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Research paper

The neurobiology of self face recognition among depressed adolescents

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ABSTRACT

Objective: Depression is linked to alterations in both emotion and self-processing. The current study used functional magnetic resonance imaging (fMRI) to assess neural activation in healthy and depressed youth to a novel task that combined emotion processing with self-face recognition.

Methods: An fMRI study involving 81 adolescents (50.6% females; $M_{age} = 14.61$, SD = 1.65) comprised of depressed (DEP, $n = 43$), and healthy controls (HC, $n = 38$). Participants completed a clinical interview and self-report measures during an initial assessment. In the scanner, adolescents completed a face recognition task, viewing emotional (happy, sad, neutral) images of their own face (self) or the face of another youth (other).

Results: DEP youth showed higher activity in the cuneus ($F = 26.29$) and post and precentral gyri ($F = 20.76$), across all conditions compared to HC. Sad faces elicited higher posterior cingulate cortex, precuneus ($F = 10.36$) and inferior parietal cortex activity ($F = 11.0$), and self faces elicited higher precuneus, fusiform ($F = 16.39$), insula and putamen ($F = 16.82$) activity in all youth. DEP showed higher middle temporal activity to neutral faces but lower activity to sad faces compared to HC, who showed the opposite pattern ($F = 12.86$). DEP also showed hypoactive mid-temporal limbic activity relative to controls when identifying their self happy face vs. neutral face, yet showed hyperactivity when identifying the other happy face vs. neutral face, and HC showed the opposite pattern ($F = 10.94$).

Conclusions: The neurophysiology of self-face recognition is altered in adolescent depression. Specifically, depression was associated with decreased activity in neural areas that support emotional and associative processing for positive self-faces and increased processing for neutral self-faces. These results suggest that depression in adolescents is associated with hypoactive emotional processing and encoding of positive self-related visual information. This abnormal neural activity at the intersection of reward and self-processing among depressed youth might have long lasting impact in self-formation and future adult self-representations, given that adolescence is a sensitive period for self-development.

1. Introduction

Adolescence is a key developmental period for the emergence of depression, as well as for transformations in self-processing and identity (Auerbach et al., 2015). In particular, increased self-processing (e.g. heightened self-consciousness or self-awareness) has been associated with depression and this association is strongest during mid-adolescence (Chen et al., 1998), suggesting that self-processing changes increase risks for depression during the adolescent transition. Depression is characterized by self-processing disturbances, which are linked to hyperactivation in cortical midline structures (CMS) (Lemogne et al., 2012). Because changes in self-processing are linked to upsurges of depression during adolescence (Chen et al., 1998), it is key to study the neural bases of self-processing in depressed adolescents. Uncovering how self-processing differs between depressed and healthy youth at the neural level may shed light on neuropsychological processes linked to onset and maintenance of depression.

Self-processing is the ability to perceive, and judge one's own states, traits, and abilities. A facet of this overarching construct, and the focus of this research, is visual self-face recognition (Hu et al., 2016). Self-

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processing is altered in depression. Negative self-directed thoughts and emotions are core depression symptoms (Gaddy and Ingram, 2014). Yet most existing work on self-processing neurophysiology in depressed populations relied on tasks that require participants to verbally reflect on stimuli in relation to themselves (See for a review of such tasks Lieberman, 2007). These facets of self-processing are subserved by midline cortical structures (MCS) such as anterior and posterior cingulate cortices (ACC, PCC), precuneus, and medial prefrontal cortex (MPFC) (Bradley et al., 2016; Heatherton et al., 2006). While these tasks are informative for a verbally explicit and predominantly cognitive definition of self-processing (Harter, 1999), they seldom engage limbic regions that enable rapid, emotionally charged self-processing. In contrast, self-face recognition does not rely on language and is enabled by limbic regions such as fusiform gyrus, amygdala, and hippocampus. For example, Kircher et al. (2001) examined self-face recognition and found it was subserved by limbic structures in addition to MCS. We propose that studying self vs. other face recognition may shed light on the neurophysiology of rapid emotional self-processes that are not always part of our explicit, verbal awareness. Specifically, we hypothesize that self-face recognition will allow access to the function of limbic, emotion processing neural structures among depressed adolescents.

1.1. Face processing neurophysiology and emotional biases in depression

There is ample research demonstrating that depression is characterized by exaggerated attention, encoding and recall of negative versus positive stimuli across many modalities (e.g. words, images, phrases (Platt et al., 2017)). Notably these cognitive and emotional biases in depression also extend to processing of socially salient stimuli such as faces (Stuhrmann et al., 2011). For example, while controls show greater limbic activation in response to subliminal happy versus sad facial expressions, depressed individuals show the opposite pattern (Stuhrmann et al., 2013).

In healthy populations, processing emotional faces is enabled by activity in the fusiform gyrus and in limbic areas such as the amygdala, insula and hippocampus (Fusar-Poli et al., 2009). Functional abnormalities in these areas during face processing have been noted among depressed compared to healthy individuals. In addition, depressed patients evidence limbic activations whereas controls show fronto-thalamic activations during processing of emotional faces (Lai, 2014; Stuhrmann et al., 2011). These reviews also show that depressed patients evidence abnormalities in the face processing network, specifically, hyperactivation to negative faces and hypoactivation to positive faces in the amygdala, insula, parahippocampal gyrus, fusiform face area, and putamen (Lai, 2014; Stuhrmann et al., 2011). Similar patterns of abnormal neural activity during face processing have been observed in depressed adults, adolescents and children. For example, depressed adults show biases towards negative emotional faces (Leppanen, 2006), as well as neural hypoactivation regarding positive faces in limbic brain regions (Barlow et al., 2012; Nejad et al., 2013). Depressed adolescents also exhibit amygdala hyperactivation versus healthy controls (Beesdo et al., 2009), and exposure to sad faces interferes with dorsolateral prefrontal cortex function during an inhibition task in depressed youth (Colich et al., 2016). This is again consistent with behavioral and imaging evidence that risk for major depression involves a bias to attend to negative and to neglect positive information.

