



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

Sarah E. Henderson^a, Ana I. Vallejo^a, Benjamin A. Ely^b, Guoxin Kang^c, Amy Krain Roy^d, Daniel S. Pine^e, Emily R. Stern^{a,b}, Vilma Gabbay^{a,b,f,*}

^a Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

^b Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA

^c Department of Radiology, Weill Cornell Medical College, New York, NY, USA

^d Department of Psychology, Fordham University, New York, NY, USA

^e National Institute of Mental Health, Bethesda, MD, USA

^f Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA

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ABSTRACT

Deficits in emotion processing, a known clinical feature of major depressive disorder (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 18 healthy controls (HC) 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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1. Introduction

Major depressive disorder (MDD) is a devastating illness that often develops during adolescence; however, most research has examined adults with 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,

* Correspondence to: Department of Psychiatry-1230, Icahn School of Medicine at Mount Sinai, Gustave L. Levy Place, New York, NY 10029, USA. Tel.: +1 212 659 1661; fax: +1 212 659 1693.

E-mail address: vilma.gabbay@mssm.edu (V. Gabbay).

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, and 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; Stuhmann 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 emotion 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 and Yurgelon-Todd, 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., 2014).

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.

2.1.1. 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 \geq eight weeks duration, raw severity score \geq 39 (i.e., T score \geq 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.

2.2.1. 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 to 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.

2.2.2. Illness severity

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, and 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 ($M=196.21$, $S.D.=33.61$, range 140–260) than physical judgments ($M=125.37$, $S.D.=36.06$, range 60–180). Therefore, all analyses were limited to the emotional judgment trials, which did not significantly differ between the MDD ($M=187.37$, $S.D.=29.97$) and HC ($M=205.55$, $S.D.=35.51$) 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

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