Neural and behavioral correlates of negative self-focused thought associated with depression

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Abstract

A central feature of major depression (MDD) is heightened negative self-focused thought (negative-SFT). Neuroscientific research has identified abnormalities in a network of brain regions in MDD, including brain areas associated with SFT such as medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC). To our knowledge no studies have investigated the behavioral and neural correlates of negative-SFT using a sentence completion task in a sample of individuals with varying depression histories and severities. We test the following hypotheses: (1) negative-SFT will be associated with depression; and (2) depression and negative-SFT will be related to resting-state functional connectivity (rsFC) for brain regions implicated in SFT. Seventy-nine women with varying depression histories and severities completed a sentence completion task and underwent resting-state functional magnetic resonance imaging (rs-fMRI). Standard seed-based voxelwise rsFC was conducted for self-network regions of interest: dorsomedial PFC (dmPFC) and pregenual ACC (pgACC). We performed linear regression analyses to examine the relationships among depression, negative-SFT, and rsFC for the dmPFC and pgACC. Greater negative-SFT was associated with depression history and severity. Greater negative-SFT predicted increased rsFC between dmPFC and pgACC seeds and dorsolateral prefrontal (dlPFC) and parietal regions; depression group was also associated with increased pgACC-dlPFC connectivity. These findings are consistent with previous literature reporting elevated negative-SFT thought in MDD. Our rs-fMRI results provide novel support linking negative-SFT with increased rsFC between self-network and frontoparietal network regions across different levels of depression. Broadly, these findings highlight a dimension of social-affective functioning that may underlie MDD and other psychiatric conditions.

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Conflicts of Interest

None.

Keywords

major depression; rumination; self-focused thought; resting-state fMRI; functional connectivity; cortical midline structures

Introduction

A central feature of major depressive disorder (MDD) is elevated negative self-focused thought (SFT) often consisting of repetitive thoughts focused on negative aspects about oneself, including feelings of worthlessness and self-blame [American Psychiatric Association, 2013]. Cognitive theories of depression have emphasized that individuals with MDD tend to interpret their experiences with a negative cognitive bias toward the self [Clark and Beck, 1999; Pyszczynski and Greenberg, 1987]. Furthermore, studies have frequently associated depression with a bias toward negative-SFT across several different measures. For example, using well-validated self-report questionnaires, greater rumination frequency [Joormann et al., 2006; Nolen-Hoeksema et al., 2008; Siegle et al., 2004] and higher levels of self-consciousness in relation to depression severity [Ingram and Smith, 1984; Smith and Greenberg, 1981] have been reported in MDD. When personality trait judgment tasks have been used to assess negative-SFT in memory, MDD has consistently been associated with enhanced memory for one's own negative personality traits [Baños et al., 2001; Bradley and Mathews, 1983; Derry and Kuiper, 1981; Dobson and Shaw, 1987]. Similarly, based on sentence completion task performance, individuals with MDD display higher proportions of negative-SFT responses [Ingram et al., 1987]. Rumination, a type of negative-SFT that involves repetitive and often uncontrollable thinking about negative aspects of oneself, has been shown to reliably predict the onset of MDD, the duration of depressive symptoms, and susceptibility to relapse [Figueroa et al., 2015; Nolen-Hoeksema et al., 2008]. Together, these studies suggest that negative-SFT may be a key social-affective factor contributing to the development and maintenance of depression.

Neuroscientific research has identified abnormalities in a network of brain regions in MDD, including brain areas associated with SFT, such as the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) [Berman et al., 2011; Davey et al., 2012; Drevets et al., 2008; Greicius et al., 2007; Mayberg, 2003; Sheline et al., 2009]. Further, task-based functional neuroimaging studies in MDD suggest that aberrant activity in these self-related brain regions, in particular the mPFC and ACC, may underlie negative-SFT in MDD [Cooney et al., 2010; Grimm et al., 2009; Johnson et al., 2009; Lemogne et al., 2009; Nejad et al., 2013; Yoshimura et al., 2010]. For example, using personality trait judgment paradigms, studies have shown that individuals with MDD have greater activity in mPFC and rostral ACC during self-related thought conditions, especially while considering whether negative personality traits are self-relevant [e.g., Lemogne et al., 2009; Yoshimura et al., 2010]. Beyond task-based neuroimaging, resting-state functional connectivity (rsFC) findings have further implicated altered mPFC and ACC connectivity in MDD and negative-SFT. For instance, depression severity and ruminative thought have been associated with heightened rsFC for the subgenual ACC and pregenual ACC (pgACC) [Berman et al., 2011; Greicius et al., 2007; Zhu et al., 2012]. Similar to findings in MDD, neuroimaging studies in

healthy individuals indicate that negative-SFT, such as rumination, is also associated with increased mPFC and ACC activity [e.g., Kross et al., 2009; Wagner et al., 2013] and connectivity [Berman et al., 2011]. Thus, neuroimaging research to date suggests that negative-SFT may be dimensionally related to connectivity of mPFC and ACC across individuals with and without MDD.

To our knowledge no studies have yet investigated the behavioral and neural correlates of negative-SFT using a sentence completion task and resting-state functional magnetic resonance imaging (rs-fMRI) in a sample of individuals with varying depression histories and severities. In the current study, we tested the hypothesis that negative-SFT would be associated with depression history and severity. We also investigated the relationships among depression, negative-SFT, and rsFC for mPFC and ACC self-related brain regions across the study sample.

