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White Matter Abnormalities Predict Residual Negative Self-Referential Thinking Following Treatment of Late-Life Depression with Escitalopram: A Preliminary Study

Lindsay W. Victoria, PhD¹, George S. Alexopoulos, MD¹, Irena Ilieva, PhD¹, Aliza T. Stein, BA², Matthew J. Hoptman, PhD^{3,4}, Naib Chowdhury, BA¹, Matteo Respino, MD¹, Sarah Shizuko Morimoto, PsyD⁵, Dora Kanellopoulos, PhD¹, Jimmy N. Avari, MD¹, and Faith M. Gunning, PhD¹

¹Weill Cornell Institute of Geriatric Psychiatry, Department of Psychiatry, Weill Cornell Medicine, White Plains, NY

²Department of Psychology, University of Texas at Austin, Austin, TX

³Schizophrenia Research Division, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY

⁴Department of Psychiatry, New York University School of Medicine, New York, NY

⁵Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT

Abstract

Background: Negative self-referential thinking is a common symptom of depression associated with poor treatment response. In late-life depression, white matter abnormalities may contribute to negative self-referential thoughts following antidepressant treatment. We investigated the association of fractional anisotropy (FA) in select regions of the negative valence system (NVS) with residual negative self-referential thoughts following treatment with escitalopram for late-life depression.

Methods: The participants were older adults with major depression and psychiatrically normal controls. Depressed participants received 12 weeks of treatment with escitalopram. To assess self-referential thinking, participants completed a Trait Adjective Task at baseline and at week 12. Baseline MRI scans included a diffusion imaging sequence for FA analyses.

Results: Participants with late-life depression differed from controls on all performance measures of the Trait Adjective Task at baseline and at 12 weeks. Depressed participants endorsed fewer negative personality traits and more positive personality traits at week 12 compared to

Author Responsible for Correspondence: Lindsay W. Victoria, PhD, Weill Cornell Institute of Geriatric Psychiatry, 21 Bloomingdale Road, White Plains, NY 10605; Telephone: 914-682-5413; Fax: 914-682-6979; liv3002@med.cornell.edu.

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Conflicts of Interest

G.S. Alexopoulos has served on the speakers' bureaus of Allergan, Lundbeck, Otsuka, and Takeda. No other authors report conflicts of interest.

baseline. Lower FA in the dorsal anterior cingulate and in the uncinate fasciculus in depressed participants was correlated with residual negative self-referential thinking (e.g., more endorsed negative adjectives, fewer rejected negative adjectives) at treatment end.

Limitations: The sample size is modest so the findings are preliminary. FA analyses were restricted to predetermined regions.

Conclusions: Negative self-referential thinking improved in depressed older adults following 12 weeks of treatment with escitalopram. Baseline FA in select white matter regions of the NVS was associated with residual negative self-referential thinking. These findings may help identify treatment targets for residual negative self-referential thoughts.

Introduction

Self-referential thinking, or making sense of one's place in the internal and external environment, is necessary for adaptive functioning. The ability to reflect on past experiences and apply them to current and future experiences facilitates goal-directed behaviors (Huang et al., 2015; Northoff et al., 2006). In individuals suffering from depression, biases in processing of both internal and external stimuli (e.g., interpreting neutral stimuli as negative, assigning greater salience to negative environmental stimuli) contribute to negative representations of the past and future, as well as negative self-referential thoughts (Beck et al., 1987; Bradley et al., 1995; Groenewold et al., 2013; Harmer et al., 2009; Hilimire et al., 2015). Negative self-referential thoughts contribute to cognitive (e.g., guilt, rumination, and self-criticism) and affective (e.g., feelings of worthlessness and sadness) symptoms of depression (Koster et al., 2011; Mennin and Fresco, 2013; Olatunji et al., 2013; Stuhmann et al., 2013). Negative self-referential thoughts are a risk factor for depression in adolescence (Wilkinson et al., 2013) and have been associated with resistance to antidepressant drugs (Jones et al., 2008; McIntyre et al., 2013). Further, the presence and severity of negative self-referential thoughts following treatment are a predictor of relapse (Michalak et al., 2011).