In summary, past research suggests that there are depression specific biases toward negative faces (limbic hyperactivation) as well as biases away from positive faces (limbic hypoactivation) across development. Similar neurobehavioral biases have been noted in young healthy samples at risk for depression. Adolescents at risk for depression perceive mild happy expressions as less intense than do healthy youth (Kerestes et al., 2016) and amygdala hyperactivity to negative emotional faces has been observed in non-depressed adolescents at risk for depression (Monk et al., 2008). Additionally, children at-risk for depression show increased amygdala and cortical activation to fearful versus neutral, and decreased activation to happy versus neutral faces in the ACC and supramarginal gyrus (Chai et al., 2015). Notably, this reduced limbic activation to happy expressions was linked to anhedonia in depressed patients (Stuhrmann et al., 2013). Finally, slower identification of happy facial expressions and faster identification of sad faces predicted onset of depression in adolescents over an 8 year period (Vrijen et al., 2016), suggesting that these biases have predictive value and constitute risk factors for depression.

1.2. The neural activity of self-face processing and recognition

Self-face recognition is a special case of face and self-processing. Viewing and recognizing our own face is supported by neural areas that enable self-processing (i.e. MCS) and by structures that support face (fusiform) and emotion processing (i.e. amygdala, hippocampus) (Phan et al., 2004; Sergerie et al., 2008; Sugiura et al., 2005). Importantly, both limbic and MCS networks have been associated with abnormal neurophysiology in depression (Nejad et al., 2013). Limbic structures are known to underlie rapid processing and encoding of, and memory for emotionally charged information (Devue and Bredart, 2011; Habel et al., 2007; Sugiura et al., 2008). Therefore, recognition of emotionally charged self-faces elicits activation in limbic structures (amygdala and hippocampus for salient emotional facial information), in MCS (i.e. ACC, PCC, MPFC and precuneus for higher order processing of self- and emotion-related information) as well as in the fusiform (Sugiura, 2015). Given previously discussed self-processing abnormalities (in verbal and explicit modalities) as well as emotional biases among depressed patients, it would be reasonable to expect abnormal limbic activation to emotionally charged self faces relative to unfamiliar faces.

1.3. Current study

The aims of this study were to test whether patterns of brain activity during emotional self-face processing differed for depressed youth compared to healthy controls. Our primary hypotheses were that, during self-face processing, depressed youth would show less MCS and limbic activation to self happy expressions compared to healthy controls, and more MCS and limbic activation to self sad and neutral faces in this age group.

An additional complexity of studying the neurobiology of depression pertains to the effects of medication on brain function. Past authors have suggested that antidepressants modulate emotional biases by increasing positive emotional processing (Harmer et al., 2009). Here we also examine the putative effects of medication (primarily antidepressants) on brain activity among depressed adolescents engaged on a self-processing task.

2. Methods

2.1. Participants and procedure

Participants (N = 81) were recruited from the brief crisis inpatient unit and among youth assessed for depression at two Universities in the U.S., from local outpatient mental health clinics, and through radio and flyer advertisements. Of the participants included in analyses, 16 of the healthy and 12 depressed youth were scanned at Site1 (n = 28), while 22 controls and 31 depressed were scanned at Site 2 (n = 53). Similar numbers of depressed and healthy control youth were scanned at the two sites: χ^2 (1) = 1.80, p = 0.18. Participants with any of the following characteristics were excluded: IQ < 70, autism spectrum disorder, substance abuse or dependency, history of seizures, left handed, primary diagnosis other than depressive disorder. Diagnosis were assigned by two experimenters for all participants recruited as patients, kappa depressive disorders = 0.86, kappa anxiety disorders = 0.43. Diagnostic discrepancies were solved by the first author, a licensed clinical

psychologist.

Psychological evaluation was completed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS, Kaufman et al., 1997) which was used to assign diagnostic group category. The Child Depression Rating Scale (CDRS, Poznanski et al., 1979) was also administered to obtain a continuous measure of depression. A puberty measure (PDS, Petersen et al., 1985) yields scores from 0 to 4 with values larger than 2.5 generally corresponding to more advance puberty. Participants' IQ were measured via the Wechsler Abbreviated Scale of Intelligence, (Wechsler, 1999). Adolescent reports of attributional style using the Children's Attributional Style Interview (Conley et al., 2001), self-esteem using the Perceived Confidence Scale for Children (Harter, 1982) and anxiety the Screen for Childhood Anxiety Related Emotional Disorders (Birmaher et al., 1997) were obtained. One to two weeks after evaluation, participants completed neuroimaging procedures.

We excluded 24 depressed adolescents with a history of abuse because no participants in the control group had a history of abuse, abuse is linked to significant structural, functional abnormalities and neuropsychological deficits (Malhi et al., 2008; Teicher and Samson, 2016), and abused patients exhibit more severe depression complicated by post-traumatic-stress symptoms (Cukor and McGinn, 2006). Groups were matched for age, sex ratio, and pubertal status (see Table 1 for participant demographics). Nine participants were excluded from analyses due to excessive head movement, defined as a maximum shift in xyz position between any two volumes of > 2 mm or maximum absolute rotation of > 0.56 rad. Shift tended to differ between groups, $F(1,78) = 4$, $p = 0.05$, ($M_{dep} = 1.2$; $M_{cont} = 0.9$), with greater movement in the depressed group, a common finding among clinically referred children and adolescents but rotation $F(1,78) = 0.7$, $p = 0.4$ was similar between diagnostic groups. There were no differences in average movement between scanning sites, $F(1,78) = 1.69$, $p = 0.9$. Please see supplement for strategies used to eliminate movement artifacts.

