et al., 2013), this study further emphasizes the importance of assessing symptoms along dimensional scales, in addition to binary categories, to enrich our understanding of the underlying neurobiology of psychiatric disorders. Future research on anhedonia and emotional processing should also focus across a larger range of psychiatric conditions.

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References

- Aarts E, Roelofs A, Turennout M. Attentional control of task and response in lateral and medial frontal cortex: brain activity and reaction time distributions. *Neuropsychologia*. 2009; 47(10):2089–99. [PubMed: 19467359]
- Adolphs R. Neural systems for recognizing emotion. *Current Opinion in Neurobiology*. 2002; 12:169–77. [PubMed: 12015233]
- Barbour T, Pruitt P, Diwadkar VA. fMRI responses to emotional faces in children and adolescents at genetic risk for psychiatric illness share some of the features of depression. *Journal of Affective Disorders*. 2012; 136(3):276–285. [PubMed: 22222174]
- Barch DM, Gaffrey MS, Botteron KN, Belden AC, Luby JL. Functional brain activation to emotionally valenced faces in school-aged children with a history of preschool-onset major depression. *Biological Psychiatry*. 2012; 72(12):1035–1042. [PubMed: 22770650]
- Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Behaviour Research Therapy*. 1997; 35(8): 785–791. [PubMed: 9256522]
- Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *Journal of Consulting and Clinical Psychology*. 1979; 47(2):343–352. [PubMed: 469082]

- Cho YT, Fromm S, Guyer AE, Detloff A, Pine DS, Fudge JL, Ernst M. Nucleus accumbens, thalamus and insula connectivity during incentive anticipation in typical adults and adolescents. *Neuroimage*. 2012; 66C:508–521. [PubMed: 23069809]
- Critchley HD. Neural mechanisms of autonomic, affective, and cognitive integration. *Journal of Comparative Neurology*. 2005; 493(1):154–66. [PubMed: 16254997]
- Cusi AM, Nazarov A, Holshausen K, MacQueen GM, McKinnon MC. Systematic review of the neural basis of social cognition in patients with mood disorders. *Journal of Psychiatry and Neuroscience*. 2012; 37(3):154–69. [PubMed: 22297065]
- Di Martino A, Scheres A, Margulies DS, Kelly AM, Uddin LQ, Shehzad Z, Biswal B, Walter JR, Castellanos FX, Milham MP. Functional connectivity of human striatum: a resting state fMRI study. *Cerebral Cortex*. 2008; 18(12):2735–47. [PubMed: 18400794]
- Epp AM, Dobson KS, Dozois DJA, Frewen PA. A systematic meta-analysis of the Stroop task in depression. *Clinical Psychology Review*. 2012; 32(4):316–328. [PubMed: 22459792]
- Fawcett J, Clark DC, Scheftner WA, Hedeker D. Differences between anhedonia and normally hedonic depressive states. *American Journal of Psychiatry*. 1983; 140(8):1027–30. [PubMed: 6869586]
- Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, Gibbons R. Time-related predictors of suicide in major affective disorder. *American Journal of Psychiatry*. 1990; 147(9):1189–94. [PubMed: 2104515]
- Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A meta-analytic study of changes in brain activation in depression. *Human Brain Mapping*. 2008; 29(6):683–95. [PubMed: 17598168]
- Fu CH, Williams SC, Brammer MJ, Suckling J, Kim J, Cleare AJ, Walsh ND, Mitterschiffthaler MT, Andrew CM, Pich EM, Bullmore ET. Neural responses to happy facial expressions in major depression following antidepressant treatment. *American Journal of Psychiatry*. 2007; 164(4):599–607. [PubMed: 17403973]
- Gabbay V, Ely BA, Babb J, Liebes L. The possible role of the kynurenine pathway in anhedonia in adolescents. *Journal of Neural Transmission*. 2012a; 119(2):253–260. [PubMed: 21786117]
- Gabbay V, Ely BA, Li Q, Bangaru SD, Panzer AM, Alonso CM, Castellanos FX, Milham MP. Striatum-Based circuitry of adolescent depression and anhedonia. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2013; 52(6):628–641. [PubMed: 23702452]
- Gabbay V, Mao X, Klein RG, Ely BA, Babb JS, Panzer AM, Alonso CM, Shungu DC. Anterior cingulate cortex 3-aminobutyric acid in depressed adolescents: relationship to anhedonia. *Archives of General Psychiatry*. 2012b; 69(2):139–149. [PubMed: 21969419]
- Gaffrey MS, Luby JL, Belder AC, Hirshberg JS, Volsch J, Barch DM. Association between depression severity and amygdala reaction during sad face viewing in depressed preschoolers: an fMRI study. *Journal of Affective Disorders*. 2011; 129:364–370. [PubMed: 20869122]
- Guyer AE, Choate VR, Grimm KJ, Pine DS, Keenan K. Emerging depression is associated with face memory deficits in adolescent girls. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2011; 50(2):180–190. [PubMed: 21241955]
- Hall LM, Klimes-Dougan B, Hunt RH, Thomas KM, Houry A, Noack E, Mueller BA, Lim KO, Cullen KR. An fMRI study of emotional face processing in adolescent major depression. *Journal of Affective Disorders*. 2014; 168:44–50. [PubMed: 25036008]
- Hansel A, von Kanel R. The ventro-medial prefrontal cortex: a major link between the autonomic nervous system, regulation of emotion, and stress reactivity? *Bio Psycho Social Medicine*. 2008; 2(21)
- Hardwick RM, Rottschy C, Miall RC, Eickhoff SB. A quantitative meta-analysis and review of motor learning in the human brain. *Neuroimage*. 2013; 67:283–297. [PubMed: 23194819]
- Henderson SE, Johnson AR, Vallejo AI, Katz L, Wong E, Gabbay V. A preliminary study of white matter in adolescent depression: relationships with illness severity, anhedonia, and irritability. *Frontiers in Psychiatry: Neuroimaging*. 2013; 4(152)
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*. 2010; 167(7):748–751. [PubMed: 20595427]