Disruptions in the negative valence system (NVS) may play a key role in the negative self-referential thoughts often present in depression. The NVS is comprised, in part, of the medial prefrontal cortex, the dorsal anterior cingulate cortex (dACC), and the amygdala, as well as anterior aspects of the default mode network (DMN), including the dorsomedial prefrontal cortex (DMPFC) and medial temporal lobes (Hamilton et al., 2012, 2011; Langenecker et al., 2014; Salomon et al., 2014). Regions of the NVS are engaged in the perception of aversive situations or stimuli (Baucom et al., 2012; Gerber et al., 2008; O'Neill et al., 2018) and the maintenance of self-referential thoughts (Andrews-Hanna, 2012; Landa et al., 2013; Sheline et al., 2009). Abnormalities of the NVS contribute to the experience of negative affect and negative representation of the self within one's environment (Andrews-Hanna et al., 2014; Simplicio et al., 2012).

Individuals suffering from depression often have abnormal resting state functional connectivity of the NVS (Dutta et al., 2014; Karim et al., 2017; Stuhmann et al., 2013). Altered patterns of functional connectivity include hyperconnectivity among anterior nodes of the DMN (e.g., DMPFC, VMPFC), as well as abnormal connectivity between anterior nodes of the DMN and other regions of the NVS, including the amygdala and the dACC

(Alexopoulos et al., 2013; Diener et al., 2012; Etkin et al., 2013; Kaiser et al., 2015; Langenecker et al., 2014). Altered functional connectivity among the amygdala, the DMPFC, and the dACC predicts poor antidepressant response and relapse of depression (Dichter et al., 2014; Fu et al., 2013; Marchetti et al., 2012; Phillips et al., 2015; Pizzagalli, 2011).

The impact of aging on the white matter is well documented and may contribute to negative self-referential thinking in late-life depression (Brickman et al., 2011; Charlton et al., 2014; Geerlings et al., 2012; Gunning-Dixon et al., 2009; Wu et al., 2011; Wu and Aizenstein, 2017). Structural white matter abnormalities in the aging brain have been associated with persistence of mood and cognitive symptoms following antidepressant treatment for late-life depression (Alexopoulos et al., 2008; Gunning-Dixon et al., 2010; Jenkins et al., 2016; Taylor et al., 2011, 2008). It has been suggested that abnormal white matter integrity in the NVS of older depressed adults interferes with the shifting of attention away from negative thoughts about one's self (Rizk et al., 2017; Taylor et al., 2015). Thus, understanding how the white matter microstructure relates to the persistence of negative self-referential thoughts in older adults with MDD may help to identify neural substrates of affective symptoms.

Diffusion imaging is well suited for the investigation of abnormal structural connectivity within networks implicated in negative self-referential processing in late-life depression. This study uses diffusion imaging to investigate the relationship of structural integrity of anterior NVS circuitry with negative self-referential thinking in depressed older adults. To investigate the specific structural abnormalities that may contribute to negative self-referential thoughts in late-life depression, we focused on white matter microstructure within three key regions: 1) The dorsomedial prefrontal cortex (DMPFC), an anterior region of the DMN that is critical for self-referential processing (Andrews-Hanna, 2012; Andrews-Hanna et al., 2014; Meyer and Lieberman, 2018; Sheline et al., 2009); 2) The dorsal anterior cingulate cortex (dACC), a hub involved in processing affective salience and directing attention towards self-relevant stimuli (Etkin et al., 2011; Groenewold et al., 2014, 2013; Shenhav et al., 2016); and 3) Uncinate fasciculus, a white matter tract that runs between the frontal and anterior temporal lobes, connecting limbic regions of the NVS involved in affective processing (e.g., amygdala) to higher order cortical regions (e.g., DMPFC) involved in directing attention and maintaining self-referential thoughts (Hau et al., 2017; Oishi et al., 2015; Olson et al., 2013; Von Der Heide et al., 2013; Zhang et al., 2012).

The primary objectives of this study were to: 1) Examine how negative self-referential thinking changes from baseline to the end of treatment of late-life depression with escitalopram; and 2) Examine whether white matter microstructure prior to treatment within NVS circuitry (DMPFC, dACC, uncinate) is associated with residual negative self-referential thinking following treatment. We hypothesized that: 1) In late-life depression, escitalopram would lead to a reduction in negative self-referential thoughts, as measured by performance on a trait adjective task; 2) In depressed older adults, abnormal white matter microstructure prior to treatment in the DMPFC, the dACC, and the uncinate would be associated with residual negative self-referential thinking at the end of 12 weeks of treatment with escitalopram.