2.2. Neuroimaging data acquisition

Neuroimaging data were collected using 3.0 T Siemens Trio MRI scanners in both Site 1 and Site 2. Structural 3D axial MPRAGE images were acquired for each participant (TR/TE: 2100 ms/3.31 ms; TI: 1050; Flip Angle 8°; Field of View: 256 ×2 00 mm; Slice-Thickness: 1 mm; Matrix: 256×200; 176 continuous slices). Mean BOLD images were then acquired with a gradient echo EPI sequence during 11 min 2 s covering 60 oblique axial slices (2.0 mm thick; TR/TE = 3340/30 ms; FOV = 200×200 mm; matrix 80×80; Flip Angle 90°), resulting in a $2 \times 2 \times 2\ mm^3$ voxel size. Please see the supplemental texts for movement correction and examination of scanner effects analyses, which yielded no significant effects.

2.3. The Emotional Self-Other Morph-Query (ESOM-Q) task

2.3.1. Experiment

In the scanner, participants saw photographs of faces ($N_{total} = 150$) displaying happy, sad, or neutral expressions presented randomly. The faces were morphed between the participant's face and a similar peer's face selected by visual examination and agreement between the two main experimenters. Participants were instructed to indicate whether the picture looked like them by pressing one of two buttons. Please see Supplemental Fig. 1 online for a depiction of the task and supplemental text for details on the generation and coding of stimulus. The experiment was conducted in a single run lasting 10 min 54 s. It consisted of 6 unique blocks of faces (self happy, other happy, self sad, other sad, self neutral, other neutral; 70 s per block). Instructions were presented at the start of each block (6 s). In addition, at the start, midpoint and end of each block, an 18 s rest period with a fixation cross (i.e. 18 rest periods) was presented with the auditory instruction, "rest now." This provided a respite from the task and established brain activity baselines that were concomitant with the start, center, and end of each condition block. Faces were displayed for 2 s followed by a 0.5 s fixation cross. Each block contained faces of only high or only low degrees of morphing between the self and the other face. Morphing between the self and the other face were scaled in 5% increments. This resulted in blocks comprised of self-faces or unfamiliar faces within happy, sad or neutral groupings, with the following means and standard deviation of morphings: **Self blocks**: $M_{self} = 83\%$, $SD = 12\%$, $Min_{self} = 65\%$, $Max_{self} = 100\%$, which means that the self faces within self blocs ranged from 100% to 65% self features in 5% increments; **Other blocks**: $M_{self} = 18\%$, $SD = 12\%$, $Min_{self} = 0\%$, $Max_{self} = 35\%$, which means that the self faces within other blocks ranged from 0% to 35% self features in 5% increments.

Blocks were presented in 5 counterbalanced task orders. Each block contained 28 photos of faces presented randomly within any given self by emotion block. Highly ambiguous stimuli, i.e. with 40–60% of self-features, were not used in any block. Within each of the 6 blocks, 4 faces were shown of high opposite percentage to the predominant block condition to avoid response sets and keep the participants engaged (Other block, 4 faces = 90% or 80% self; Self block, 4 faces = 90% or 80% other), following methods used by Kircher et al.(2001). The

Table 1
Demographic Differences across Depressed and Healthy Control Groups.

Predictors and Demographics	Healthy Control n = 38	Depressed n = 43	Comparison Statistic
Scanning Sites			
Site 1	16	12	$\chi 2\ (1) = 1.79$
Site 2	22	31	
Depressive Disorders			
Major Depressive Disorder (MDD)	0	28	
Dysthymia	0	2	
Depressive Disorder NOS	0	13	
Comorbidities for Depressed (K-SADS)			
Anxiety Disorders	0	29 (67.4%)	
Agoraphobia	0	4	
Anxiety Disorder NOS	0	12	
Generalized Anxiety Disorder	0	10	
Panic Disorder	0	1	
Separation Anxiety	0	1	
Social Phobia	0	1	
Eating Disorders	0	1	
Age: *M* (*SD*)	14.46 (1.52)	14.73 (1.76)	$F(1,79) = 0.55$
Puberty	2.9 (0.09)	3.1 (0.09)	$F(1,79) = 0.135$
IQ: M (*SD*)	116.89 (12.30)	109.02 (11.89)	$F(1,79) = 8.56^{**}$
Sex			
Male	19 (50.00%)	21 (48.84%)	$\chi^2\ (1) = 0.01$
Female	19 (50.00%)	22 (51.16%)	$\chi^2\ (4) = 4.39$
Ethnicity			
White	29 (76.31%)	28 (65.11%)	
African American	1 (2.63%)	5 (11.63%)	
Hispanic	1 (2.63%)	4 (9.30%)	
Asian/Asian American	3 (7.89%)	2 (4.65%)	
Mixed	4 (10.53%)	4 (9.30%)	
Family Structure			
Married	31 (70.27%)	31 (72.09%)	$\chi^2\ (3) = 1.06$
Cohabiting	2 (5.41%)	3 (6.98%)	
Separated/Divorced	3 (5.41%)	5 (11.63%)	
Single	2 (5.41%)	4 (9.30%)	
Family Income	6.11 (75–100k)	5.14 (50–75k)	$F(1,79) = 3.73^{+}$
Any Medication	0	22 (51.2%)	
Antidepressants	0	19 (44.2%)	
Stimulants	0	7 (1.6%)	
Anxiolytics	0	2 (4.7%)	
Antipsychotics	0	1 (2.3%)	

$^{+}p < 0.1$. $^{*}p < 0.05$. $^{**}p < 0.01$.

hemodynamic response function (HRF) lasts about 12 s and peaks between 5 and 8 s (Kruggel and von Cramon, 1999). Exposure (2 s) to these 4 "opposite" faces is too fast to significantly alter the HRF for the predominant block condition. Indeed, we found that excluding the "opposite" faces from our analysis yielded quantitatively similar patterns of results (data not shown). Stimuli, accuracy of recognition, and reaction time data were recorded with e-prime software.

2.4. Analyses

2.4.1. Neuroimaging data analysis

Data were preprocessed and analyzed with Statistical Parametric Mapping software, Version-12 (SPM12; http://www.fil.ion.ucl.ac.uk/spm). Data for each participant were realigned to the first volume in the time series to correct for head motion. Realigned images were co-registered with the subject's anatomical image, segmented, normalized to a standard Montreal Neurological Institute (MNI) template, and spatially smoothed with a Gaussian kernel of 7 mm full-width at half-maximum (FWHW). Trials were modeled with the Canonical HRF. First-level fixed-effect models were calculated for each participant producing statistical images for each of the 6 stimulus types relative to fixation baseline: self-face and other face (with happy, neutral or sad expressions).