Materials and Methods

Participants

Participants included seventy-nine women between the ages of 18 and 45 (mean age = 27.6 ± 7.0). All participants were screened for psychopathology using the Structured Clinical Interview for the DSM-IV modified to assess DSM-5 criteria [SCID-I/P for DSM-IV-TR; First et al., 2002]. Exclusion criteria included: lifetime history of psychosis or mania; current substance use disorder (i.e., within the last 6 months); significant risk for suicide; claustrophobia; daily nicotine use; self-reported use of antidepressants/other psychotropic medications; hormonal contraceptive use; peri- or postmenopausal signs; highly irregular periods; recent pregnancy or breastfeeding (i.e., within the last 6 months); illicit drug use within 4 weeks of participation. Note, all eligible participants self-reported that they had not used antidepressants or other psychotropic medications within a timeframe based on the half-life of that particular drug (e.g., had not used fluoxetine for at least 30 days prior to participation). Many of the participants had previously taken antidepressant medications and reported a variety of reasons (e.g., side effects) for not currently taking medication. To confirm no illicit drug use, we performed urine drug tests during 3 of the 7 study visits (diagnostic interview and 2 fMRI scans). We tested for marijuana, cocaine, opiate, methamphetamine, and amphetamine. We also asked participants about illicit drug use during every study session. It is important to also mention that participants did not receive psychotherapeutic treatment as part of this study nor was psychotherapy an exclusionary criterion.

Of 85 participants who were eligible, 80 completed neuroimaging sessions, with full data available for 79 participants (75% White, 16% Asian, 6% Black). Participants had different levels of depression history forming three separate groups: (1) no history of depression (n = 30; NoDep); (2) history of depression, but not currently depressed (n = 15; PastDep); and (3) currently depressed, meeting the diagnostic criteria for a DSM-5 Depressive Disorder (n = 34; CurrentDep). Subjects with no history of depression (NoDep group) also had no history of any other psychological conditions, with the exception of one subject who received a diagnosis of Social Phobia in partial remission during the SCID interview. While we did not explicitly recruit women with anxiety disorders, presence of anxiety disorders was not an

exclusionary criterion (Table I). There were no significant group differences in demographic variables, but as expected there were significant differences in depression severity (Table I).

Participants were recruited from the Madison, WI area through flyers posted on community bulletin boards and websites, email advertisements to University of Wisconsin-Madison faculty, staff, and students, and advertisements mailed to counseling centers and clinics. All participants provided written informed consent in accordance with the local IRB. Participants were paid for their participation.

Study Procedures

The data reported herein are taken from a larger NIH R01-funded study investigating the effects of cortisol on cognitive and neural function in depression. In the larger study, all participants took part in seven study visits, including 2 fMRI scans: 1 placebo scan and 1 hydrocortisone scan. Placebo and hydrocortisone administration was double-blind and randomized across two fMRI scan sessions which were typically one week apart (5–61 days apart). Note: hydrocortisone was not given as a therapeutic agent; instead it was given to test for alterations in neurocognitive response to cortisol (i.e., hydrocortisone). One hour prior to each scan, participants received a pill containing either placebo or 20 mg hydrocortisone (order of drug administration randomized and double-blind). Data reported here are taken from the placebo day fMRI scan. To account for potential differences due to scan order in the current study, we investigated the relationship between scan order and all behavioral and neural variables of interest.

Depression Measure

Depression severity was measured with the Beck Depression Inventory-II (BDI-II) at each visit (Beck et al., 1961). We used the average of BDI-II scores from the two fMRI scan visits. To reduce negative skew in the distribution of BDI-II we applied a square root transformation of BDI-II data [van Minnen et al., 2005; as in Roelofs et al., 2013]. For tables and scatter plots, BDI-II scores were back-transformed to accurately reflect the BDI-II score range.

Negative-SFT Measure

Negative-SFT was measured using the sentence completion task [Exner, 1973]. For the sentence completion task, 30 different sentence stems were given to participants to complete as they wished (e.g., "I think…", or "My father…"). Each response was coded for focus and valence [Exner, 1973; Ingram and Smith, 1984]. Reliability and validity for the sentence completion task as a measure of SFT has been reported in large samples of non-psychiatric and psychiatric participants [Exner, 1973].

Sentence completion task responses were coded based on type of focus, including SFT and other-focused [as in Exner, 1973]. SFT responses referred to the self with little regard for other persons, while other-focused responses discussed the characteristics, mental states, or actions of other people. Total focus scores corresponded to the sum of all responses for each response category. To examine negative-SFT, each response was also coded in terms of the

overall valence: positive, negative, or neutral (e.g., negative-SFT, positive-SFT) [as in Ingram and Smith, 1984]. See Table II for examples.

Two raters trained in sentence completion coding and blind to depression group status coded responses in two steps. First, each rater separately coded responses for focus and valence for all participants. Interrater reliability was calculated for all ratings and adequate reliability was found for all response categories. Specifically, SFT, other-focused, negative-SFT, and positive-SFT responses had intraclass correlation coefficients of .83, .82, .84, .90, respectively, which was within acceptable limits [Exner, 1973]. Second, the raters discussed responses for each participant and agreed on final codes for each response (e.g., SFT and negative valence), which were used in the analyses. Based on our hypotheses for the current study and previous research using the same sentence completion task [Ingram et al., 1987; Ingram and Smith, 1984], only the proportion of negative-SFT responses (number of negative-SFT responses/total SFT responses) were used.