Methods

Participants

Participants in this study included older adults with major depression and psychiatrically normal older adults. Participants were recruited by the Weill Cornell Institute of Geriatric Psychiatry through radio and print advertisement and through our hospital outpatient psychiatry services. Participants with late-life depression (N = 20) had a diagnosis of major depression without psychotic features and a score ≥ 20 on the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). Psychiatrically normal control participants (N = 20) had no history or presence of any psychiatric disorder or use of psychotropic agents. Participants provided written informed consent as approved by the Institutional Review Boards of Weill Cornell Medicine and the Nathan Kline Institute for Psychiatric Research.

Individuals were excluded if they had: 1) a plan or intent to commit suicide in the near future; 2) a score < 26 on the Mini Mental State Exam (MMSE; Folstein et al., 1975); 3) past diagnosis or evidence of dementia or mild cognitive impairment on exam (MCI); 4) a neurodegenerative brain disease; 5) an acute or severe medical illness, e.g., metastatic cancer, brain tumors, liver or kidney failure, myocardial infarction, or stroke within three months preceding the study; 6) treatment with medications associated with depression, e.g., steroids, reserpine, tamoxifen, or alpha-methyl-dopa; 7) contraindication to MRI, e.g., cardiac pacemaker, biomedical implant, claustrophobia; 8) current involvement in psychotherapy. Additionally, depressed older adults were excluded if they had: 1) a history or presence of substance abuse within 6 months of study entry or any psychiatric disorder other than major depression or generalized anxiety disorder; 2) a previous failure to respond to an adequate dose and duration of treatment with escitalopram.

Treatment

The participants with late-life depression received 12 weeks of treatment with escitalopram as part of this study. Treatment began with 10 mg/day escitalopram for one week, followed by an increase to the target dose of 20 mg/day. Participants who were unable to tolerate 20 mg/day received a daily dose of 15 or 10 mg for the remainder of their study participation. Participants unable to tolerate 10 mg/day exited the study.

Assessment

In participants with late-life depression, a diagnosis of major depression was made by Structured Clinical Interview for DSM Disorders (SCID) criteria. Further, depressive symptom severity was assessed with the HAM-D prior to study entry. Two clinician investigators specialized in geriatric psychiatry reached consensus on the diagnosis of major depression and ruled out the possibility of MCI based on review of neuropsychological tests and overall function. If MCI was suspected, a comprehensive neuropsychological battery was administered.

At study entry, baseline depressive symptom severity was assessed with the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) in both depressed and control participants. Overall cognitive function was assessed with the Mattis

Dementia Rating Scale (DRS; Mattis, 1988), which includes domains for attention, initiation/perseveration, construction, conceptualization, and memory. Clinical diagnosis was made by study clinicians whereas research assessments were administered by trained and reliable research assistants of the Weill Cornell Institute of Geriatric Psychiatry.

Trait Adjective Task

Depressed and control participants completed a Trait Adjective Task (Fossati et al., 2003) to measure self-referential processing at baseline and treatment end (week 12). Participants viewed a series of adjectives corresponding to personality traits one at a time and were asked to decide if each adjective described them or not. Participants viewed a total of 80 adjectives; 40 of the adjectives had positive valence (e.g., *happy, friendly, punctual*) and 40 adjectives had negative valence (e.g., *sad, lonely, grumpy*). Positive and negative adjectives were selected from a normed word list and matched for word length, frequency, and arousal. The degree of desirability of positive adjectives was comparable to the degree of undesirability of negative adjectives (Anderson, 1968).

The adjectives were displayed on a Dell laptop with a 14-inch monitor in white text on a black background using e-Prime stimulus presentation software (Psychology Software Tools). Each trial consisted of a 2000 ms fixation display and a 500 ms adjective presentation. Participants used a computer mouse to make their self-referential responses following the adjective presentation, pressing the left button to indicate “yes” for words that described them or the right button to indicate “no” for words that did not describe them. The outcome variables of interest were the number of endorsed positive traits, endorsed negative traits, rejected positive traits, and rejected negative traits.

