Self-compassion and dorsolateral prefrontal cortex activity during sad self-face recognition in depressed adolescents

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Background: Given the prevalence of adolescent depression and the modest effects of current treatments, research ought to inform development of effective intervention strategies. Self-compassion is inversely associated with depression, and self-compassion interventions have demonstrated promising effects on reducing depression. However, little is known about the neural mechanisms underlying that relationship. Maladaptive self-processing is a characteristic of depression that contributes to the onset and chronicity of depression. Because our own face is an automatic and direct cue for self-processing, this study investigated whether self-compassion was associated with neural responses during sad vs. neutral self-face recognition and explore their relationship with depression severity in depressed adolescents and healthy controls. **Methods:** During fMRI, 81 depressed youth and 37 healthy controls were instructed to identify whether morphed self or other faces with sad, happy, or neutral expressions resembled their own. **Results:** Self-compassion correlated negatively with activity during sad vs. neutral self-face recognition in the right dorsal anterior cingulate cortex in the total sample, and in the right posterior cingulate cortex/precuneus in healthy controls, respectively. In depressed adolescents, higher self-compassion correlated with *lower* activity during sad vs. neutral self-face recognition in the right dorsolateral prefrontal cortex (DLPFC), implying that less cognitive effort might be needed to avoid dwelling on sad self-faces and/or regulate negative affect induced by them. Moreover, higher self-compassion mediated the relationship between lower DLPFC activity and reduced depression severity. **Conclusions:** Our findings imply that DLPFC activity might be a biological marker of a successful self-compassion intervention as potential treatment for adolescent depression.

Keywords: fMRI; depression; adolescence; self-compassion; self-processing.

Depression is one of the most burdensome mental illnesses (Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2015) and is a robust predictor of suicide (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015). The onset of major depressive disorder often occurs during adolescence (Steinberg & Morris, 2001), partly due to the development of neural circuitry underlying self-processing which results in heightened self-consciousness and susceptibility to peer influence (Sebastian, Burnett, & Blakemore, 2008). Self-processing involves the perceptions, memories, and representations of one's self. Research has shown that depressed individuals show excessive self-focus and negatively biased self-processing (Beck, 2008; Bradley et al., 2016). In particular, excessive self-focus is thought to lead to self-regulatory cycles that attempt to reduce the perceived discrepancy between the current self and a salient "ideal" standard (Carver & Scheier, 1998), and failure to exit such cycles might cause onset or endurance of depression (Beck, 2008; Pyszczynski & Greenberg, 1987). Because adolescence is a key window for self-identity development characterized by heightened self-focus and introspection (Sebastian et al., 2008), to inform future treatment strategies for adolescent depression, we need to identify psychological dimensions that modify depressed adolescents' maladaptive self-processing, especially the neural mechanisms underlying such dimensions.

Self-compassion is an emotional and cognitive regulatory strategy which involves self-kindness, recognition of our common humanity and mindfulness and reduced self-judgment, isolation and over-identification in the face of negative life events (Neff, 2003b; Terry & Leary, 2011). Self-compassion is inversely associated with depression among adults (MacBeth & Gumley, 2012; Neff, 2003a; Trompetter, de Kleine, & Bohlmeijer, 2017; Van Dam, Sheppard, Forsyth, & Earleywine, 2011) and adolescents (Marsh, Chan, & MacBeth, 2018; Neff & McGehee, 2010; Tanaka, Wekerle, Schmuck, Paglia-Boak, & Team, 2011), and less rumination, avoidance and worry mediate that inverse relationship (Krieger, Altenstein, Baettig, Doerig, & Holtforth, 2013; Raes, 2010). Self-compassion interventions have demonstrated promising effects on reducing depression and/or distress among patients with diabetes or cancer (Campo et al., 2017; Friis, Johnson, Cutfield, & Consedine, 2016) and adolescents (Bluth, Gaylord, Campo, Mullarkey, & Hobbs, 2016). Considering that self-compassion involves coping processes "to alleviate one's suffering and to heal or soothe oneself with kindness" through a "recognition of one's common humanity" (Neff, 2003a), self-compassion may be a protective dimension that modulates maladaptive negative self-processing found in depressed youth.

So far, few studies have examined the neural basis of self-compassion. It has been found that state-level self-reassurance engaged the temporal pole and insula in response to negative vs. neutral events (Longe et al., 2010), while the traditionally studied trait-level self-compassion was negatively associated with the functional connectivity between ventromedial prefrontal cortex (VMPFC) and right amygdala during negative vs. neutral social feedback (Parrish et al., 2018). To our knowledge, no study has investigated how self-compassion relates to neural activity during self-processing, let alone the neural basis underlying the relationship between self-compassion and depression. Nevertheless, studies on the neural basis of self-processing in depressed patients have begun to shed light on this topic.

Lemogne et al. (2009) found that both depressed patients and healthy controls (HCs) activated medial prefrontal cortex (MPFC) in self-judgements vs. general judgements, but depressed patients showed greater activity in dorsomedial prefrontal cortex (DMPFC) and dorsolateral prefrontal cortex (DLPFC), as well as increased functional connectivity between them and dorsal anterior cingulate cortex (dACC). Such findings may represent the neural correlates of excessive self-focus (MPFC), its subsequent conflict monitoring (dACC), and a secondary compensatory mechanism attempting to use cognitive control (DLPFC) to exit the self-critical regulatory cycles in depressed patients. On the other hand, Bradley et al. (2016) found that both depressed adolescents and HCs activated cortical midline structures (CMS) in response to self-judgments compared to general judgments, but depressed youth recruited the posterior cingulate cortex (PCC) and precuneus more for positive self-judgments. These findings suggest that CMS and DLPFC hyperactivity may underlie maladaptive self-processing in depressed patients.