Whole brain level principal analyses compared groups using a 2nd level full factorial model with the t-contrast images generated by the single-subject analyses described above as within subject factors, allowing for examination of BOLD activity differences between groups and group by condition effects. This model had one between group factor and two within group factors, specifically: a 2 group (Healthy Controls or Depressed) by 2 Self Conditions (Self, Other) by 3 Emotion (Happy, Neutral, Sad) with medication, income, IQ and scanning site as covariates [(1)] included in SPM12. To correct for multiple comparisons, we calculated whole-brain, voxel-wise and cluster extent thresholds via Monte Carlo simulations using 3dClustSim in AFNI_v.16.3.08, software also used to estimate intrinsic smoothness (12.5, 15.7, 13.1). This resulted in a voxel-wise threshold of $p < 0.001$ and the following cluster (k) - extent thresholds: 2(diagnostic group) by 2(Self, Other) by 3(happy, sad, neutral): $k = 201$ voxels, for a $p_k < 0.001$. Follow up *t*-test contrasts in SPM12 and Repeated Measures Analyses of Variance (RM-ANOVAS) in SPSS 23 respectively, were used to confirm interactions. For depressed only, a full factorial model with a 3 (emotional condition: happy, sad, and neutral) × 2 (self-face or other face) × 2 (medication group) design was run with income, IQ and scanning sites as covariates in SPM12 software, intrinsic smoothness (12.0, 14.7, 12.3) and $k = 181$ voxels threshold. Given the potential role of anxiety in facial emotion processing, post-hoc analyses compared adolescents who were depressed and anxious versus adolescents who were depressed only versus controls (classified by the K-SADS). This analysis did not explain results yielded by the primary full model described in [(1)]. For all analyses, time series for brain activity for significant clusters were extracted using the "eigenvariates" function in SPM 12 to confirm the direction of interactions, to conduct post-hoc exploratory correlations with symptoms in SPSS23 and for graphing purposes. Tables and figures show results that meet the necessary cluster size requirements.

3. Results

3.1. Behavioral results

3.1.1. Reaction Time (RT)

A 2(self vs. other) x 3(emotion: happy, sad, or neutral) x 2(depressed vs. control) RM-ANOVA revealed a significant main effect of self, $F(1,142) = 8.30$, $p < 0.005$, and a significant interaction between self and valence, $F(2, 142) = 3.75$, $p < 0.03$. All subjects responded more slowly to high-self ($M = 896.0$, $SE = 16.3$) than to low-self faces ($M = 857.0$, $SE = 17.6$), and this effect was most pronounced for happy faces ($M = 924.1$, $SE = 21.1$). Reaction time did not vary by group.

3.1.2. Accuracy of recognition

A second RM-ANOVA with the same predictors examined subjects' accuracy in identifying faces. For faces that contained 65% or more of the participants features (i.e. 65% > = self-face), the correct response was considered "self."

There was significant main effect of emotion valence condition present for all participants across diagnostic group and within all self or other face conditions, $F(2,152) = 14.0$, $p < 0.01$. Specifically, all participants showed better accuracy of identification for happy ($M = 0.76$, $SE = 0.03$) than neutral ($M = 0.69$, $SE = 0.02$) or sad faces ($M = 0.70$, $SE = 0.02$).

A significant self by emotion interaction, $F(2,152) = 8.98$, $p < 0.01$, showed that all participants (regardless of diagnostic group) were more accurate to identify the self-face for the happy emotional condition, yet were more accurate identifying the other face for the neutral emotional condition. In other words, within the 3 emotionally charged self blocks (happy, neutral or sad) the happy-self face elicited higher accuracy in all participants, whereas among the 3 emotionally charged other blocks it was the neutral unfamiliar face that elicited higher accuracy. Self-features did not influence the identification of sad faces. There were no significant effects of diagnostic group on accuracy of recognition.

Table 2
Areas of Significant Neural Activity during Emotionally Charged Self and Other Face Processing in Depressed versus Control Youth.

Main Effect of Group	Cluster Size (K)	p(K)	Hemisphere	MNI			F
				x	y	z	
Cuneus	398	0.000	Right	0	−94	4	26.29
Postcentral Gyrus, Precentral Gyrus	550	0.000	Right	60	−16	34	20.76
Main Effect of Emotion							
Inferior Parietal Lobule, Precuneus	205	0.000	Left	−36	−74	44	11.00
Precuneus, Posterior Cingulate	440	0.000	Both	0	−50	36	10.36
Main Effect of Self Condition							
Inferior Temporal Gyrus	236	0.000	Left	−48	−68	−2	16.86
Insula, Putamen	403	0.000	Right	36	0	6	16.82
Precuneus, Fusiform	1326	0.000	Right	22	−64	58	16.39
Group by Emotion Condition							
Middle Temporal Gyrus	393	0.000	Left	−64	−40	−4	12.86
Group by Self by Emotion Conditions							
Medial Temporal Cluster: Hippocampus, Parahippocampus, Amygdala	323	0.000	Right	24	−2	−18	10.94
Medial Temporal Cluster: Hippocampus, Parahippocampus, Fusiform, Amygdala	280	0.000	Left	−28	−28	−12	9.76