MRI Procedures

Image Acquisition.—MRI data were acquired at baseline from all depressed and control participants. The MRI scanning sessions were conducted at the Center for Biomedical Imaging and Neuromodulation (C-BIN) of the Nathan Kline Institute for Psychiatric Research. The CBIN is equipped with a Siemens 3T Tim Trio scanner with a 32-channel head coil. MRI scan sequences included a T2-weighted dual echo FLAIR and a high-resolution whole brain T1-weighted MPRAGE. Structural MRI data were acquired with a 37-direction echo planar diffusion tensor imaging (DTI) sequence (TR = 9000 ms; TE = 91 ms; b-value = 1000 s/mm², 72 slices, FoV = 256 mm, voxel size = 2 mm isovoxel), which allowed for whole brain coverage. An additional seven images had b=0s/mm².

Image Processing.—White matter integrity was assessed with the extraction of Fractional Anisotropy (FA) values from the DTI scan sequence images. FA was quantified with FSL’s Tract-Based Spatial Statistics approach (TBSS; Smith et al., 2006). The TBSS analysis approach creates a white matter “skeleton” image derived from each participant’s major white matter tracts at the whole brain level. DTI data were corrected for head motion and eddy current artifact using affine registration, then the corrected images were fit with a diffusion tensor model, assigning an FA value to each voxel based on the principal eigenvector of water diffusivity along white matter tracts within that voxel. Individual FA maps were nonlinearly registered to a standard space FA target to generate a mean FA

skeleton, and the mean image was thresholded at a value of 0.2 for voxelwise analyses. To identify FA on a voxel-by-voxel basis within the predefined regions of interest, FA skeletons were restricted to the DMPFC, dACC, and uncinate (Figure 1). We used the Harvard-Oxford Cortical and Subcortical atlases to identify the three regions of interest, and created binary FA masks based on the atlas segmentation of these regions. We selected these regions for FA extraction because of their proposed role in self-referential thinking.

Data Analysis

We conducted independent samples t-tests to compare demographics, clinical symptoms, and overall cognitive functioning between the participants with late-life depression and psychiatrically normal control participants at baseline. We conducted 2×2 repeated measures ANOVAs to investigate the interaction of adjective response (endorsed vs. rejected) and valence (positive vs. negative) at baseline and week 12. Finally, we investigated the association between baseline white matter integrity and self-referential processing at week 12 by correlating extracted baseline FA values with week 12 Trait Adjective Task performance. Pearson correlation coefficients are reported for this analysis. Two-tailed significance tests with a threshold of $p < 0.05$ were used in all statistical comparisons.

Results

This study included 40 older adults (aged 60–85 years). Of these, 20 met criteria for major depression (8 males, 12 females) and 20 had no history or presence of psychopathology (8 males, 12 females). As expected, the participants with late-life depression had higher levels of depression severity than controls (Table 1). At baseline, the participants with late-life depression and the control participants did not differ in age or overall cognitive function.

In participants with late-life depression, depression severity (MADRS) decreased from baseline to week 12 (baseline $M(SD) = 26.25(3.33)$; week 12 $M(SD) = 10.33(7.44)$; $t(11) = 8.11$, $p < 0.001$). In controls, as expected, there was no significant change in MADRS from baseline to week 12 (baseline $M(SD) = 1.21(1.55)$; week 12 $M(SD) = 1.37(1.54)$; $t(18) = -0.45$, $p = 0.66$).

Treatment

The 20 participants with late-life depression received treatment with escitalopram at the target dose of 20 mg daily. Week 12 analyses were restricted to participants who completed the 12 weeks of escitalopram treatment and the Adjective Task at both baseline and week 12 (depressed: $N = 12$; controls: $N = 20$). Reasons for missing depressed participant data at week 12 included: participants' refusal to continue participation in the study ($N = 4$), early termination due to escitalopram side effects ($N = 2$), early termination of participation at family member's request ($N = 1$), and Adjective Task not administered at termination visit ($N = 1$).

In the 12 participants with late-life depression who completed 12 weeks of escitalopram treatment and the Adjective Task, the average escitalopram daily dose was 17.08 mg ($SD = 3.96$, Median = 20 mg, Range = 10–20 mg).