Compared to self-descriptive psychological attributes that elicit primarily verbally mediated self-processing, the self-face is an automatic and more direct cue for investigating self-processing (Kircher et al., 2001). Empirical studies and meta-analyses have shown that among healthy adults, while both verbal and facial self-processing engage the dACC and precuneus/PCC activity (Hu et al., 2016; Platek, Wathne, Tierney, & Thomson, 2008; Sugiura et al., 2005), verbal self-processing additionally activates the MPFC (D'Argembeau et al., 2007; Hu et al., 2016; Northoff et al., 2006), and recognizing our own face particularly activates a right lateral cortical network, including the right DLFPC (Hu et al., 2016; Morita et al., 2008; Platek et al., 2008). These networks are altered in depressed adolescents during emotional self-face recognition. Compared to HCs, depressed youth displayed increased right DLPFC activity during self-other face recognition, decreased MPFC and limbic (amygdala/hippocampus) activity during happy self vs. other face recognition (Quevedo et al., 2016), and decreased limbic (amygdala/hippocampus) and fusiform activity during happy versus neutral self vs. other face recognition (Quevedo et al., 2018). Furthermore, depressed adolescents displayed greater amygdala functional connectivity with DLPFC, DMPFC and precuneus during self-other face recognition compared to HCs (Alarcón, Sauder, Teoh, Forbes, & Quevedo, 2019). Abnormal brain function has also been noted during the processing of unfamiliar faces, for example Henderson et al. (2014) found that depression severity correlated positively with activity in VMPFC, insula and limbic regions (e.g., amygdala, putamen) during sad face-processing among depressed adolescents. Collectively, these studies yielded cortical neural loci of maladaptive self-processing in depressed youth, perhaps especially for self-face recognition. These studies converge on altered (often heightened) DLPFC activity and higher limbic to DLPFC connectivity in depressed youth during self-other face recognition compared to healthy youth, again suggesting higher cognitive effort and/or compensatory cognitive control to counteract (or engage on) harsh self-judgments or ruminative thinking during self-processing.

The current study

The goal of this paper is to investigate whether neural activity during self-face recognition in loci previously associated with maladaptive self-processing among depressed adolescents and adults (e.g., CMS and DLPFC) relates to self-compassion and might further explain the inverse relationship between self-compassion and depression. Due to a lack of evidence on this topic, this study is both novel and exploratory in its aims.

Because self-compassion is regarded as a protective psychological dimension against depression and sadness, our study focused on neural activity elicited by sad self-face recognition. Given that self-compassion entails less negative self-processing in response to suffering and negative events (Neff et al., 2018), we hypothesized: that self-compassion would be associated with reduced neural activity elicited by sad vs. neutral self-face recognition in regions undergirding abnormal self-processing in depressed youth, such as CMS (e.g., MPFC, ACC, PCC/precuneus) and DLPFC, which would in turn relate to reduced depression severity. If the hypotheses above were supported, we would further explore whether the data fitted one of the three models that described the relationship between neural activity during sad vs. neutral self-face, self-compassion, and depression severity (Figure 1). We only set up models with self-compassion as the antecedent variable of depression severity because previous research showed that self-compassion interventions reduced depression (Bluth et al., 2016; Campo et al., 2017; Friis et al., 2016), implying a causal effect of self-compassion upon depression severity. These hypotheses were tested separately (1) in the total sample comprised of both HCs and depressed adolescents, as well as (2) in the HC and (3) in the depressed sub-sample.

Methods

Participants

Recruitment and screening procedures were fully described in previous publications (Alarcón et al., 2019; Quevedo et al., 2016) and are only briefly presented here. Adolescents and their caregiver(s) were recruited from psychiatric clinics at the Universities of Minnesota (in Minneapolis) and Pittsburgh. Exclusion criteria included: IQ < 70, primary diagnosis other than depression, and left-handedness. Depression and presence of other psychiatric disorders were diagnosed by clinical evaluations with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) interview (Kaufman et al., 1997). All clinical interviews were videotaped and scored to determine diagnostic agreement. Three PhD-level experts in child development reviewed and scored the videotapes with 98% agreement in symptoms severity and diagnosis. Given high comorbidity of anxiety and depression, a common comorbidity in both adolescent and adult patients, depressed adolescents with a comorbid diagnosis of anxiety disorder were not excluded. In the present study, 72.84% (N = 59) of the depressed sample also qualified for an anxiety disorder. Diagnostic discrepancies (i.e., disagreements between the coders) were resolved by the senior author, a licensed clinical psychologist. A total of 82 depressed adolescents (DEPs) and 37 HCs consented to participate in the study. This is a rather large total sample size for an imaging study. One participant whose brain images showed a large area of signal dropout in the right visual cortex was excluded from analyses. The final sample consisted of 81 DEPs (62 scanned at the Minneapolis site and 19 at the Pittsburgh site) and 37 HCs (21 at the Minneapolis site and 16 at the Pittsburgh site). Sample characteristics are presented in Table S1. Eight out of the 118 participants were excluded from behavioral analyses because their behavioral responses during the fMRI task were missing. This study was approved by the Institutional Review Boards at both the Universities of Minnesota and Pittsburgh.

Measures

Self-compassion was measured using the Self-Compassionate Reaction Inventory (SCRI) (Terry, Leary, Mehta, & Henderson, 2013), which lists eight common negative events, and for each event, participants are asked to endorse two responses from four given reactions – two of which are self-compassionate and two of which are not self-compassionate. A total score is calculated by summing up the number of self-compassionate responses endorsed (ranging from 0-16). Scores in this questionnaire have been shown to highly correlate with those of Neff's (2003a) Self-Compassion Scale and the two scales have comparable patterns of convergent and discriminant validity (Terry et al., 2013). A continuous measure of depression severity was measured using the Children's Depression Rating Scale - Revised (CDRS-R) (Poznanski & Mokros, 1996), which was widely used and showed good reliability among adolescents ($\alpha = 0.74 \sim 0.92$) (Mayes, Bernstein, Haley, Kennard, & Emslie, 2010).