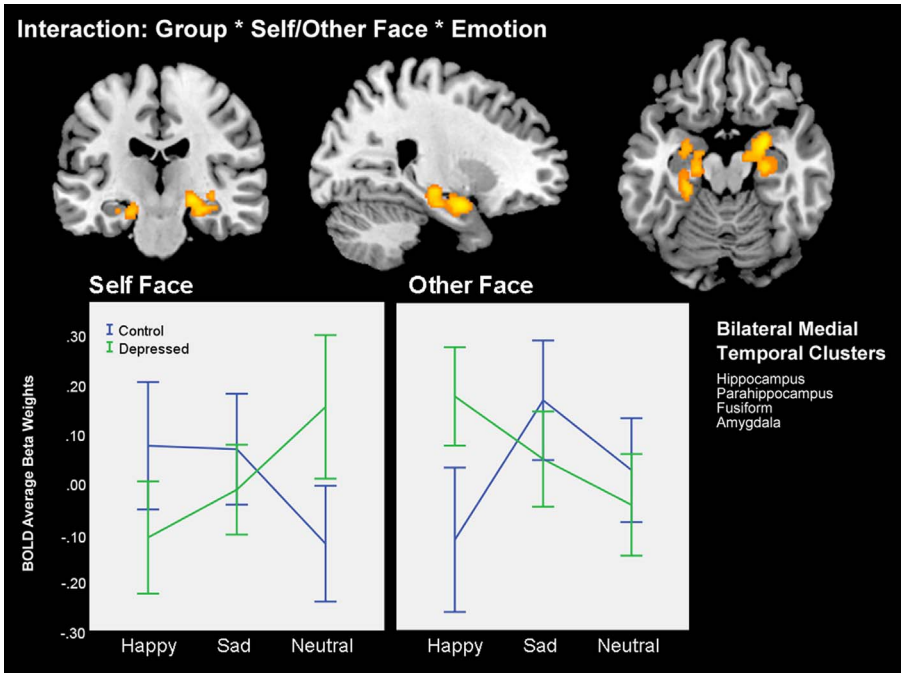

Fig. 1. Group by Self by Emotion Interaction. During self face recognition depressed youth show higher activity in medial temporal limbic areas to the neutral but less to the happy expression, while controls show the opposite patterns. During recognition of other faces depressed participants showed higher activity in this clusters to the happy face and less to the neutral face, while controls show the opposite pattern. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2. Neuroimaging results

3.2.1. Group by Self by Emotion Interaction

A 3-way interaction group (depressed vs. control) x self condition (self vs. other) x emotion (happy vs. sad vs. neutral) was noted (Table 2). Specifically, a whole-brain significant effect was seen in clusters encompassing bilateral medial temporal limbic and face-processing structures: the hippocampus, parahippocampus, amygdala and fusiform cortex; $F_{Right\ and\ Left}$ (2, 470) = 10.94, 9.76. To clarify this 3-way interaction, follow up *t*-test contrasts in SPM 12 were conducted, and the same bilateral medial temporal clusters (k) were noted: Right cluster MNI = 28 −38, 2, k_{size} = 2141; Left cluster MNI = −28 −28 −12, k_{size} = 326. This 3-way interaction is represented in line graphs in the lower portion of Fig. 1, and it is described below split by the self condition, first for the self face and next for the other face.

3.2.2. Self Face

Fig. 1 (left panel) show that depressed youth show less medial temporal limbic activity to the happy expression versus the neutral expression during self-recognition. Controls show the opposite: more activity to the happy expression versus the neutral **e**xpression during self-recognition, as confirmed by both SPM 12 *t*-test contrasts and within-subject contrasts $F(1, 79) = 23.50$, $p < 0.01$ in SPSS. The groups, however, did not differ in activity during the sad expressions.

3.2.3. Other face

Fig. 1 (right panel) shows that depressed youth exhibited more activity for the happy vs. the neutral expression during recognition of the other face, $F(1, 42) = 8.50$, $p < 0.01$. By contrast, controls did not differ in activity between the neutral and happy expression during recognition of other faces, $F(1, 37) = 2.19$, $p = 0.15$. As before, the groups do not differ for the sad facial expressions $F(1, 79) = 2.47$, $p = 0.12$ and neither group shows different levels of brain activity between the sad and neutral facial expressions.

An alternate way of visualizing and describing this 3-way interaction (Supplemental Fig. 3) is if we subtract neural activity during the neutral faces from activity during the happy faces and call that variable "happy vs. neutral facial expression" the interaction can be described as follows: depressed youth show more medial temporal limbic activity for the happy vs. neutral facial expression while processing other faces and less activity for the happy vs. neutral facial expression while processing their own face. By contrast healthy control youth show more medial temporal limbic activity for the happy vs. neutral facial expression while processing their own face and show close to 0 activity for happy vs. neutral facial expressions for the other face. This is depicted in the upper right corner of supplemental figure 3.

3.2.4. Group by emotion interaction

Fig. 2 and Table 2 show that depressed youth show higher left middle temporal gyrus (MTG) activity to all neutral faces compared to controls, who show lower activity to neutral faces. However, depressed youth show less activity to all sad faces compared to controls, who show more activity in this area $F(2,470) = 12.86$. Both groups have similar MTG activity in this area to all happy faces.

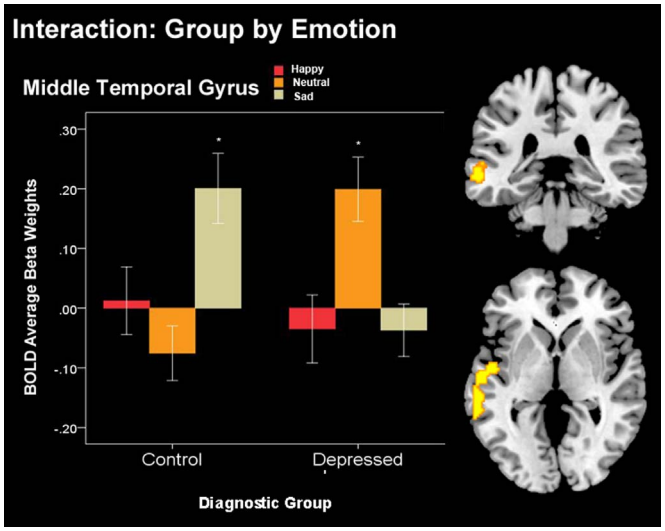

Fig. 2. Group by Emotion Condition Interaction. Depressed participants showed higher activity in the left middle temporal gyrus (MTG) for neutral faces but lower for sad faces, while healthy controls showed the opposite pattern. The groups do not differ on MTG activity for happy faces. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