Data Acquisition

All structural and functional magnetic resonance imaging (MRI) data were acquired using a 3T GE MRI scanner (Discovery MRI 750; GE Medical Systems, Waukesha, WI) equipped with an 8-channel radio-frequency coil array (GE Healthcare, Waukesha, WI). High-resolution T1-weighted structural images were acquired using a weighted BRAVO pulse sequence (TI: 450ms, TR/TE/flip angle (FA): 8.16ms/3.2ms/12°, matrix: 256×256×160, field of view (FOV): 215.6mm, slice thickness: 1mm, voxel size: 1mm×1mm×1mm^3, slices: 156). rs-fMRI images were acquired using T2*-weighted Echo Planar Imaging (EPI) sequence (TR/TE/FA: 2150ms/22ms/79˚, matrix: 64×64, FOV: 22.4cm, slice thickness: 3.5mm, voxel size: 3.5mm×3.5mm×3.5mm^3, slices: 40 sagittal) using thinner slices and shorter echo time in order to minimize signal dropout in ventromedial prefrontal cortex. For the resting-state scan (~10 minutes), the participants were instructed to remain "calm, still, and awake" with their eyes open fixating on a cross back-projected onto a screen via an LCD projector (Avotec, Stuart, FL).

Preprocessing and Motion Analysis for rs-fMRI Data

The rs-fMRI data were processed using AFNI [Cox, 1996] and FSL (FMRIB Software Library; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). First, a rigid-body volume registration was implemented to compensate for subjects' motion (3dvolreg, 4th volume as the base image volume). Next, field map correction was performed using sagittal field maps (collected via a 3D SPGR sequence; TR/TE/FA: 5ms/1.8ms/7˚, matrix: 192×128×44, FOV: 230mm, slice thickness: 3.5mm) to geometrically unwarp EPIs to reduce distortion caused by magnetic field inhomogeneities [IDEAL sequence; Reeder et al., 2005; and FMRIB Software Library; Woolrich et al., 2009]. Next, the following preprocessing steps were performed: (1) slice-time corrected EPI volumes (3dTshift, using 1st volume as a reference), (2) omitted first three volumes (3dcalc), (3) aligned EPI data to their respective T1-weighted anatomical (align_epi_anat.py) and transformed to Talairach atlas space (Talairach and Tournoux, 1988; LPI) in a single interpolation to 2×2×2mm^3 voxels, (4) the 3D+time series were despiked (3dDespike), and (5) temporally filtered (band-pass: 0.009 Hz < f < 0.08 Hz) and spatially smoothed with a 6-mm full-width half-maximum (FWHM) Gaussian kernel (3dBandPass).

Normalized T1 anatomical images were also segmented into gray matter, white matter, and cerebrospinal fluid (CSF) using FAST in FSL [Zhang et al., 2001]. White matter and CSF segments were used as masks to extract a representative time series from each tissue type.

We also examined motion for each subject, as individual differences in subject motion can contribute to resting-state correlations [Power et al., 2015]. Five subjects (NoDep, n = 2; PastDep, n = 2; CurrentDep, n = 1) were excluded based on the following criteria: mean framewise motion displacement > 3 mm (i.e., volume to volume movement across the time series), and/or total scan time < 4 min after censoring all time points with framewise motion displacement > .2 mm and extreme timeseries displacement (i.e., time points where > 10% of voxels were outliers) [Power et al., 2015]. These thresholds were selected to provide the most conservative criteria for motion correction [Power et al., 2012; Yan et al., 2013]. As in previous work [e.g., Ciric et al., 2017], average root-mean-squared (RMS) displacement was used as a summary measure of subject motion. Importantly, there were no significant associations between average RMS and depression group ($F_{2,71} = 0.53$, $p > 0.5$), depression severity ($r = .08$, $p > 0.5$), or proportion of negative-SFT responses ($r = -.02$, $p > 0.9$).

Functional Connectivity Analysis

We performed seed-based voxelwise rsFC analyses [Biswal et al., 1995] for two mPFC seed regions of interest (ROIs) implicated in SFT (dmPFC: −2, 38, 16; pgACC: −2, 34, 2; both ROIs coordinates reported in MNI space) [Murray et al., 2015]. For each participant, the mean resting-state BOLD time series from each seed ROI was included in a GLM (3dDeconvolve) with nine regressors of no interest: (1–6) six motion parameters (three translations, three rotations) obtained from the rigid body alignment of EPI volumes and their six derivatives, (7) white matter time series, (8) ventricular (CSF) time series, and (9) a second-order polynomial to model baseline signal and slow drift. To further control for subject motion within the GLM, volumes were censored for excessive motion, as described above.

To create the correlation maps for each seed ROI, we performed the following steps: (1) used GLM output to convert R^2 values to correlation coefficients (r), (2) used Fisher's r-to-z transform to convert r to z-scores and corrected for degrees of freedom [Philippi et al., 2015]. The resulting z-score maps were then entered into the second-level statistical analyses.

Statistical Analyses

Behavioral data analyses—We performed two separate analyses, using group-based and regression approaches, to examine the association between depression history or severity and negative-SFT in the full sample (n = 79). For the group analysis, we performed one-way ANOVAs with depression group as the independent variable (NoDep, PastDep, CurrentDep) and proportion of negative-SFT responses as the dependent variable. For the regression analysis, we regressed the proportion of negative-SFT responses onto depression severity.