fMRI task

Participants completed the Emotional Self-Other Morph-Query (ESOM-Q) task within 1-2 weeks after their clinical assessment. This task was described in previous publications (Alarcón et al., 2019; Quevedo et al., 2018; Quevedo et al., 2016). See Supplements for details about stimuli generation of this task. In the scanner, participants were exposed to photographs of 150 faces displaying happy, sad, or neutral expressions with the task of identifying whether the picture looked like them or not, by pressing one of two buttons with fingers on the right hand (Figure 2). The task consisted of one run and lasted 10 mins 54 secs. It was comprised of six different blocks of faces (self-happy, other-happy, self-sad, other-sad, self-neutral, other-neutral). Instructions were presented at the beginning of each block and lasted 6 sec each. At the start, the halfway and the end of each 70 sec block an 18 sec rest period (12 rest periods in total) with a presented fixation cross was announced by the phrase “rest now”. Each face was displayed for 2 sec followed by a 0.5 sec fixation cross. Blocks contained faces with high (i.e., self blocks) or low degrees (i.e., other blocks) of facial morphing between the self and the other face. This resulted in blocks comprised of self faces or unfamiliar faces within happy, sad or neutral categories. Blocks were presented in 5 counterbalanced task orders and each contained 28 photos of faces presented randomly with regards to morphing percentages within any given self by emotion block, with the following means and standard deviation of morphs: **Self blocks**: M_{self}=83%, SD=12%, Min_{self}=65%, Max_{self}=100%; **Other blocks**: M_{self}=18%, SD=12%, Min_{self}=0%, Max_{self}=35%. Ambiguous stimuli (i.e., with 40%-60% of self-features) were not used in any block. Within each of the 6 blocks, 4 faces of high opposite percentage in self level were shown to avoid response sets and keep the participants attentive to the actual identity of the faces (Other block four faces=90% or 80% self; Self block four faces=90% or 80% other). These incongruent faces were excluded from all present analyses. E-Prime Software was used to present stimuli and record reaction time and accuracy.

fMRI data acquisition

Neuroimaging data were collected using 3T Siemens Trio MRI scanners at the two data collection sites. Structural 3D axial MPRAGE images were acquired in the same session (TR/TE: 2,100 ms/3.31 ms; TI: 1,050; flip angle = 8◦; FOV: 256 × 200 mm; matrix = 256 × 200; 176

slices, slice thickness =1 mm). Mean blood oxygenated level depended activity (BOLD) images were obtained using a gradient echo EPI sequence (TR/TE = 3,340/30 ms, flip angle = 90°, FOV = 200 × 200 mm; matrix 80 × 80; 60 slices, slice thickness = 2 mm).

Image pre-processing

Scans were preprocessed with SPM12. Data for each participant was realigned to the first volume in the time series to correct for head motion. Realigned images were co-registered with subject's anatomical image, segmented, normalized to the MNI template, and spatially smoothed with a Gaussian kernel of 7mm FWHM. Volumes with movement > 2 mm or rotations > 0.587 or that had global signal intensities greater than 9 were removed from first-level analysis using Artifact Detection Tools (ART) software (http://web.mit.edu/swg/software.htm).

Self-report analyses

Independent-sample t-tests were conducted to determine whether self-compassion and depression severity differed between diagnostic groups (DEP/HC). Moderation analyses were performed with Preacher and Hayes's (2008) PROCESS package to test whether self-compassion had a main effect on depression severity and whether diagnostic group moderated the effect. Bias-corrected 95% confidence intervals (CIs) of the effects were estimated with bootstrap simulations of 5,000 iterations and were evaluated for statistical significance using the criteria of excluding zero in the CIs.

fMRI analyses

Imaging data were processed and analyzed with SPM12. Block design first level analyses were conducted with the rest period and 4 incongruent faces in each block (condition) excluded from modeling. First-level general linear models (GLMs) with predictors including six conditions (sad self, neutral self, happy self, sad other, neutral other, happy other) and nuisance regressors (including six movement parameters) were estimated for each participant at each voxel, resulting in t-statistic images for each of the six conditions. Contrasted images of sad self > neutral self were created for second-level analyses. Because our main hypotheses were only about sad self-face processing, fMRI analyses about happy self-face and sad other-face processing are described in the Supplements.

Identification of neural correlates of self-compassion during sad vs. neutral self-face recognition in the total sample. Neural correlates of self-compassion were examined in the total sample. We also explored whether the correlates of self-compassion would differ by diagnostic group. Specifically, a second-level whole-brain regression model with self-compassion, diagnostic group (DEP/HC) and a self-compassion by diagnostic group interaction as covariates of interest, and with scanning site (Minneapolis or Pittsburgh) as confounding covariate, were estimated. Whole-brain cluster-extent thresholds of $p_{FWE} < .05$ were calculated using Monte Carlo and 3dClustSim in AFNI 18 with a voxel-wise threshold of $p_{uncorr} < .001$. Average BOLD activations of each cluster were extracted for visualization and correlation analyses with depression severity.

Identification of neural correlates of self-compassion during sad vs. neutral self-face recognition in the HC and in the DEP sub-sample separately. Analyses with the same details as in the total sample were conducted in the HC and in the DEP sub-sample separately, the only difference being that there were no diagnostic group or group by self-compassion interaction regressor in the models.

Exploratory mediation analysis. To examine whether the following three variables, (1) self-compassion, (2) the neural substrates of self-compassion during sad vs. neutral self-face recognition and (3) depression severity, fitted one of the three mediation models as depicted in Figure 1, we first tested whether the neural substrates of self-compassion correlated with depression severity in the total sample as well as in the HC and in the DEP sub-sample separately. If the correlation in any (sub-) sample was significant, mediation analysis was further performed with Preacher and Hayes's (2008) PROCESS package.

Results

Self-report results

Independent-sample t-tests showed that DEPs reported lower levels of self-compassion than HCs, $t(116) = -7.30$, $p<.001$ (DEP: 7.00 ± 4.51, HC: 13.11 ± 3.48), and higher depression severity than HCs, $t(116) = 23.06$, $p<.001$ (DEP: 63.32 ± 14.49, HC: 20.27 ± 5.76). Moderation analysis showed that both the main effect of self-compassion (95% CIs: [-0.35, -0.14]) and the diagnostic group by self-compassion interaction effect (95% CIs [-0.25, -0.01]) were significant. Further analyses showed that the conditional effect of self-compassion on depression severity was significant in DEPs (95% CIs: [-0.45, -0.22]), but not in HCs (95% CIs: [-0.27, 0.18]). Behavioral results on response time and accuracy can be found in the Supplements.

fMRI activity results

Neural correlates of self-compassion during sad vs. neutral self-face recognition in the total sample. Whole-brain analysis showed that self-compassion related negatively to activity in the dACC ($r = -0.17$, $p = .059$) during sad vs. neutral self-face recognition in the total sample (Table 1; Figure 3a), yet no suprathreshold clusters were found related to either diagnostic group or its interaction with self-compassion. On the other hand, no suprathreshold clusters related to self-compassion, diagnostic group or their interaction during happy vs. neutral self-face recognition in the total sample (see Supplements). While no suprathreshold clusters related to self-compassion or diagnostic group during sad vs. neutral other-face recognition in the total sample, self-compassion and diagnostic group showed an interaction effect in the left inferior parietal lobule

(IPL) extending to postcentral gyrus and superior parietal lobule (Table S2). Specifically, the correlation between self-compassion and IPL activity is stronger in healthy controls than in depressed youth (see Supplements).