- Jappe, LM. Master's Thesis. University of Minnesota; 2013. An fMRI study of emotional face processing in adolescent major depression. Retrieved from http://conservancy.umn.edu/bitstream/147495/1/Jappe_umn_0130M_13486.pdf
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36(7):980–988. [PubMed: 9204677]
- Kaufman, AS.; Kaufman, NL. Manual for the Kaufman Brief Intelligence Test. Circle Pines, MN: American Guidance Service; 1990.
- Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. The neural correlates of anhedonia in major depressive disorder. *Biological Psychiatry*. 2005; 58(11):843–853. [PubMed: 16043128]
- Killgore WDS, Yurgelon-Todd DA. Ventromedial prefrontal activity correlates with depressed mood in adolescent children. *Developmental Neuroscience: NeuroReport*. 2005; 17(2):167–171.
- Krebs RM, Boehler CN, Roberts KC, Song AW, Woldorff MG. The involvement of the dopaminergic midbrain and cortico-striatal-thalamic circuits in the integration of reward prospect and attentional task demands. *Cerebral Cortex*. 2011; 22(3):607–15. [PubMed: 21680848]
- Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, Frangou S, Ecker C, Phillips ML. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biological Psychiatry*. 2004; 55(6):578–587. [PubMed: 15013826]
- Lin A, Adolphs R, Rangel A. Social and monetary reward learning engage overlapping neural substrates. *Social Cognitive and Affective Neuroscience*. 2012; 7(3):274–281. [PubMed: 21427193]
- Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews*. 2011; 35:1219–36. [PubMed: 21185861]
- McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G, Wagners KD, Asarnow JR, Ryan ND, Birmaher B, Shamseddeen W, Mayes T, Kennard B, Spirito A, Keller M, Lynch FL, Dickerson JF, Brent DA. 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):404–11. [PubMed: 22449646]
- Mingtian Z, Shuqiao Y, Xiongzhao Z, Jinyao Y, Xueling Z, Xiang W, Yingzi L, Jian L, Wei W. Elevated amygdala activity to negative faces in young adults with early onset major depressive disorder. *Psychiatry Research*. 2012; 201(2):107–112. [PubMed: 22398297]
- Peluso MAM, Glahn DC, Matsuo K, Monkul ES, Najt P, Zamarripa F, Li J, Lancaster JL, Fox PT, Gao J, Soares JC. Amygdala hyperactivation in untreated depressed individuals. *Psychiatry Research: Neuroimaging*. 2009; 173(2):158–161.
- 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]
- Pine DS, Lissek S, Klein RG, Mannuzza S, Moulton JL, Guardino M, Woldehawariat G. Face-memory and emotion: associations with major depression in children and adolescents. *Journal of Child Psychology and Psychiatry*. 2004; 45(7):1199–1208. [PubMed: 15335340]
- Rademacher L, Salama A, Grunder G, Spreckelmeyer KN. Differential patterns of nucleus accumbens activation during anticipation of monetary and social reward in young and older adults. *Social Cognitive and Affective Neuroscience*. 2013 Epub ahead of print.
- Roberson-Nay R, McClure EB, Monk CS, Nelson EE, Guyer AE, Fromm SJ, Charney DS, Leibenluft E, Blair J, Ernst M, Pine DS. Increased amygdala activity during successful memory encoding in adolescent major depressive disorder: an fMRI study. *Biological Psychiatry*. 2006; 60(9):966–973. [PubMed: 16603133]
- Shad MU, Muddasani S, Rao U. Gray matter differences between healthy and depressed adolescents: A voxel-based morphometry study. *Journal of Child and Adolescent Psychopharmacology*. 2012; 22(3):190–197. [PubMed: 22537357]

- Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biological Psychiatry*. 2001; 50(9):651–658. [PubMed: 11704071]
- Spijker J, de Graaf R, Ten Have M, Nolen WA, Speckens A. Predictors of suicidality in depressive spectrum disorders in the general population: results of the Netherlands Mental Health Survey and Incidence Study. *Social Psychiatry and Psychiatric Epidemiology*. 2010; 45(5):513–521. [PubMed: 19618093]
- Stevens FL, Hurley RA, Hayman LA, Taber KH. Anterior cingulate cortex: unique role in cognition and emotion. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2011; 23:121–125. [PubMed: 21677237]
- Stuhrmann A, Suslow T, Dannlowski U. Facial emotion processing in major depression: a systematic review of neuroimaging findings. *Biology of Mood and Anxiety Disorders*. 2011; 1:1–17. [PubMed: 22738418]
- Surguladze S, Brammer MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, Williams SC, Phillips ML. A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biological Psychiatry*. 2005; 57(3):201–209. [PubMed: 15691520]
- Suslow T, Konrad C, Kugel H, Rumstadt D, Zwieterlood P, Schoning S, Ohrmann P, Bauer J, Pyka M, Kersting A, Arolt V, Heindel W, Dannlowski U. Automatic mood-congruent amygdala responses to masked facial expressions in major depression. *Biological Psychiatry*. 2010; 67(2):155–160. [PubMed: 19748075]
- Taylor KS, Seminowicz DA, Davis KD. Two systems of resting state connectivity between the insula and cingulate cortex. *Human Brain Mapping*. 2009; 30(9):2731–2745. [PubMed: 19072897]
- Tottenham N, Tanaka JW, Leon AC, McCarry T, Nurse M, Hare TA, Marcus DJ, Westerlund A, Casey BJ, Nelson C. The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Research*. 2009; 168(3):242–249. [PubMed: 19564050]
- 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*. 2002; 82(1):9–20. [PubMed: 15465572]
- Yang TT, Simmons AN, Matthews SC, Tapert SF, Frank GK, Max JE, Bischoff-Grethe A, Lansing AE, Brown G, Strigo IA, Wu J, Paulus MP. Adolescents with major depression demonstrate increased amygdala activation. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49(1):42–51. [PubMed: 20215925]

Figure 1.