To provide external validation of the relationship between negative-SFT from the sentence completion task and repetitive thought, we also measured self-reported rumination using the

22-item Ruminative Responses Scale (RRS) [Treynor et al., 2003]. Examples items from the RRS include: "Go someplace alone to think about your feelings", "Think, what am I doing to deserve this", and "Think about how alone you feel". Participants rated their frequency of each item on a scale ranging from 1 (almost never) to 4 (almost always). The total RRS score corresponded to the sum of all responses. We performed a bivariate correlation between total RRS scores and the proportion of negative-SFT responses.

rsFC data analyses—To examine the relationships among depression, negative-SFT, and rsFC, we performed multivariate regression analyses (3dttest++ in AFNI) for dmPFC and pgACC seed ROIs for three separate models: (1) depression group, (2) depression severity, and (3) the proportion of negative-SFT responses. Age was also included as a covariate in all models, as age was significantly associated with rsFC for dmPFC and pgACC seed ROIs (Supplementary Table I). All rsFC analyses were conducted using seventy-four participants, as five participants were excluded due to excessive motion. To correct for multiple comparisons, we implemented a family-wise error (FWE) correction approach at the cluster level using a whole-brain mask [3dClustSim in AFNI version updated August 2016; Carp, 2012; Forman et al., 1995] and applied cluster-extent thresholding. To address the non-Gaussian nature of fMRI data [Eklund et al., 2016], the autocorrelation function (-acf) was used to calculate the FWHM for each subject (3dFWHMx in AFNI). The cluster-extent threshold corresponded to the statistical probability ($\alpha = 0.05$, or 5% chance) of identifying a random noise cluster at a predefined voxelwise threshold of $p < 0.001$ (uncorrected). Using this whole-brain FWE cluster correction, a cluster-corrected size of 137 voxels was significant at $p_{FWE} < 0.05$ in the rsFC regression analyses. Regression results were overlaid on the normalized mean anatomical image.

To statistically account for potential differences in scan order (i.e., either placebo or hydrocortisone), we also performed follow-up regression analyses for all significant rsFC results. We first extracted the average z-score from all significant clusters identified for each subject, and then ran separate regressions (in R) to examine the association between the average z-score for each significant cluster and the proportion of negative-SFT responses, after controlling for scan order.

We also conducted supplemental moderation analyses for all significant rsFC results to determine whether depression history or severity moderated the association between negative-SFT and rsFC. Moderation analyses were completed in SPSS (version 24; SPSS/IBM, Chicago, IL) using the macro PROCESS (Andrew F. Hayes, Ohio State University, Columbus, OH). Separate models with either depression history/depression severity or negative-SFT as a moderator, were tested for all significant rsFC results: X = negative-SFT or depression history, Y = average z-scores from the significant cluster identified in rsFC analyses, and M = depression history/M = depression severity/M = negative-SFT. To evaluate the significance of the moderation effect, standard non-parametric bootstrapping procedures were performed with 5000 samples [as in Hosking et al., 2017]. All moderation models also included age as a covariate.

Lastly, we performed mediation analyses for all significant rsFC results from regression models with depression (either depression history or severity) to determine whether

negative-SFT mediated the relationship between depression and rsFC. Mediation analyses were completed in SPSS (version 24; SPSS/IBM, Chicago, IL) using the macro PROCESS (Andrew F. Hayes, Ohio State University, Columbus, OH). Separate models with negative-SFT as a mediator were tested for all significant rsFC results from regression models with depression: X = depression history/X = depression severity, Y = average z-scores from the significant cluster identified in rsFC analyses, and M = negative-SFT. Given that depression history was a multicategorical independent variable (three groups: NoDep, PastDep, CurrentDep), when depression history was in the model we followed the procedures for mediation analyses with multicategorical independent variables [as in Hayes and Preacher, 2014], to examine the relative indirect and direct effects of each depression history group (PastDep or CurrentDep) relative to the control group (NoDep). Similar to the moderation analyses, standard non-parametric bootstrapping procedures were performed for the mediation analyses with 5000 samples. All mediation models also included age as a covariate.

Results

Depression and Negative-SFT

Consistent with previous research on depression and negative-SFT, there was a significant effect of depression group for negative-SFT ($F_{2,76} = 6.82$, $p < 0.01$, $\eta^2 = .15$), with the CurrentDep group demonstrating a greater proportion of negative-SFT responses than the NoDep group ($t(62) = 3.68$, $p < 0.001$, $d = .93$) (Table III). Although the CurrentDep group had more negative-SFT responses than the PastDep group, the difference between the two groups was marginal ($t(47) = 1.60$, $p = 0.11$, $d = .47$). On average the PastDep group displayed a greater proportion of negative-SFT responses than the NoDep group, however, the difference between the groups was not significant ($t(43) = 1.34$, $p = 0.19$, $d = .41$). Similar to the group analyses, using depression severity as a continuous variable, we found a significant positive relationship between depression severity and the proportion of negative-SFT responses ($B = 6.35$, $t(77) = 4.43$, $p < 0.001$, $\eta_p^2 = .20$) (Supplementary Figure 1). Follow-up analyses revealed no significant correlations between scan order and depression history/severity or negative-SFT (each $p > 0.6$). There was a significant correlation between negative-SFT and rumination scores ($r = 0.39$, $p < 0.01$), providing some support for a relationship between negative-SFT and repetitive thought in the current study.

rsFC, Depression, and Negative-SFT

In line with prior rsFC studies in MDD, there was a significant association between depression group and rsFC for the pgACC. Depression group was related to increased rsFC between pgACC and dorsolateral prefrontal cortex (dlPFC), postcentral gyrus extending to supplementary motor area (SMA), and superior temporal gyrus (Figure 1); the CurrentDep group revealed significantly greater rsFC than both the PastDep and NoDep groups (Table IV). In contrast to depression group results, there were no significant associations between depression severity and rsFC for the dmPFC or pgACC seed ROIs.