Neural correlates of self-compassion during sad vs. neutral self-face recognition in the HC sub-sample. Whole-brain analysis showed that self-compassion related negatively to activity in the right PCC extending to precuneus (r = -0.62, p < .001) during sad vs. neutral self-face recognition in the HC sub-sample (Table 1; Figure 3b). On the other hand, no suprathreshold clusters were linked to self-compassion during happy vs. neutral self-face recognition in the HC sub-sample (see Supplements), and self-compassion related *positively* to activity in the left post-/precentral gyrus, the left insula and the right postcentral gyrus during sad vs. neutral other-face recognition in the HC sub-sample (see Table S2 and Supplements).

Neural correlates of self-compassion during sad vs. neutral self-face recognition in the DEP sub-sample. Whole-brain analysis showed that self-compassion related negatively to activity in the right DLPFC (r = -0.42, p < .001) during sad vs. neutral self-face recognition in the DEP sub-sample (Table 1; Figure 3c). On the other hand, no suprathreshold clusters were linked to self-compassion during happy vs. neutral self-face recognition or during sad vs. neutral other-face recognition in the DEP sub-sample (see Supplements).

Exploratory mediation analysis. We first conducted correlation analyses between depression severity and activity in the neural substrates of self-compassion during sad vs. neutral self-face recognition identified above in the various samples. Depression severity and neural activity were uncorrelated in both the total sample (dACC: r = -0.07, p = 0.48) and the HC sub-sample (PCC/precuneus: r = -0.11, p = 0.53). In the DEP sub-sample, however, right DLFPC activity during sad vs. neutral self-face positively correlated with depression severity (r = 0.33, p = 0.003).

Given that right DLPFC activity during sad vs. neutral self-face recognition related to both self-compassion and depression severity, mediation analyses were conducted with models depicted in Figure 1. As shown in Figure 4, these analyses showed that the direct effect of right DLPFC activity on depression severity became insignificant once self-compassion was added into the model (Model 1). The indirect effect via self-compassion (95% CIs: [3.16, 9.05]) was significant, indicating that higher self-compassion mediated the relationship between lower DLPFC activity during sad vs. neutral self-face recognition and reduced depression severity. On the other hand, the indirect effect was not significant in either Model 2 or Model 3, and neural activity correlates of self-compassion during sad vs. neutral *other*-face were uncorrelated with depression severity in any (sub-) sample (see Supplements).

Discussion

Our study provides the first evidence that higher right DLPFC activity during self-processing (operationalized as sad vs. neutral self-face recognition) is associated with lower self-compassion and higher depression severity in depressed adolescents. Self-compassion was negatively associated with activity during sad vs. neutral self-face recognition in the dACC in the total sample and in the PCC/precuneus in healthy controls, respectively, but these regions' activities were not significantly associated with depression severity. In depressed adolescents, however, lower right DLPFC activity during sad vs. neutral self-face recognition was associated with both higher self-compassion and lower depression severity. Furthermore, higher self-compassion fully mediated the relationship between lower DLPFC activity and reduced depression severity among just the depressed youth (N=81; Figure 4).

CMS activity and self-compassion. We found that higher self-compassion was associated with lower dACC activity during sad vs. neutral self-face recognition in the total sample, and with lower right PCC/precuneus activity in the HC sub-sample. These structures comprise CMS that have been broadly proposed to enable self-processing (Northoff & Bermpohl, 2004; Uddin, Iacoboni, Lange, & Keenan, 2007), with the dACC involved in assigning salience to the physical self (Hu et al., 2016) and the PCC in getting "caught up" in one's experience (Brewer, Garrison, & Whitfield-Gabrieli, 2013). Previous research has found that self-processing activate these regions in both healthy populations and depressed patients (Alarcón et al., 2019; Bradley et al., 2016; Lemogne et al., 2009; Quevedo et al., 2016). It has been proposed that self-compassion might promote hypo-egoic (i.e., psychological states characterized by relatively little involvement of the self) responses to negative events (Johnson & O'Brien, 2013; Leary & Terry, 2012; Neff & Seppälä, 2016) by involving the concept of common humanity rather than seeing oneself as separate from others (Neff, 2008). Our findings on the inverse relationship between low self-compassion and dACC as well as PCC/precuneus activity (loci within CMS) during sad self-face recognition lends some support to this speculation. In addition to self-processing, the dACC is also associated with conflict monitoring (MacDonald, Cohen, Stenger, & Carter, 2000) and the PCC/precuneus with attentional focus (Leech & Sharp, 2014) and experiential immersion (Brewer et al., 2013). Our findings suggest that adolescents higher in self-compassion might show less vigilant attentional focus or self-involvement (Cavanna & Trimble, 2006; Fransson & Marrelec, 2008) when processing negative self-relevant stimuli (e.g., sad self-face) and/or experience less mental conflicts regarding negative self-relevant cues. However, we did not find significant correlations between dACC or PCC/precuneus activity and depression severity, which suggests that lower activity in these regions during sad vs. neutral self-face recognition does not explain the inverse relationship between self-compassion and depression severity in our study.

DLPFC activity and self-compassion. Within the depressed sub-sample, we found that higher self-compassion was associated with lower right DLPFC activity during sad vs. neutral self-face recognition. Moreover, we found no association between self-compassion and DLPFC activity, but rather *positive* associations between self-compassion and activity in empathy-related regions (e.g., insula, postcentral gyrus, IPL) among healthy controls during sad vs. neutral *other*-face recognition (see Supplements). These findings appear to imply that the inverse association between self-compassion and DLPFC activity is specific to sad self-face recognition. Self-compassion involves less self-criticism during personal failures (Neff et al., 2018) and might promote soothing regulatory responses to negative events that reduce threat system activation and depressive symptoms (Johnson & O'Brien, 2013; Leary & Terry, 2012; Neff & Seppälä, 2016). Our findings provide further evidence to this line of research at the neural level. The higher DLPFC activity associated with lower self-compassion might represent engagement of higher cognitive control (Diamond, 2013; Miller & Cohen, 2001) to avoid dwelling on the sad self-faces or deployment of cognitive regulatory processes to dampen negative emotions elicited by them (Etkin, Büchel, & Gross, 2015; Ochsner & Gross, 2005). Alternatively, heightened DLPFC might underpin ruminative self-critical thoughts elicited by recognizing the sad self-face (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010). This implies that self-compassionate depressed adolescents might be more able to swiftly process negative self-relevant stimuli without dwelling on self-recrimination or might be better at regulating the negative emotions induced by them without engaging cognitive control resources. Because the right DLPFC was consistently activated during self-face recognition in past research (Hu et al., 2016; Morita et al., 2008; Platek et al., 2008), its lower activation during sad self-faces in self-compassionate depressed adolescents might be due to reduced over-identification with the sad-face stimuli or less need of associative cognitive resources for a simple self-face recognition task.