(A) Increased activity in response to sad faces as illness severity increased in the ventromedial prefrontal cortex, right anterior insula, bilateral putamen and thalamus; (B) Increased activity in response to fearful faces as illness severity increased in bilateral thalamus and right anterior insula. RAI orientation. Voxel-wise threshold of $p = 0.005$, clusters > 607 voxels.

Figure 2. Reduced activity in response to happy faces as anhedonia severity increased in (A) left anterior insula and cerebellum; (B) Middle frontal gyrus/dorsal anterior cingulate cortex (BA 8/32). RAI orientation. Voxel-wise threshold of $p = 0.005$, clusters > 607 voxels.

Table 1

Demographic and Clinical Characteristics of Adolescents with Major Depression (MDD) and Healthy Controls

Characteristic	MDD Subjects (N=19)	Healthy Controls (N=18)
Age (Range)	17.3 ± 2.4 (12–20)	16.0 ± 1.5(13–19)
Gender (female/male)	13/6 (68/32%)	10/8 (56/44%)
Ethnicity (Caucasian/African American/Hispanic/Asian/Other)	9/2/6/0/2 (47/11/32/0/10%)	6/6/1/3/2 (33/33/6/17/11%)
Illness History		
Episode Duration in Months (Range)	15.05±11.15 (4–48)	0
Number of MDD Episodes	1 (n=16), 2 (n=3)	0 (n=18)
Suicide Attempts (Range)	0.2± 0.5 (0–2)	0
Medication-naïve/Medication-free	16/3 (84/16%)	18/0 (100/0%)
¹ CDRS-R (Range)	48.9 ± 6.8 (39–64)	19.4 ± 2.6 (17–27)
² BDI-II (Range)	27.2 ± 12.7 (11–51)	2.5 ± 3.0 (0–10)
³ BSSI (Range)	6.1 ± 10.1 (0–37)	0.1 ± 0.3 (0–1)
Anhedonia (Range)	6.5 ± 2.8 (1–10)	1.4 ± 0.7 (1–3)
Current Comorbidity		
⁴ ADHD	2 (11%)	0
⁵ GAD	11(58%)	0
Other Anxiety Disorders	5 (26%)	0

¹ Children's Depression Rating Scale-Revised

² Beck Depression Inventory, Second Edition

³ Beck Scale of Suicidal Ideation

⁴ Attention Deficit Hyperactivity Disorder

⁵ Generalized Anxiety Disorder

Table 2

Activations for Main Effects of Group $\times$ Face Valence ANCOVA

Region	Cluster	t	X	Y	Z
<u>Main Effect Group</u>					
None					
<u>Main Effect Face Valence</u>					
L Precuneus, PCC, visual cortex	89635	106.71	-4	-79	41
L VMPFC/DMPFC/VACC	24653	42.94	-11	57	1
R Inferior Temporal Gyrus	6096	34.86	60	-20	-1
R DLPFC (BA 8)	5069	39.12	28	21	48
R Visual Cortex	1153	14.33	36	-62	-8
R Cerebellum	1137	24.94	33	-82	-30
L Anterior Insula	897	20.58	-31	12	7
R PCC	870	21.07	21	-25	29
L Inferior Temporal Gyrus	852	18.35	-55	-11	21
R MFG (BA 6)	836	22.05	57	0	14
R MFG (BA 6)	704	17.75	55	-3	36

Note: Clusters of > 607 voxels whose global maxima meets an F -threshold of 6.07 ($p < 0.005$, corrected to $p < 0.05$) are reported. Peak x, y, z coordinates, R = right, L = left. BA = Brodmann area. PCC = posterior cingulate cortex. VMPFC = ventromedial prefrontal cortex. DMPFC = dorsomedial prefrontal cortex. VACC = ventral anterior cingulate cortex. DLPFC = dorsolateral prefrontal cortex. MFG = medial frontal gyrus.