Trait Adjective Task Performance

At baseline and week 12, participants with late-life depression significantly differed from control participants on all Trait Adjective Task measures. Compared to controls, depressed participants endorsed fewer positive traits, endorsed more negative traits, rejected more positive traits, and rejected fewer negative traits (Table 2).

In participants with late-life depression, Trait Adjective Task performance significantly differed from baseline to week 12 (Figure 2). Relative to baseline, following 12 weeks of escitalopram treatment, depressed participants endorsed more positive traits ($t(11) = 2.24$, $p = 0.05$), endorsed fewer negative traits ($t(11) = -3.08$, $p = 0.01$), and rejected more negative traits ($t(11) = 2.63$, $p = 0.02$) than at baseline. There was no significant change in number of positive traits rejected from baseline to week 12 ($t(11) = -1.68$, $p = 0.12$). There were larger effects of treatment on negative adjective responses from baseline to week 12 in depressed participants (endorsed negative traits: Cohen's $d = 0.90$; rejected negative traits: Cohen's $d = -0.70$; endorsed positive traits: Cohen's $d = -0.58$; rejected positive traits: Cohen's $d = 0.46$). In controls, there was no difference in adjective task performance from baseline to week 12.

There was also no significant correlation between depressive symptom severity (MADRS score) and Trait Adjective Task performance in participants with late-life depression at baseline and week 12.

There was a significant interaction of adjective response (endorsed vs. rejected) and valence (positive vs. negative) in participants with late-life depression (Figure 3). This relationship was observed at baseline ($F(1,20) = 9.88$, $p = 0.005$) and week 12 ($F(1,12) = 21.94$, $p = 0.001$). There was also a significant interaction of change in adjective response and valence from baseline to week 12 ($F(1,12) = 7.59$, $p = 0.02$), such that depressed participants are more likely to endorse positive adjectives and reject negative adjectives following treatment. This finding indicates a consistent pattern of the relationship between positive and negative adjective responses in depressed participants at both baseline and week 12 and supports a decrease in negative self-referential thinking and an increase in positive self-referential processing following 12 weeks of escitalopram treatment for late-life depression.

Baseline Trait Adjective Performance and FA.—In participants with late-life depression, there was no significant correlation between baseline FA in the DMPFC, dACC, or uncinate and any Trait Adjective Task measure (Table 3).

Week 12 Trait Adjective Task Performance and FA.—In participants with late-life depression, baseline FA in the right dACC was associated with response to positive and negative adjectives following 12 weeks of escitalopram treatment (Table 3). Higher baseline right dACC FA predicted response to negative adjectives (fewer endorsements and more rejections) at the end of treatment. These correlations were also significant when controlling for change in depressive symptom severity (MADRS score) from baseline to week 12 (endorsed negative: $r(8) = -0.82$, $p = 0.004$; rejected negative: $r(9) = 0.62$, $p = 0.05$). Lower baseline FA in the right uncinate was associated with endorsement of negative adjectives at week 12. This correlation was significant when controlling for change in depressive

symptom severity (MADRS score) from baseline to week 12 ($r(8) = -0.71$, $p = 0.02$). There was no significant association of FA in the right or left DMPFC and response to negative adjectives at treatment end.

Discussion

The principal finding of this study is that abnormalities in white matter microstructure within the negative valence system (NVS) are associated with residual negative self-referential thoughts in older adults with major depression after 12 weeks of treatment with escitalopram. Specifically, lower fractional anisotropy (FA) in the white matter of the dACC and the uncinate prior to treatment was associated with greater negative self-referential responses to a Trait Adjective Task at treatment end.

This is the first study to document a link between white matter abnormalities, as measured by FA, within the NVS and residual negative self-referential thinking following antidepressant drug treatment in late-life depression. FA is a measure of anisotropic diffusion. It may be subdivided into axial diffusion (i.e., parallel to the primary direction of diffusion) and radial diffusion (i.e., perpendicular to the primary direction of diffusion) (Beaulieu, 2002). We acknowledge that FA accounts for multiple sources of white matter abnormalities, including both axonal coherence and demyelination (e.g., Douaud et al., 2011; Song et al., 2002). Therefore, the FA values reported offer a broad view of white matter microstructure, taking into consideration a range of underlying physiological dysfunctions that may contribute to altered white matter integrity in aging (Kochunov et al., 2007; Marques et al., 2016; Salat et al., 2005) and depression (Osoba et al., 2013; Thomas et al., 2003).