Mediating role of self-compassion. Lower right DLPFC activity during sad vs. neutral self-face recognition was associated with reduced depression severity among depressed youth, and higher self-compassion fully mediated their relationship. Moreover, neural activity correlates of self-compassion during sad vs. neutral *other*-face recognition were uncorrelated with depression severity in any (sub-) sample (see Supplements). These findings appear to suggest that the association between self-compassion, its neural substrates and depression severity is specific to sad self-face recognition. Previous findings with the same dataset found that compared to HCs, depressed adolescents showed higher activity in the right DLPFC during self-other face recognition (Quevedo et al., 2016), and higher DLPFC activity during self-referential processing has also been reported in depressed adults (Lemogne et al., 2009). These results suggest that lower self-compassion might be linked to greater need for cognitive control, self-focused rumination, and/or engagement of cognitive effort during sad vs. neutral self-face recognition and more severe depressions among adolescents. The association between heightened DLPFC activity and lower self-compassion/higher depression severity might be due to the role of DLPFC as the structure enabling self-focused rumination. Rumination is a maladaptive form of self-processing and affect dysregulation that characterizes depression (Cooney et al., 2010). Sad self-face recognition might have temporarily heightened depressed adolescents' rumination concerning their distress and/or engaged the same cognitive processes for redirecting such distress. It is possible that perceived discrepancies between one's current state (or one's sad-self face) and a salient self-relevant standard might have led to regulatory attempts to decrease the discrepancy and/or to avoid self-focus (Lemogne et al., 2009; Ochsner & Gross, 2005). On the other hand, our previous findings with the same dataset found that depressed youth showed greater amygdala connectivity with DLPFC during self-other face recognition compared to HCs (Alarcón et al., 2019). Thus, lower DLPFC activity linked to higher self-compassion might represent less need for cognitive control to regulate distress (including strong emotions borne by limbic areas such as the amygdala) elicited by negative self-relevant stimuli. If these speculations were true, lower DLPFC activity and/or amygdala connectivity with this area might represent (among a host of other processes) a biological marker for more acceptance of personal negative information or less need for top-down regulation of elicited emotional experiences and reduced depression.

Limitations. This study has several limitations. First, although depression was the primary diagnosis, some participants had co-morbid anxiety disorder, though it is quite common particularly among young patients. Second, our findings are correlational rather than causal. Studies with intervention validated for adolescents (Bluth et al., 2016) are needed to provide direct evidence to the causal relationship between DLPFC activity during sad vs. neutral self-face recognition, self-compassion and depression severity. Thirdly, we only presented sad faces among negative emotions in the present study, so it is not known whether the present findings are general to faces of all negative emotions (e.g., angry, disgusted, and fearful faces) or specific to sad faces. Likewise, it is not clear whether the present findings are general to all types of self-processing or specific to self-face processing. Future studies should examine the neural activity correlates of self-compassion in tasks with more negative emotions (e.g., fear, anger) as well as verbal self-processing. Lastly, the scale (SCRI) by which we measured self-compassion is not widely used and does not assess mindfulness and over-identification. Though the SCRI correlates highly with the more widely-used measure of self-compassion (Terry et al., 2013), i.e., Neff's (2003a) Self-Compassion Scale (SCS), future studies should test the replicability of our findings with the SCS.

In addition, future researcher may examine to what degree our findings are generalizable across different age groups, given that age was found to moderate the associations between SCS scores and depression (Bluth, Campo, Futch, & Gaylord, 2017) or other psychopathological problems (e.g., social anxiety; Werner et al., 2012). It is also important for future research to supplement the self-report measure with a behavioral measure of self-compassion comprised of behaviors that are theoretically linked to self-compassion and reflect a stance of caring and respect for oneself.

Conclusions

Higher self-compassion relates to lowered neural responses in the right DLPFC during sad vs. neutral self-face recognition and mediates the relationship between lower DLPFC activity and reduced depression severity among depressed adolescents. These results advance our understanding of the neural mechanisms of self-compassion and suggest that DLPFC activity might be a biological marker of a successful self-compassion intervention as a potential treatment for adolescent depression.

Conflicts of interest. Dr. Richard J. Davidson is the founder, president, and serves on the board of directors for the non-profit organization, Healthy Minds Innovations, Inc.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 1. Neural activity correlates during sad vs. neutral self-face recognition ($p_{uncorr} < 0.001$ at voxel level, cluster-level $p_{FWE} < 0.05$)

Covariate of Interest	Region	Cluster Size (K)	Hemisphere	MNI coordinates x	y	z	*T*
Total sample							
Self-compassion (-)	dACC, BA24/32	116	Left/Right	-6	20	26	4.08
Diagnostic group	No suprathreshold clusters						
Self-compassion by diagnostic group interaction	No suprathreshold clusters						
HC sub-sample							
Self-compassion (-)	PCC/precuneus, BA30/23/29	208	Right	12	-42	14	5.07
DEP sub-sample							
Self-compassion (-)	DLPFC (MFG), BA10	151	Right	34	38	10	4.75

dACC, dorsal anterior cingulate cortex; BA, Brodmann area; PCC, posterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; MFG, middle frontal gyrus