As predicted, negative-SFT was significantly related to enhanced rsFC for both the dmPFC and pgACC seed ROIs (Table V). For the dmPFC, greater negative-SFT was associated with

enhanced rsFC with the left inferior parietal lobule (IPL) (Figure 2A). Similarly, for the pgACC, greater negative-SFT was associated with increased rsFC with several regions including the dlPFC, precuneus extending to middle temporal gyrus, inferior parietal cortex, and paracentral lobule extending to SMA (Figure 2B). Importantly, follow-up analyses indicated that there were no significant effects of scan order for any of the rsFC findings (each $p > .6$).

In supplemental moderation analyses, the relationships between depression group and rsFC for the pgACC were not moderated by negative-SFT (each $p > 0.5$). Similarly, the associations between negative-SFT and rsFC for dmPFC and pgACC were not moderated by either depression group or severity (each $p > .2$). Finally, in the mediation analyses with depression group as a multicategorical independent variable (Supplementary Figure 2), negative-SFT did significantly mediate the relationship between depression group and rsFC for pgACC. Relative to the NoDep group, the CurrentDep group had greater rsFC between pgACC and dlPFC as well as pgACC and postcentral gyrus/SMA as a result of the mediating effect of negative-SFT on rsFC (Supplementary Tables II, III). Negative-SFT was not a significant mediator for the PastDep group (Supplementary Tables II, III, IV, V).

Discussion

To our knowledge, this is the first study to use a sentence completion task and rs-fMRI to examine the behavioral and neural correlates of negative-SFT in a sample of individuals with varying depression history and severity. Our results supported our hypotheses, demonstrating significant relationships between negative-SFT and depression, as well as between depression, negative-SFT, and rsFC of self-related brain regions. Behaviorally, negative-SFT varied by depression group, with the currently depressed group exhibiting greater negative-SFT than the no depression history group. Interestingly, there was no significant difference in negative-SFT between the currently depressed and past depression groups. In the regression analysis, negative-SFT was associated with higher depression severity across the sample. Neurally, negative-SFT was significantly related to increased rsFC between the dmPFC and pgACC seeds and dlPFC and medial and lateral parietal regions. Depression group was also associated with significantly increased rsFC between pgACC and dlPFC, as well as other parietal and temporal regions. For the currently depressed group, negative-SFT significantly mediated the relationship between depression group and rsFC between pgACC and dlPFC as well as pgACC and postcentral gyrus/SMA. Below, we discuss each of these major findings in turn.

Our observation that currently depressed individuals had greater negative-SFT than individuals with no depression history closely parallels two previous behavioral studies using the sentence completion task in MDD [Ingram et al., 1987] and subclinical depression [Ingram and Smith, 1984]. The present results are also consistent with a large body of clinical and behavioral research linking depression and depression severity with elevated negative-SFT across different self-report and behavioral measures [Baños et al., 2001; Bradley and Mathews, 1983; Clark and Beck, 1999; Derry and Kuiper, 1981; Dobson and Shaw, 1987; Ingram and Smith, 1984; Joormann et al., 2006; Nolen-Hoeksema et al., 2008; Siegle et al., 2004; Smith and Greenberg, 1981]. Based on extant research, it has further

been proposed that patterns of negative-SFT, such as rumination or negative cognitive styles, may serve as a vulnerability factor for the development and recurrence of depression [Alloy et al., 2006; Burcusa and Iacono, 2007; McLaughlin and Nolen-Hoeksema, 2011; Watkins, 2015]. Consistent with this hypothesis, in the present study negative-SFT was elevated in both the current and past depression groups, with no significant difference in levels of negative-SFT between the two groups. Lastly, we found a significant correlation between negative-SFT on the sentence completion task and self-reported rumination, providing some external validation for a relationship between negative-SFT and repetitive thought [Watkins, 2008].

Regarding the rsFC analyses, negative-SFT was associated with enhanced connectivity between dmPFC and left IPL, two of the main brain regions of the default mode network (DMN). These results extend prior task-based and rs-fMRI studies which associate MDD with hyperactivity and connectivity of the DMN [Kaiser et al., 2015; Sheline et al., 2009]. Based on research implicating the DMN in SFT [Buckner et al., 2008; Gusnard et al., 2001; Qin and Northoff, 2011; Whitfield-Gabrieli et al., 2011], researchers have proposed that DMN hyperconnectivity may be related to elevated negative-SFT in depression [Berman et al., 2011; Kaiser et al., 2015; Philippi and Koenigs, 2014; Sheline et al., 2009; Whitfield-Gabrieli and Ford, 2012]. Indeed, previous rs-fMRI research has identified significant correlations between elevated DMN connectivity and greater rumination in both subclinical and MDD populations [Berman et al., 2011; Hamilton et al., 2011; Zhu et al., 2012], which is consistent with our findings. Note, the left IPL cluster identified in our study also extends into the anterior inferior parietal lobule, which is part of the frontoparietal network (FPN) [Vincent et al., 2008], suggesting that negative-SFT in depression may also be associated with altered dmPFC-FPN connectivity.