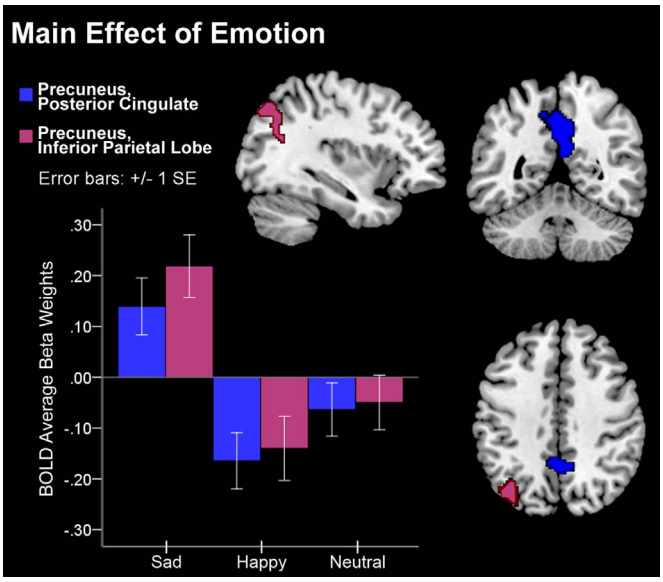

Fig. 3. Main Effect of Emotion. All participants show higher precuneus, parietal and posterior cingulate cortex activity to sad faces versus all other faces. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2.5. Main effect of emotion

Fig. 3 and Table 2 shows that all participants showed higher activity in the posterior cingulate (PCC), precuneus, and inferior parietal lobe for all sad faces compared to all neutral and happy faces, $F(2,470) = 11.00\text{-}10.36$.

3.2.6. Main effect of group

Fig. 4 and Table 2 show that the depressed group had lower activity in the cuneus but higher activity in postcentral and precentral gyri compared to the control group.

3.2.7. Main effect of self condition

Table 2 shows that all participants showed more activity in right precuneus, fusiform, insula and putamen and left inferior temporal gyrus to the self versus other faces, $F(1,470) = 16.86\text{-}16.82\text{-}16.39$. See Supplemental Fig. 2 online.

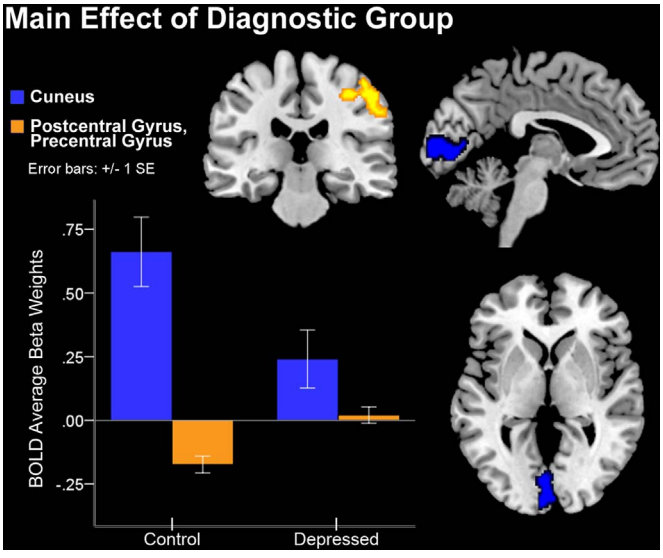

Fig. 4. Main Effect of Group. Compared to healthy controls, depressed adolescents show lower cuneus but higher postcentral gyrus activity during a self recognition task across all three emotional (happy, sad, neutral) and self conditions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2.8. Effects of medication within depressed

Analyses showed an effect of medication in the right superior and inferior parietal lobule, $F(1,43) = 28.59$, and in the left, $F(1,43) = 16.37$, and right, $F(1,43) = 15.66$, inferior and middle frontal gyrus, see Supplemental Table 1. Medicated depressed youth showing *lower* brain activity than non-medicated youth during all conditions in those areas There was an interaction effect between medication and self condition in the superior temporal gyrus $F(1,43) = 17.76$. Medicated depressed youth showed *lower* brain activity than non-medicated during the other face condition.

4. Discussion

4.1. Summary of results

Depressed youth showed lower MTL activity while recognizing their own happy versus their own neutral faces compared to controls who showed the opposite pattern. Depressed youth showed higher MTL activity while recognizing a stranger's happy versus neutral face, whereas controls did not differ in activity (Fig. 1). Depressed youth had higher left middle temporal gyrus (MTG) activity to all neutral faces compared to controls, but less activity to all sad faces compared to control (Fig. 2). All participants showed higher PCC and inferior parietal lobe activity to sad faces (Fig. 3). Depressed youth also showed lower cuneus activity than controls, but higher post- and precentral gyrus activity for all conditions (Fig. 4). In all participants, we observed higher precuneus, PCC and parietal cortex activity while viewing sad faces and higher activity in the right precuneus, fusiform, insula and putamen for all self versus other faces. Finally, medicated depressed youth showed less activity in the right superior and inferior parietal lobule and in the left and right inferior and middle frontal gyrus compared to non-medicated youth across all conditions.

4.2. Group by self by emotion interaction

Our primary hypotheses were that, during self-face recognition, depressed youth would show less MCS and limbic activation to all happy expressions compared to healthy controls, and more MCS and limbic activation to self sad faces. These predictions were partially supported. Depressed youth showed less activation in MTL than controls when recognizing their own happy versus neutral faces (see Fig. 1, lower left corner line graph), but also higher MTL activity when recognizing their neutral self-face condition compared to controls. These patterns of neural activity were reversed for the other-face condition, with depressed showing higher MTL activity during recognition of happy other-faces and lower during neutral other-faces (Fig. 1, lower right corner line graph). However, we did not observe differences for MCS activity between the groups.