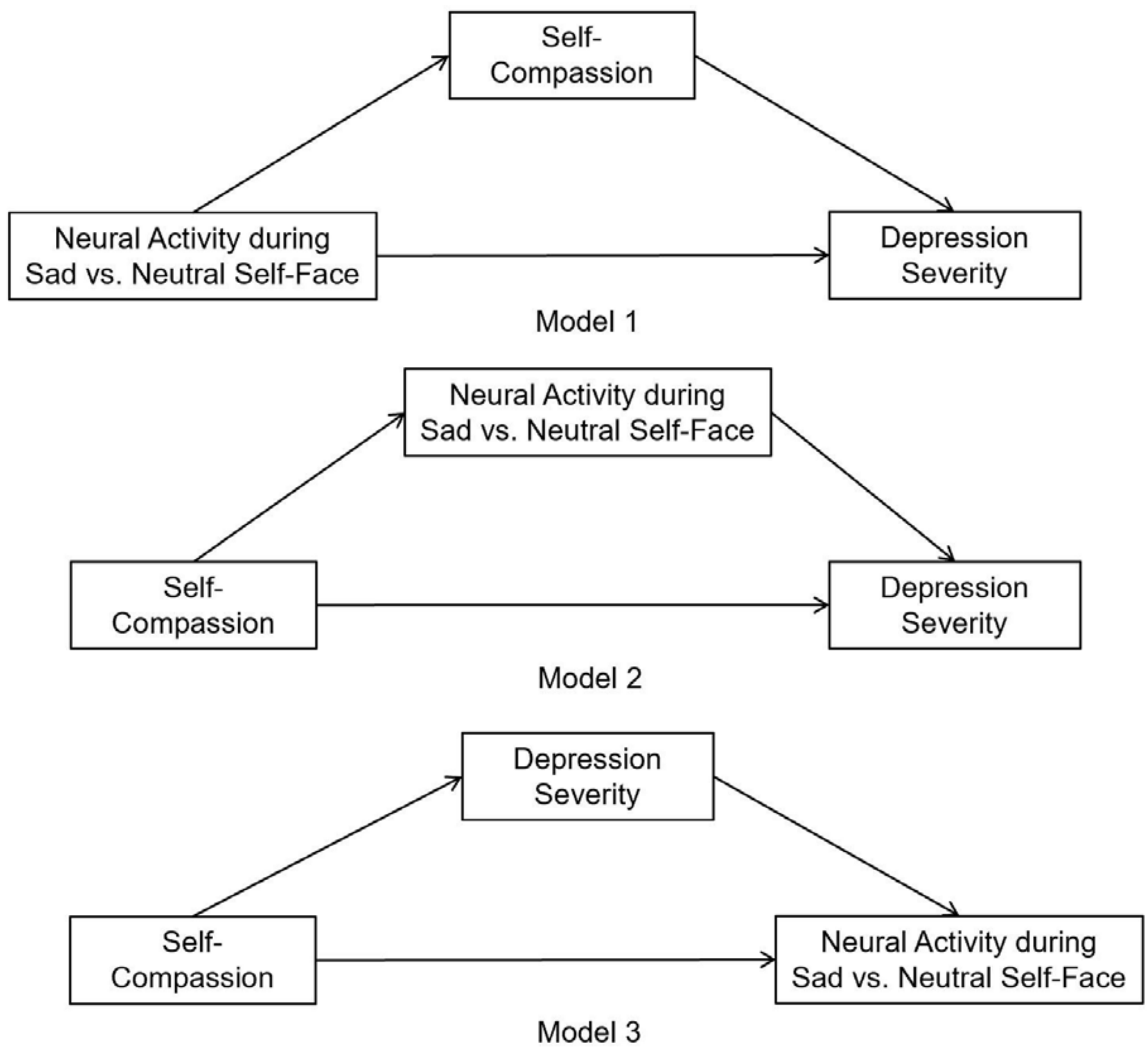

Figure 1. Three mediation models were set up to explore the relationship between self-compassion, its neural activity correlates during sad vs. neutral self-face recognition, and depression severity.

Figure 2. The emotional self-other morph query (ESOM-Q) task entails recognizing the self versus an unfamiliar face via button press. The faces were displayed in random order within six blocks across happy, sad and neutral faces.

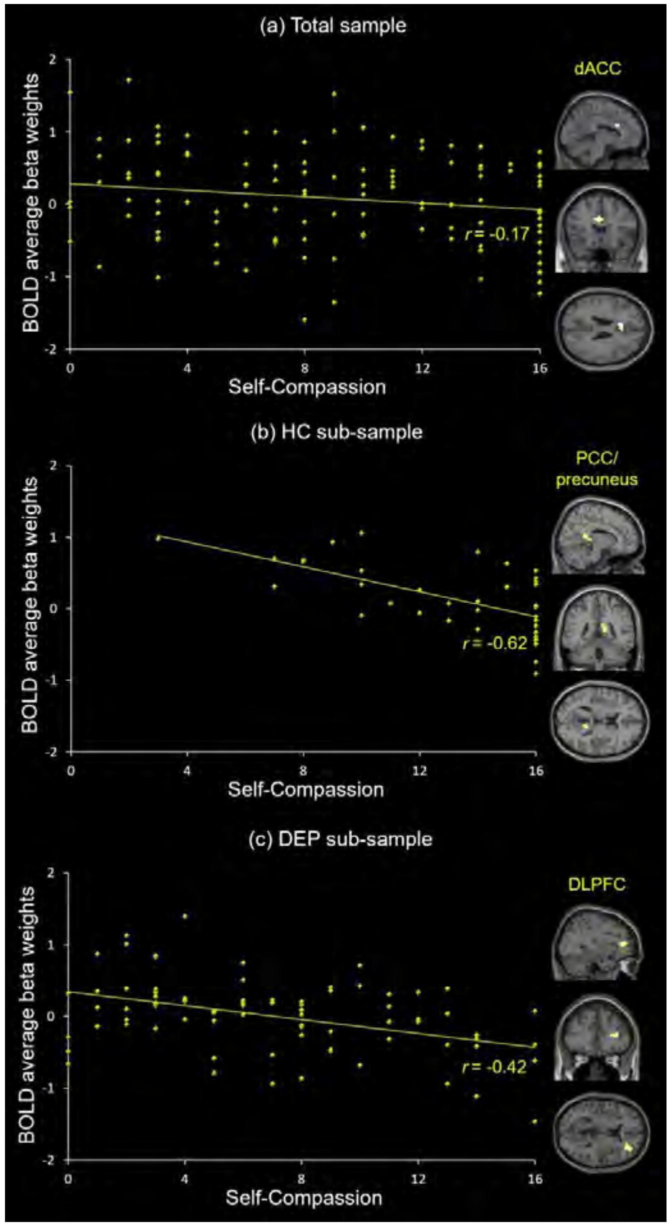

Figure 3. Neural correlates of self-compassion. (a) Self-compassion is negatively associated with dACC activity during sad vs. neutral self-face recognition in the total sample. (b) Self-compassion is negatively associated with right PCC/precuneus activity during sad vs. neutral self-face recognition in the HC sub-sample. (c) Self-compassion is negatively associated with right DLPFC activity during sad vs. neutral self-face recognition in the DEP sub-sample.