There is growing evidence for altered connectivity between mPFC regions and dlPFC in MDD. For example, a meta-analysis of 25 seed-based rsFC studies in MDD found consistently heightened connectivity between mPFC, including pgACC, and dlPFC in MDD [Kaiser et al., 2015]. Similarly, in a task-based fMRI study, individuals with MDD exhibited greater connectivity between pgACC and dlPFC while engaging in self-related thought as compared with healthy controls [Lemogne et al., 2009]. Together, these studies are consistent with our findings associating current depression and negative-SFT with greater connectivity between pgACC and dlPFC. Our results may also be relevant to literature reporting dlPFC dysfunction in MDD [Koenigs and Grafman, 2009; Mayberg, 2003]. For example, individuals with MDD tend to display abnormal dlPFC activity during tasks involving cognitive control [e.g., Dichter et al., 2009], negative emotion regulation [e.g., Heller et al., 2013], and rumination [Cooney et al., 2010]. However, further research using both task-based and rs-fMRI in MDD will be required to establish the relationship between functional activity of dlPFC and resting-state connectivity with dlPFC in depression.

The results linking negative-SFT with greater rsFC between pgACC and lateral prefrontal and posterior parietal regions are also consistent with network perspectives of depression [Drevets et al., 2008; Mayberg, 2003; Whitfield-Gabrieli and Ford, 2012]. Specifically, our findings mirror rsFC studies in MDD, which reliably demonstrate increased rsFC between the DMN, including pgACC, and the FPN, including the dlPFC and posterior parietal cortex

[Kaiser et al., 2015]. Our results are also consistent a functional near-infrared spectroscopy study showing increased rsFC of the FPN in late life depression [Rosenbaum et al., 2016]. Whereas the DMN is implicated in SFT or internally focused attention [Buckner et al., 2008], the FPN is associated with cognitive control and externally focused attention [Fox et al., 2005; Seeley et al., 2007]. The DMN and FPN are typically negatively correlated at rest [Fox et al., 2005], flexibly coupled during autobiographical memory tasks [Spreng et al., 2010], and increased anti-correlation between these networks is associated with better working memory performance [Hampson et al., 2010]. Thus, one possible interpretation of increased DMN-FPN connectivity in MDD is that FPN regions are over-recruited to accommodate the elevated negative-SFT occurring in depression at the cost of paying attention to the external world [Kaiser et al., 2015]. Interestingly, this neurobiological explanation aligns with theoretical accounts of heightened SFT in depression, which emphasize an impaired ability to turn attention to external stimuli when the situation requires it [Ingram, 1990].

The findings relating negative-SFT and current depression with increased rsFC between pgACC and postcentral gyrus/SMA may be relevant to the regulation of negative emotion in MDD. Although the SMA is known to play an important role in motor planning and motor imagery [Goldberg, 1985], recent research indicates that the SMA may also be involved in the regulation of emotion [Kohn et al., 2014], in particular of negative emotions [e.g., Rodigari and Oliveri, 2014]. For example, a recent transcranial magnetic stimulation study found that repetitive stimulation to the SMA increased the perceived valence of negative emotional stimuli in healthy individuals [Rodigari and Oliveri, 2014]. Neuroimaging research has revealed abnormal structure and function of SMA in depression [Liu et al., 2012; Zhang et al., 2016]. Thus, dysfunction of SMA may contribute to enhanced negative emotions in MDD, including related to oneself.

There are some limitations to the present study that should be noted. First, while we investigated negative-SF using a validated SCT [Exner, 1973], it is possible that the type of SF recruited by this task was more automatic as opposed to controlled. Researchers have suggested that these different types of SF may rely on partially different neural correlates [Lemogne et al., 2009]. Future research will therefore be needed to examine the neural correlates of both automatic and controlled SF tasks in depression. Second, we examined the relationship between negative-SFT and rs-fMRI, so it is unclear whether the same brain regions and networks would be recruited during fMRI tasks that explicitly engage negative-SFT in individuals with depression. However, task-based fMRI studies to date suggest that similar patterns of connectivity, in particular of mPFC and ACC regions, are found during paradigms where individuals with depression actively engage in negative-SFT [Nejad et al., 2013 for review]. Third, only female participants were included in the present study, thus it remains unknown whether these results would generalize to a male population with depression. Further research could investigate whether the neural and behavioral correlates of negative-SFT in depression differ in men versus women. Fourth, we did not collect information about participation in psychotherapy for depression in the present study. Psychotherapeutic treatment for depression has demonstrated effects on neurobiology and behavior [e.g., Crowther et al., 2015; McGrath et al., 2013], including specifically related to negative-SFT [Yoshimura et al., 2014; Yoshimura et al., 2017]. Therefore, future research

will be required to further examine the effects of psychotherapy on rsFC of dmPFC and pgACC regions and negative-SFT for individuals with varying depression histories and severities. Fifth, because we did not specifically recruit for anxiety disorders in the present study, we did not have adequate statistical power to test whether clinically significant anxiety moderates the effects of negative-SFT on rsFC. Finally, consistent with a dimensional approach to psychopathology [Insel et al., 2010], our study recruited individuals with a broad range of severity of depressive symptoms, which made it somewhat difficult to estimate the duration and total number of depressive episodes. This limits comparison with past studies adopting a categorical approach focused on MDD and more severe forms of depression. However, this dimensional approach is also a strength of the current study in that we included mild and moderate forms of depression in addition to MDD.