MTL areas sustain several functions. The hippocampus and parahippocampus enable declarative memory, fear conditioning, and retrieval of emotional memories (Bellace et al., 2013). The amygdala enables classical fear conditioning (Klumpers et al., 2015) appetitive motivations, emotional salience, and emotionally charged memories (Neugebauer, 2015; Toyoda et al., 2011). It is also an area engaged by face processing (Fusar-Poli et al., 2009). The fusiform enables social cognition and face processing (Kanwisher et al., 1999; Tong et al., 2000). As noted, the interaction effect was observed in these MTL regions but not in MCS (i.e. right precuneus), which was instead more active in all participants for the self face. This suggest that depressed non-maltreated and healthy controls engaged MCS equally when recognizing their own versus others' emotional faces, but they differ in functions that are enabled by the MTL. However, in a larger sample of depressed youth, including youth who experienced abuse, depressed

suicidal youth showed hypoactivity in both MCS and MTL structures (Quevedo et al., 2016). Together, our present and previous published results suggest that abuse and/or suicidality might be linked to impairment in functions supported by both MCS and limbic structures (for example both emotional salience and awareness of positive-self cues). By contrast, non-maltreated depressed youth might experience positive self-cues as less emotionally salient but they could have similar MCS-mediated awareness of such cues as controls. To confirm that these are in meaningful neuropsychological differences between sub-populations of depressed youth, future research would need to employ tasks that contrast emotional salience (e.g. note the emotion) with awareness of self-referential cues (e.g. identify your face) in these groups.

MTL hypoactivation during recognition of the happy versus neural self-face among depressed youth is consistent with literature showing low positive affect and reduced saliency of rewards as fundamental to the pathophysiology of depression, perhaps especially in adolescence (Davey et al., 2008). Depressed patients evidence hyperactivation to negative and hypoactivation to positive faces, particularly in the amygdala, insula, parahippocampal gyrus, fusiform face area, and putamen (Stuhrmann et al., 2011). Our findings suggest that, during self-face recognition, these biases are focused on self-relevant cues. These results might pertain first to the uniqueness of self-relevant information, and second to how depression disturbs normative positive biases (i.e. preferential emotional responses to the self happy face versus other happy faces) that characterize healthy self processing (Ma and Han, 2010). Future research contrasting distinct functions enabled by the MTL (encoding, retrieval, emotional saliency, identity) should be conducted in depressed and healthy adolescents.

As part of the 3-way interaction, we observed higher MTL activity in depressed adolescents, relative to controls, while recognizing the other happy versus the other neutral face. Limbic hyperactivation during recognition of unfamiliar happy faces in depression was surprising, as previous studies have reported limbic *hypoactivation* to unfamiliar happy faces in depression (Fu et al., 2007). However, those studies did not include both blocks of self and unfamiliar faces or require identity recognition. MTL activation signals information that is important in the current environmental demands, and thus its engagement during a given stimulus is likely to be context dependent and to vary according to subjective experience (Zaretsky et al., 2010). A self-recognition task changes the emotional salience attributed to familiar and unfamiliar emotional faces, and this context-dependent modulation appears to differ in healthy and depressed individuals. Another possibility is that among depressed participants, disadvantageous social comparison elicited by face recognition might be exacerbated. Perhaps, exposure to other's happy expressions are more salient *in comparison* with their own given that in this study depressed youth reported lower self-esteem and attributional style versus healthy controls.

Higher MTL responses to neutral self-faces but not to sad self-faces in depressed youth is intriguing. Neutral self-faces might have been perceived by depressed youth as more negatively salient versus sad faces. It might be that restrained neutral self-expressions might have been perceived by depressed youth as closer to their own experience of sadness than their overt sad self faces. Alternatively, neutral self faces might have been perceived as more threatening, given their ambiguity. Research suggests that neutral faces are processed differently by individuals with MDD, anxiety and schizophrenia (Filkowski and Haas, 2016). Combined with lower limbic activity during happy self-faces, higher MTL activity during neutral self-face recognition might reflect higher negative emotional salience of neutral self-cues versus happy cues, perhaps due to symptoms, such as anxiety, anhedonia and/or restricted affect that are common to these disorders with altered neural function to neutral faces (Filkowski and Haas, 2016). This notion is supported by post-hoc correlations showing that higher MTL activity during neutral self face recognition was linked to higher adolescent reported anxiety in the whole sample (Supplementary Table 2). Thus, the ambiguity of neutral self faces might have been very salient for the more anxious youth within the depressed group. It must be noted, however, that categorical comparisons of anxious depressed versus depressed and control youth did not yield this MTL cluster. These ideas are thus speculative, and future work should examine how self-processing and emotion might interact in ways that influence the activity of MTL areas. Ultimately, which mental processes explain the results need to be tested by employing both self versus other processing and other unfamiliar faces (e.g. distinguishing two unfamiliar faces) across emotional conditions, labeling of emotions, passive viewing, and self vs. other recognition to determine whether emotional saliency, processing of self-cues, or a combination of the two explain the current findings.

4.3. Group by emotion interaction

Our hypothesis that depressed adolescents would differ in neural activity while viewing sad self faces compared to controls was not confirmed. Instead all participants showed higher MCS activity (precuneus, PCC and parietal cortex) for all sad faces. Higher neural activation during processing of sad faces is consistent with previous work showing greater attention towards sad faces among depressed individuals (Vrijen et al., 2016). However, a group by emotion interaction showed that depressed youth had higher middle temporal gyrus (MTG: BA 21, 22 and 42 which included some insula) activity to all neutral versus all sad faces compared to healthy controls, who showed the opposite pattern. The groups did not differ on MTG activity for all happy faces. The MTG has been shown to respond to identity "cross-classification", i.e. to both facial and vocal identity processing (Awwad Shiekh Hasan et al., 2016), and it is also engaged during self versus other face recognition (Verosky and Todorov, 2010). Methodological differences likely play a role in our results, as limbic responses to negative expressions in depression may depend on the nature of the task. Combining self and unfamiliar faces, as well as emotionally valenced non-face images, may enable future studies to out whether these discrepancies are due to emotional valence or to social comparison differences (i.e. between the self and other faces for emotional conditions) between depressed and healthy adolescents.