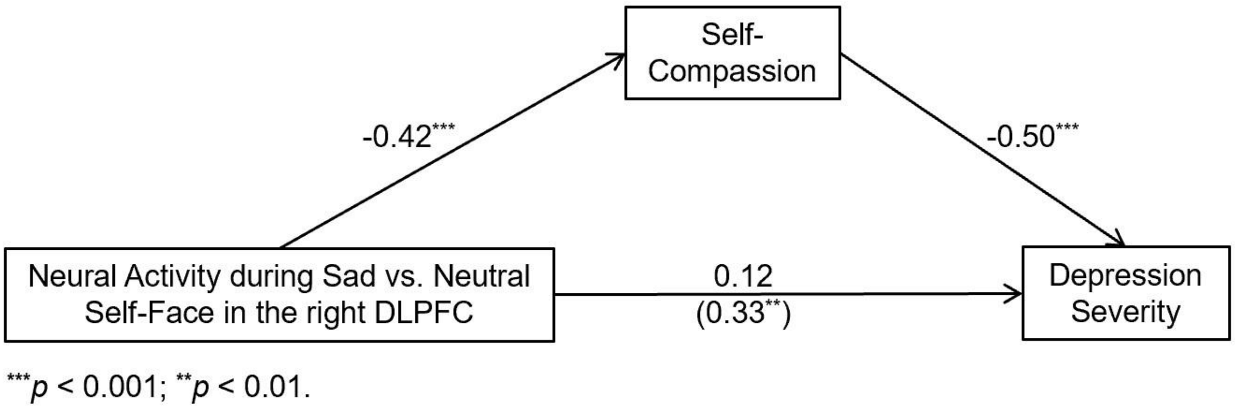

Figure 4. Higher self-compassion fully mediates the relationship between lower right DLPFC activity during sad vs. neutral self-face recognition and reduced depression severity in the depressed sub-sample.

Supplements

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Table of Content

- **Sample characteristics**

Table S1. Sample characteristics

Variable	Depressed Youth (n=81)	Healthy Controls (n=37)
Age: M±SD[Range]	14.94±1.68 [11.30-17.80]	14.48±1.54 [12.00-16.90]
Sex		
Male	27 (33.33%)	20 (54.05%)
Female	54 (66.67%)	17 (45.95%)
Race/Ethnicity:		
White	46 (56.79%)	28 (75.68%)
African American	8 (9.88%)	1 (2.70%)
Hispanic or Latino	10 (12.35%)	1 (2.70%)
Native American	2 (2.47%)	0
Asian	3 (3.70%)	3 (8.11%)
Multi-racial	10 (12.35%)	4 (10.81%)
Others	2 (2.47%)	0
Puberty: Late State/Completed	71 (87.65%)	29 (78.38%)
Annual Household Income:		
< $24,999	20 (24.69%)	2 (5.41%)
$25,000 ~ 49,999	21 (25.93%)	5 (13.51%)
$50,000 ~ 99,999	20 (24.69%)	14 (37.84%)
$100,000 ~ 149,999	12 (14.81%)	12 (32.43%)
> $150,000	5 (6.17%)	4 (10.81%)
Parent Marital Status		
Married	46 (56.79%)	30 (81.08%)
Living with Partner	8 (9.88%)	2 (5.41%)
Separated/Divorced	13 (16.05%)	3 (8.11%)
Singer/Never Married	10 (12.35%)	2 (5.41%)
Widowed	2 (2.47%)	0 (0%)
Depression Diagnosis		
Major Depressive Disorder	55 (67.90%)	N/A
Dysthymia	4 (4.94%)	N/A
Depressive Disorder-NOS	22 (27.16%)	N/A
Comorbid Anxiety	59 (72.84%)	N/A
Medication Use: (non-exclusive)		
Antidepressant	33 (40.74%)	N/A
Antipsychotic	6 (7.41%)	N/A
Mood Stabilizing	1 (1.23%)	N/A
Stimulant	10 (12.35%)	N/A
Anxiolitic	6 (7.41%)	N/A
Any Medication	40 (49.38%)	2 (5.41%)
Depression severity: M±SD[Range]	64.00±13.82 [36-93]	20.27±5.76 [17-44]
Self-compassion: M±SD[Range]	7.00±4.51 [0-16]	13.11±3.48 [3-16]

- **Stimuli generation for the Emotional Self-Other Morph-Query (ESOM-Q) task**

Photographs of the participants' faces with three expressions (happy, sad and neutral) were obtained during the intake visit under standardized conditions. The researcher would model the face required for each emotional expression (e.g., smiling for the happy face), and/or instruct the participant to recall a memory associated with the emotion prior to taking the photograph. The researcher also elicited expressions by causing the participant to laugh via jokes or instructing the participant to intensify the expression (e.g., turning down the corners of the mouth or furrowing the brow). Any of - or all these strategies were used as necessary. Participant's photographs were then mirror transposed and non-facial attributes (hair, ears, large scars, or pimples) were removed. Faces were presented against a black background. A non-familiar teen face (from available photographs of previous participants) of similar gender, race, maturity and attractiveness was paired with each participant. Two experimenters agreed in the selection of the appropriate non-familiar face via visual inspection. The individual faces were then manipulated, "morphed," with their assigned unfamiliar face, (other participants in the sample) in 5% increments using Abrosoft FantaMorph software (Abrosoft, 2011). This resulted in 21 composites that ranged from 0% self and 100% other to 100% self and 0% other. The purpose was to have several novel but easy to recognize pictures of a face to prevent habituation. The potential influence of diagnosis on the emotional intensity of the stimulus faces shown in the scanner, as well as their fit within a unique category of emotion (e.g. neutral, happy or sad expressions) was examined. Ten trained research assistants, blind to diagnosis, scored the face stimuli for the 100% self-face with neutral, happy and sad expressions for emotional category of expression, with higher scores indicating better fit for the sought emotional category. Specifically, they rated how neutral the neutral faces were on a 1 to 5 scale, and how happy or sad the emotionally-valenced faces were. Additionally, they rated physical attractiveness for the participant's face regardless of emotion on a 1 to 10 scale. A repeated measures ANOVA (3 groups by 4 ratings) showed that diagnostic groups did not differ in emotional intensity or physical attractiveness of pictures, $F(2, 113) = 0.23$, $p= 0.79$.