Given the high risk for recurrence in MDD [Burcusa and Iacono, 2007], these findings may have important clinical implications for the development of targeted treatments aimed at reducing negative-SFT and restoring network connectivity in MDD. Preliminary studies using therapies that target negative-SFT, such as rumination-focused cognitive behavioral therapy, provide some support for the efficacy of such an approach [Watkins, 2015]. More broadly, these findings highlight a dimension of social-affective function that might underlie not only MDD but also other psychiatric conditions, such as post-traumatic stress disorder [Bryant and Guthrie, 2007; McLaughlin and Nolen-Hoeksema, 2011; Philippi and Koenigs, 2014]. Consistent with a dimensional perspective of mental health [Insel et al., 2010; Widiger and Edmundson, 2014], future research will be necessary to determine the precise relationships among negative-SFT and severity of symptoms across a range of psychiatric disorders.

Clinical studies have also begun to investigate the neural mechanisms of therapeutic change before and after successful treatment of MDD. Across different therapeutic interventions, reduced depressive symptoms were associated with normalization of DMN connectivity at rest [Li et al., 2013; Liston et al., 2014], and reduced activity and connectivity of the mPFC and pgACC while engaging in negative-SFT [Yoshimura et al., 2014; Yoshimura et al., 2017]. Moreover, treatment studies using transcranial magnetic stimulation for depression have shown normalization of rsFC between mPFC and dlPFC [e.g., Liston et al., 2014]. An important question for future research is whether pretreatment levels of negative-SFT would predict changes in rsFC within the DMN or between DMN and FPN following treatment. The use sentence completion tasks to measure treatment outcomes could provide another more cost-effective alternative to tracking treatment success through neuroimaging, above and beyond levels of depression.

Conclusion

In summary, we replicated previous research in MDD, revealing an association between negative-SF thought and depression history and severity. We also demonstrated novel results linking negative-SF with rsFC within and between neural networks involved in internally and externally focused attention. These findings highlight a key dimension of social-affective functioning that may cut across different psychiatric disorders.

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Supplementary Material

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Acknowledgments

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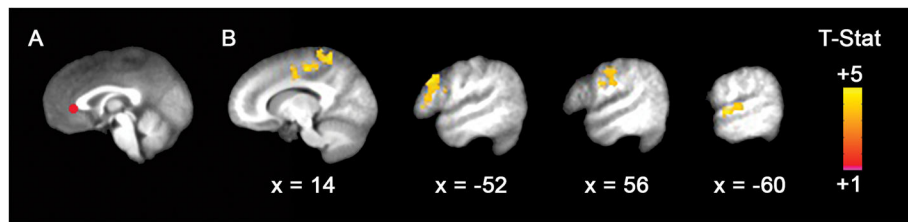
Figure 1. Depression group was associated with connectivity between pgACC and prefrontal, parietal, and temporal cortex

A. pgACC seed ROI; B. *Images from left to right:* depression group was associated with greater connectivity between pgACC and right medial postcentral gyrus (x = 14), left middle frontal gyrus extending to dorsolateral PFC (dlPFC; x = −52); right postcentral gyrus (x = 56), and right superior temporal gyrus (x = −60). The seed ROI and all results are displayed on the group average structural MRI in MNI-space. All results survived whole-brain cluster correction ($p_{FWE} < 0.05$, $p = 0.001$ uncorrected).
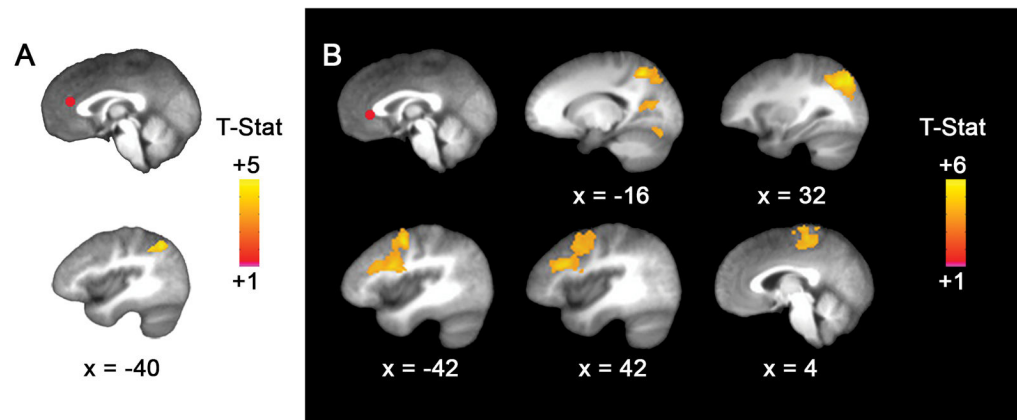
Figure 2. Negative self-focused thought was associated with connectivity between mPFC regions and parietal and temporal cortex

A. *Top*: dmPFC seed ROI; *Bottom:* Higher proportion of negative self-focused responses was associated with greater connectivity between dmPFC and left inferior parietal lobule; B. *Top images from left to right:* pgACC seed ROI; higher proportion of negative self-focused responses was associated with greater connectivity between pgACC and left precuneus (x = −16), right precuneus extending to middle temporal gyrus (x = 32); *Bottom images from left to right*: higher proportion of negative self-focus was associated with greater connectivity between pgACC and left middle frontal gyrus extending to dorsolateral PFC (dlPFC; x = −42), right middle frontal gyrus extending to dlPFC (x = 42), and right paracentral lobule extending to SMA (BA 6; x = 4). The seed ROIs and all results are displayed on the group average structural MRI in MNI-space. All results survived whole-brain cluster correction ($p_{FWE} < 0.05$, $p = 0.001$ uncorrected).