4.4. Heightened activity to sad faces

Higher precuneus, PCC and parietal cortex activity was noted for all sad faces in all participants. This is consistent with engagement of regulatory strategies, as higher PCC and precuneus activity has been observed during regulation of negative emotions (Koenigsberg et al., 2010). Alternatively, this finding might indicate higher attention dedicated to all negative faces, as these areas are engaged to a greater extent as negative valence increases (Posner et al., 2009). Finally, sad expressions might require higher engagement of MCS to solve the self-recognition task due to increased regulatory demands. More research is necessary to establish whether this is an effect of valence or of self-relevance processing in the context of negative valence.

4.5. Main effect of group

Depressed youth showed lower cuneus activity, but higher post- and precentral gyrus activity than controls for all conditions. The cuneus is supports visual processing and stereoscopic vision (Nakodomari et al., 1999). Its activity is also associated in meta-analyses primarily with judgments of others (Denny et al., 2012) and in Bipolar I patients, higher cuneus volume is linked to better inhibitory control (Haldane et al., 2008), which might be less well supported by the cuneus during the present task for the depressed participants. Finally, the post- and precentral gyrus support sensorimotor functions (Cooke and Graziano, 2004). This activation might represent a compensatory mechanism and/or a higher need for behavioral preparedness to respond to the task among depressed youth.

4.6. Effect of self condition

Higher precuneus, fusiform, inferior temporal gyrus, insula and putamen activity for recognition of self versus other faces, replicate prior findings of a right sided mid-cortical preferential activity for self faces (Sugiura et al., 2005) as well as involvement of the precuneus and fusiform, which index greater personal saliency and face-related stimuli (Kircher et al., 2000; Platek et al., 2006, 2008).

4.7. Effects of medication

Medication was a covariate in our main analyses, but comparing medicated versus unmedicated depressed youth yielded lower prefrontal and parietal activity during all conditions. Previous work also suggests that medication diminishes cortical activity in depressed patients during self-referential processing (Lemogne et al., 2010). It is possible that medication lowers the need for higher cognitive resources during social and self cognition but it is unknown whether this is also the case for other non-social cognitive processes.

4.8. Reaction time and accuracy

Unlike other studies (e.g., Auerbach et al., 2015) we found no behavioral differences in judging faces as "self" or "other" in terms of reaction times or accuracy. This is not an unusual finding, several studies examining emotion processing report neural, but not behavioral, differences between clinical and control groups (e.g., Beesdo et al., 2009; Monk et al., 2008). Methodological differences likely explain the results. First our study did not require participants to make evaluations about themselves. Presence of circuitry but not behavioral differences may indicate differences in how depressed versus non-depressed adolescents *implicitly* evaluate themselves regardless of behavior. Second, prior studies focused on the emotional valence of stimuli or/and involved passive exposure to emotionally valenced stimuli. Our task required self recognition, so emotional valence may have been less salient to detect diagnostic status in behavioral measures. Third we eliminated the most ambiguous stimuli (face morphs between 45% and 60%) which restricted the range of emotionally charged stimuli where valence could have influenced reaction time and accuracy.

4.9. Limitations

Twenty two out of 43 depressed youth were medicated, yet covarying for medication yielded significant brain activity differences between healthy and depressed youth. Notably, the same results were yielded when covariates were not included in the model. Nevertheless, the mechanisms for activation differences during self-processing in depression and for modulation of cortical activity by medication within depressed youth should be further examined. Depression might influence the production of the participant's facial expressions that were used as stimuli. However, ratings of the intensity of facial expressions yielded no differences between groups. Subtle differences in emotional expressions of depressed versus control participants might still be present as ratings were not conducted using a standardized empirical method, yet it is unlikely that this would explain neurophysiological results, given absence of reaction time (RT) differences as well as similar accuracy for self-recognition. More likely, the actual emotional intensity of the presented self-faces was similar between the groups, but depressed youth differ in perceptual processes, emotional saliency and self-awareness regarding positive self-relevant and neutral ambiguous facial information.

5. Conclusion

Given that depression is linked to alterations in both emotion and self-processing, the current study assessed neural activation in healthy and depressed youth to a novel task that combined emotion processing with self-face recognition. Depression was associated with decreased brain activity in regions that support emotional and associative processing while viewing positive self-faces. In addition, depressed adolescents showed increased limbic and cortical processing, measured via BOLD fmri activity, for neutral self-faces. These results suggest that depression in adolescents is associated with hypoactive associative and emotional processing of positive self-related visual information and hyperactive processing for this same information in others. These emotional and cognitive biases could have implications for reward processing more generally and for self-development in particular, given that adolescence is a sensitive period for self-processing.

Clinical relevance

Self-development is a key developmental task during adolescence. The ways in which socially significant self -relevant signals (e.g. the self face) are used and remembered might have long lasting impact in social behavior and mental health. This might be particularly the case during adolescence, given how young people use images of their faces ("selfies") as an extension of the self, to which significant attention and time is devoted to create and influence social circles. There is still no knowledge about how use of the self face or processing of other faces in virtual social networks is influencing long term self-development or depression risks. However, technology-based social comparison and feedback-seeking has been associated with depressive symptoms over time (Nesi and Prinstein, 2015) and social media has been found to impact self-esteem and body image (Richards et al., 2015). Given our findings of low activity in areas supporting emotional, associative and memory processes during recognition of the self happy face among depressed youth, clinicians may need to examine how depressed or at-risk adolescents use the self face as a means of communication, and possibly begin to address how the evaluations of their face versus others in social media might be increasing or perpetuating existing risks for mental illness. Conversely, the self face might serve as a new intervention tool to perhaps train associations and memories that youth construct around their own images. Changing emotional associations regarding the self face (for example by pairing it with positive memories and/or re-directing attention to flattering features) might be a way to forestall the emergence or perpetuation of emotional biases that eschew positive self-relevant information in at-risk or depressed youth.

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Appendix A. Supporting information

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