- **Behavioral results on response time and accuracy**

Mixed repeated-measures ANOVAs with Group (DEP, HC) by Self (self-face, other-face) by Emotion (happy, neutral, sad) were carried out to test whether response time (RT) or accuracy in the ESOM-Q task was different across groups or conditions.

Results of repeated measures ANOVAs showed that Self had a main effect on RT such that participants responded on average slower during self-face recognition compared to other-face recognition: $F(1, 106) = 8.97$, $p = .003$ (self: 897.90±145.06ms; other: 853.19±179.02ms); and an interaction effect between Self and Emotion on RT, $F(2, 212) = 3.21$, $p = .044$. Multiple comparisons showed that the RT for happy self-face recognition (916.60±171.26ms) was slower than that for other-face recognition (847.63±209.93ms), $t(107) = 3.81$, $p<.001$; the RT for neutral self-face recognition (896.19±169.77ms) was slower than that for neutral other-face recognition (855.34±187.25ms): $t(107) = 2.55$, $p = .012$; and no significance difference was found on the RT between sad self-face (880.91±178.08) and sad other-face condition (856.61±210.04). No other significant main effects or interaction effects on RT were found.

Results showed that Emotion had a main effect on accuracy: $F(2, 216) = 11.56$, $p < .001$ (happy: 0.78±0.20; neutral: 0.72±0.17; sad: 0.72±0.18); and an interaction effect between Emotion and Self on accuracy: $F(2, 216) = 10.08$, $p<.001$. Multiple comparisons showed that the accuracy for happy self-face (0.81±0.23) was higher than that for happy other-face (0.76±0.24): $t(109) = 2.01$, $p=.047$; the accuracy for neutral self-face (0.69±0.18) was lower than that for neutral other-face (0.75±0.18): $t(109) = 4.93$, $p<.001$; and no significance difference was found on the accuracy between sad self-face (0.73±0.18) and sad other-face (0.72±0.22). No other significant main effects or interaction effects on accuracy were found.

- **Additional fMRI analyses and results to happy vs. neutral self-face recognition**

Additional fMRI analyses.

Contrasted images of happy self > neutral self were created based on statistical images generated from the first-level analyses described in the main text. The details of the second-level analyses were the same as those described in the main text, the only difference being that contrasted images of happy self > neutral self, instead of sad self > neutral self, were used.

Additional fMRI results.

Neural correlates of self-compassion during happy vs. neutral self-face recognition in the total sample. No suprathreshold clusters were found related to self-compassion, diagnostic group or the interaction between them during happy vs. neutral self-face recognition in the total sample.

Neural correlates of self-compassion during happy vs. neutral self-face recognition in the HC sub-sample. No suprathreshold clusters were found related to self-compassion during happy vs. neutral self-face recognition in the HC sub-sample.

Neural correlates of self-compassion during happy vs. neutral self-face recognition in the DEP sub-sample. No suprathreshold clusters were found related to self-compassion during happy vs. neutral self-face recognition in the DEP sub-sample.

- **Additional fMRI analyses and results to sad vs. neutral other-face recognition**

Additional fMRI analyses.

Contrasted images of sad other > neutral other were created based on statistical images generated from the first-level analyses described in the main text. The details of the second-level analyses were the same as those described in the main text, the only difference being that contrasted images of sad other > neutral other, instead of sad self > neutral self, were used.

Additional fMRI results.

Neural correlates of self-compassion during sad vs. neutral other-face recognition in the total sample. No suprathreshold clusters were found related to self-compassion or diagnostic group during sad vs. neutral other-face recognition in the total sample, but the self-compassion by diagnostic group interaction showed an association with activity in the left inferior parietal lobule (IPL) extending to postcentral gyrus and superior parietal lobule (Table S2). Specifically, self-compassion related positively to activity in the left IPL ($r = 0.53$, $p = .001$) in the HC sub-sample but not significantly in the DEP sub-sample ($r = -0.09$, $p = .44$). However, IPL activity did not significantly relate to depression severity in either sub-sample (HC: $r = -0.10$, $p = .55$; DEP: $r = 0.14$, $p = .22$).

Neural correlates of self-compassion during sad vs. neutral other-face recognition in the HC sub-sample. Whole-brain analysis showed that self-compassion related positively to activity in the left postcentral gyrus extending to precentral and supramarginal gyrus ($r = 0.66$, $p < .001$), the left insula extending to lateral orbitofrontal gyrus ($r = 0.59$, $p < .001$) and the right postcentral gyrus ($r = 0.59$, $p < .001$) during sad vs. neutral other-face recognition in the HC sub-sample (Table S2). However, activity in none of these regions related significantly with depression severity (left postcentral gyrus: $r = -0.07$, $p = .69$; left insula: $r = -0.09$, $p = .61$; right postcentral gyrus: $r = 0.06$, $p = .74$).

Neural correlates of self-compassion during sad vs. neutral other-face recognition in the DEP sub-sample. No suprathreshold clusters were found related to self-compassion during sad vs. neutral other-face recognition in the DEP sub-sample.

Table S2. Neural activity correlates during sad vs. neutral other-face recognition ($p_{uncorr} < 0.001$ at voxel level, cluster-level $p_{FWE} < 0.05$)

Covariate of Interest	Region	Cluster Size (K)	Hemisphere	MNI coordinates x	y	z	*T*
Total sample							
Self-compassion	No suprathreshold clusters						
Diagnostic group	No suprathreshold clusters						
Self-compassion by diagnostic group interaction	Inferior parietal lobule/postcentral gyrus/ superior parietal lobule, BA40	125	Left	-32	-44	52	4.24
HC sub-sample							
Self-compassion (+)	Post-/precentral gyrus/supramarginal gyrus, BA6/4/3	277	Left	-60	-16	40	5.93
	Insula/lateral orbitofrontal cortex, BA47/13	107	Left	-40	18	-6	4.69
	Postcentral gyrus, BA3/4/1/6	94	Right	52	-16	52	4.40
DEP sub-sample							
Self-compassion	No suprathreshold clusters						

Supporting references

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