Table I

Depression Group Characteristics

	NoDep ($n = 30$)	PastDep ($n = 15$)	CurrentDep ($n = 34$)
Age[a]	27.1 (7.6)	28.0 (5.8)	27.9 (7.1)
Education Level[b]			
High school diploma/equivalent	0	1	0
Some college, no degree	12	4	10
Associate's degree	1	1	1
Bachelor's degree	7	6	11
Master's degree	8	3	10
Doctoral degree	2	0	2
Race[b]			
White	22	13	25
Asian	5	2	6
African American	3	0	1
Unknown	0	0	2
BDI-II[c]	0.9 (1.4)	1.3 (1.8)	19.5 (10.0)[*]
Depressive Episodes[d]			
0–1	n/a	5	5
2	n/a	4	4
3	n/a	3	4
4	n/a	2	6
5	n/a	0	1
6	n/a	0	3
7	n/a	0	1
9 or greater	n/a	1	10
Current Major Depressive Episode Duration[e]	n/a	n/a	24.2 (56.0)
Current Anxiety Disorder[f]	1	3	24
RRS[g]	35.8 (8.7)	46.4 (9.4)	62.8 (12.8)

[a] Participant age for the sample ranged from 18 to 45 years.

[b] There were no significant group differences in education level ($\chi^2(10) = 7.48$, $p > 0.6$) or race ($\chi^2(4) = 3.32$, p > 0.5).

[c] BDI-II = Beck Depression Inventory-II; BDI-II scores ranged from 0 to 49;

[*] expected group differences were found for depression severity ($F_{2,76} = 73.95$, $p < 0.001$).

[d] There was no significant difference between depression groups in number of depressive episodes in one's lifetime ($\chi^2(9) = 9.01$, $p > 0.4$).

[e] Duration of major depressive episode is reported in average months.

[f] Number of participants with a current anxiety disorder diagnosis based on SCID were different between groups ($\chi^2(2) = 33.44$, $p < 0.001$).

[g] RRS = Ruminative Responses Scale; total RRS scores ranged from 24 to 82.

Table II

Examples of SCT responses for self-focus by valence category

SCT Stem	Self-Negative	Self-Positive
I am	"pathetic."	"happy with who I am."
Others	"are disappointed in me."	"think I am always happy and smiling."

Table III

Negative self-focused responses

	NoDep (n = 30)	PastDep (n = 15)	CurrentDep (n = 34)
Negative self-focus[a]	*.13 (.11)****	*.18 (.13)*[+]	*.25 (.15)***
Positive self-focus[a]	.33 (.17)	.34 (.20)	.27 (.17)[−]

[a] Proportion of negative and positive out of total self-focused responses; proportion of negative self-focus ranged between 0 and .57 and proportion of positive self-focus ranged between 0 and .76.

Hypothesized relationships are in italics.

[−] $p > .1$,

[+] $p = .1$,

[*] $p < 0.05$,

[**] $p < 0.01$,

[***] $p < 0.001$.

Table IV

Regression results using connectivity for seeds ROIs and depression group

Seed ROI	Cluster location	MNI coordinates (x, y, z)	Cluster size (voxels)	t-value	Average connectivity[a] NoDep (n = 28)	Average connectivity PastDep (n = 13)	Average connectivity CurrentDep (n = 33)
pgACC	R. postcentral gyrus extending to SMA[b]	14, −50, 65	1,065	4.92	0.09 (1.9)	0.58 (2.5)	2.76 (2.3)[*]
	L. middle frontal gyrus extending to dlPFC[b]	−53, 22, 34	469	4.82	−0.76 (2.2)	−0.27 (2.8)	2.18 (2.8)[*]
	R. postcentral gyrus	66, −20, 41	443	4.60	0.10 (2.2)	−0.68 (2.9)	2.86 (2.5)[*]
	L. superior temporal gyrus (BA 22)	−61, −6, 0	153	4.77	0.60 (3.1)	0.90 (3.3)	3.89 (3.1)[*]

All regression results were significant after controlling for age (pFWE = 0.05, uncorrected p = 0.001).

[a] Average connectivity scores correspond to z-scores; means and standard deviations are reported for each depression group.

[b] SMA = supplementary motor area, dlPFC = dorsolateral prefrontal cortex.

[*] The CurrentDep group had significantly greater connectivity than both the PastDep and NoDep groups (each $p < 0.05$).

Table V

Regression results using connectivity for seeds ROIs and negative self-focus

Seed ROI	Cluster location	MNI coordinates (x, y, z)	Average raw connectivity value[*]	Cluster size (voxels)	t-value
dmPFC	L. inferior parietal lobule	−40, −61, 45	1.49	414	4.79
pgACC	L. precuneus	−16, −60, 49	1.74	4,429	5.71
	R. precuneus extending to middle temporal gyrus (BA 39)	30, −78, 39	0.79	3,263	6.02
	L. middle frontal gyrus extending to dlPFC	−42, 5, 52	0.87	1,819	5.59
	R. middle frontal gyrus extending to dlPFC	42, 21, 29	1.05	1,813	5.07
	R. paracentral lobule extending to SMA (BA 6)	4, −34, 59	1.47	1,160	4.79

All regression results were significant after controlling for age (pFWE = 0.05, uncorrected p = 0.001).

[*] Raw connectivity values correspond to average z-scores across the sample.

dlPFC = dorsolateral prefrontal cortex; SMA = supplementary motor area.