Table 3

Activations for Group $\times$ Face Valence Interaction for Significant Clusters

Region	Cluster	t	X	Y	Z	Group	Happy β	Sad β	Fear β	Neutral β
L Super Temporal Gyrus	1514	24.37	-56	4	-1	HC	.02 (.03)	.01 (.03)	-.01 (.03)	-.02 (.03)
						MDD	-.06 ^a (.03)	-.11 ¹ (.03)	-.09 ^b (.03)	-.09 ² (.02)
R Putamen	647	21.22	31	-13	1	HC	-.03 (.02)	-.00 (.02)	-.04 (.02)	-.02 (.02)
						MDD	-.04 (.02)	-.06 ^c (.02)	-.03 (.02)	-.01 (.02)
L Premotor Cortex (BA 6)	710	16.02	-40	-7	47	HC	.04 (.02)	.03 (.03)	.05 (.03)	.04 (.03)
						MDD	.01 (.02)	-.00 (.03)	.04 (.03)	.03 (.03)

Note: Clusters of > 607 voxels whose global maxima meets an F -threshold of 6.07 ($p < 0.005$, corrected to $p < 0.05$) are reported. Peak x, y, z coordinates, β = average beta value from clusters, followed by standard error in parentheses. R = right. L = left. BA = Brodmann area. Superscript numbers refer to significant findings in post-hoc analyses.

1, 2 : greater deactivation in the STG in MDD compared to HC in response to sad ($p = 0.009$) and neutral ($p = 0.043$) faces, respectively. Superscript letters refer to trends.

a, b : greater deactivation in the STG in MDD compared to HC in response to happy ($p = 0.076$) and fearful ($p = 0.081$), respectively.

c : greater deactivation in the putamen in MDD compared to HC in response to sad faces ($p = 0.067$).

Table 4

Activations for Dimensional Analyses With Illness and Anhedonia Severity

Region	Cluster	t	β	X	Y	Z
<u>Happy: Depression</u>						
None						
<u>Sad: Depression Positive Correlation</u>						
R Thalamus/Putamen/STG	3270	4.72	.011	24	-20	-2
L Anterior Insula/Putamen	2294	4.55	.010	-36	16	6
R VMPFC (BA 10)	1053	4.62	.019	0	55	-8
L Postcentral Gyrus (BA 3)	714	4.45	.013	-56	-15	30
R Fusiform Gyrus (BA 20)	690	4.15	.024	32	-36	-17
L Amygdala	659	5.03	.014	-20	-7	-7
<u>Fear: Depression Positive Correlation</u>						
R DACC (BA 32)	661	4.92	.011	9	11	36
R Thalamus	716	4.54	.010	22	-26	-1
L Thalamus	622	3.61	.009	-21	-24	-2
R Anterior Insula	607	3.71	.013	46	10	-1
<u>Neutral: Depression Negative Correlation</u>						
R Precentral Gyrus	926	6.88	-.012	30	-30	51
L VLPFC (BA 47)	661	3.80	-.017	-33	27	-11
<u>Happy: Anhedonia Negative Correlation</u>						
R MFG/DACC (BA 8/32)	1464	5.11	-.042	2	31	39
L Anterior Insula	1108	6.60	-.037	-30	22	-3
R Premotor Cortex (BA 6)*	841	3.91	-.041	26	4	47
R Cerebellum	1793	4.71	-.043	31	-56	-40
L Cerebellum	1209	3.42	-.036	-39	-47	-52
<u>Sad: Anhedonia Positive Correlation</u>						
L Anterior Insula*	888	6.09	.029	-32	9	7
R Thalamus*	796	5.32	.028	16	-7	-7
R Caudate*	698	4.47	.030	34	-14	-6
L Putamen/Amygdala*	610	4.39	.032	-25	-8	-5

Region	Cluster	t	β	X	Y	Z
Fear: Anhedonia						
None						
Neutral: Anhedonia						
None						

* Cluster did not remain significant when anhedonia and illness severity were both entered in to model.

Note: Clusters of > 607 voxels whose global maxima meets a t-threshold of 3.29 ($p < 0.005$, corrected to $p < 0.05$) are reported. β = average beta value from clusters. Peak x, y, z coordinates. R = right. L = left. BA = Brodmann area. VMPPFC = ventromedial prefrontal cortex. DACC = dorsal anterior cingulate cortex. VLPFC = ventrolateral prefrontal cortex. MFG = medial frontal gyrus.