Lower FA was shown to predict residual negative self-referential thinking in the dACC, which plays a role in the processing of positive and negative information and uses affectively valenced information to direct attention and motivate future response selection (Bush et al., 2000; Northoff and Bermpohl, 2004; Shenhav et al., 2016). The uncinate is a white matter tract that projects along the midline and connects the limbic, affective processing regions of the NVS with the higher cortical regions, critical for the maintenance of self-referential thoughts (Lemogne et al., 2012; Northoff and Bermpohl, 2004). Depressive episodes are characterized by preferential processing of negative information about a person's self (Bargh and Tota, 1988; Gotlib et al., 2004; Wagner et al., 2015). Thus, aging related microstructural abnormalities in the dACC and in the uncinate may disrupt functional connections within the NVS (Nejad et al., 2013; Steffens et al., 2011) and interfere with normalization of self-representation, leading to residual negative self-referential thoughts (LeMoult et al., 2017; Renner et al., 2015; Schmaling et al., 2002).

Consistent with earlier literature, depressed participants in this study had more negative self-referential thoughts than psychiatrically normal control participants. Treatment with escitalopram improved negative self-referential thoughts in depressed participants (i.e., increased endorsement of positive traits, decreased endorsement of negative traits, and increased rejection of negative traits). Improvement in negative self-referential negative thinking was not fully accounted for by improvement in depressive symptomatology since

there was no significant correlation between severity of depression and Trait Adjective Task performance both before and after treatment. The improvement in negative self-referential thinking following treatment with an antidepressant is in accord with literature suggesting that antidepressant drug administration modulates emotional processing in depressed patients very early in treatment, before changes occur in mood and other depressive symptoms occur (Harmer et al., 2009). It has been suggested that antidepressants improve self-referential thoughts by normalizing abnormal patterns of activation in NVS regions by increasing neural activation of the dACC (Di Simplicio et al., 2012, Hilimire et al., 2015).

Limitations

The findings of this study should be viewed in the context of its limitations, which include its small sample size and the restriction of FA analyses to predetermined regions. Based on the small sample size, findings of this study should be considered preliminary in need of replication. FA analyses selectively focused on brain regions related to the study hypotheses. Therefore, we cannot assert that the association between FA and Trait Adjective Task performance is exclusively linked to microstructural white matter abnormalities within the dACC and uncinate and not a result of global white matter disruption or volume loss, which are common in aging and in depression. Future studies should consider whole-brain measures of white matter microstructural abnormalities.

Conclusions

In conclusion, older adults with major depression had more negative self-referential thoughts than non-depressed older individuals. Twelve-week treatment with escitalopram improved self-referential thinking in the depressed group. White matter microstructural abnormalities in the dACC and the uncinate, predicted residual negative self-referential thoughts at the end of treatment. These two structures connect limbic and cortical regions of the NVS and, when impaired, may prevent normalization of processing related to negative self-referential thinking. If these findings are replicated, these the dACC and the uncinate may serve as targets for neurostimulation approaches, alone or in conjunction with focused psychotherapy in depressed older patients with persistent negative views about themselves (Alexopoulos & Arean, 2014; Fresco & Mennin, 2013).

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References

- Alexopoulos GS, Hoptman MJ, Yuen G, Kanellopoulos D, Seirup JK, Lim KO, Gunning FM, 2013 Functional connectivity in apathy of late-life depression: A preliminary study. *J. Affect. Disord* 149, 398–405. 10.1016/j.jad.2012.11.023 [PubMed: 23261142]

- Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Klimstra S, Lim KO, Hoptman MJ, 2008 Microstructural white matter abnormalities and remission of geriatric depression. *Am. J. Psychiatry* 165, 238–244. 10.1176/appi.ajp.2007.07050744 [PubMed: 18172016]
- Andrews-Hanna JR, 2012 The brain's default network and its adaptive role in internal mentation. *Neuroscientist* 18, 251–270. 10.1177/1073858411403316 [PubMed: 21677128]
- Andrews-Hanna JR, Smallwood J, Spreng RN, 2014 The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Ann. N. Y. Acad. Sci* 1316, 29–52. 10.1111/nyas.12360 [PubMed: 24502540]
- Bargh JA, Tota ME, 1988 Context-dependent automatic processing in depression: Accessibility of negative constructs with regard to self but not others. *J. Pers. Soc. Psychol* 54, 925–939. 10.1037/0022-3514.54.6.925 [PubMed: 3397867]
- Baucom LB, Wedell DH, Wang J, Blitzer DN, Shinkareva SV, 2012 Decoding the neural representation of affective states. *Neuroimage* 59, 718–727. 10.1016/j.neuroimage.2011.07.037 [PubMed: 21801839]
- Beaulieu C, 2002 The basis of anisotropic water diffusion in the nervous system - A technical review. *NMR Biomed* 15, 435–455. 10.1002/nbm.782 [PubMed: 12489094]
- Beck AT, Brown G, Steer RA, Eidelson JI, Riskind JH, 1987 Differentiating Anxiety and Depression: A Test of the Cognitive Content-Specificity Hypothesis. *J. Abnorm. Psychol* 96, 179–183. 10.1037/0021-843X.96.3.179 [PubMed: 3680754]
- Bradley BP, Mogg K, Millar N, White J, 1995 Selective processing of negative information: effects of clinical anxiety, concurrent depression, and awareness. *J. Abnorm. Psychol* 104, 532–536. 10.1037/0021-843X.104.3.532 [PubMed: 7673577]
- Brickman AM, Sneed JR, Provenzano FA, Garcon E, Johnert L, Muraskin J, Yeung LK, Zimmerman ME, Roose SP, 2011 Quantitative approaches for assessment of white matter hyperintensities in elderly populations. *Psychiatry Res. - Neuroimaging* 193, 101–106. 10.1016/j.psychresns.2011.03.007
- Bush G, Luu P, Posner MI, 2000 Cognitive and emotional influences in anterior cingulate cortex. *Trends.Cogn Sci* 4, 215–222. 10.1016/S1364-6613(00)01483-2 [PubMed: 10827444]
- Charlton RA, Lamar M, Zhang A, Yang S, Ajilore O, Kumar A, 2014 White-matter tract integrity in late-life depression: Associations with severity and cognition. *Psychol. Med* 44, 1427–1437. 10.1017/S0033291713001980 [PubMed: 24041297]
- Di Simplicio M, Norbury R, Harmer CJ, 2012 Short-term antidepressant administration reduces negative self-referential processing in the medial prefrontal cortex in subjects at risk for depression. *Mol. Psychiatry* 17, 503–510. 10.1038/mp.2011.16 [PubMed: 21358707]
- Dichter GS, Gibbs D, Smoski MJ, 2014 A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. *J. Affect. Disord* 172, 8–17. 10.1016/j.jad.2014.09.028 [PubMed: 25451389]
- Diener C, Kuehner C, Brusniak W, Ubl B, Wessa M, Flor H, 2012 A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *Neuroimage* 61, 677–685. 10.1016/j.neuroimage.2012.04.005 [PubMed: 22521254]
- Douaud G, Jbabdi S, Behrens TEJ, Menke RA, Gass A, Monsch AU, Rao A, Whitcher B, Kindlmann G, Matthews PM, Smith S, 2011 DTI measures in crossing-fibre areas: Increased diffusion anisotropy reveals early white matter alteration in MCI and mild Alzheimer's disease. *Neuroimage* 55, 880–890. 10.1016/j.neuroimage.2010.12.008 [PubMed: 21182970]
- Dutta A, McKie S, Deakin JFW, 2014 Resting state networks in major depressive disorder. *Psychiatry Res. - Neuroimaging* 224, 139–151. 10.1016/j.psychresns.2014.10.003
- Etkin A, Egner T, Kalisch R, 2011 Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn. Sci* 15, 85–93. 10.1016/j.tics.2010.11.004 [PubMed: 21167765]
- Etkin A, Gyurak A, O'Hara R, 2013 A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues Clin. Neurosci* 15, 419–429. [PubMed: 24459409]
- Folstein MF, Folstein SE, McHugh PR, 1975 "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res* 12, 189–198. 10.1016/0022-3956(75)90026-6 [PubMed: 1202204]

- Fossati P, Hevenor SJ, Graham SJ, Grady C, Keightley ML, Craik F, Mayberg H, 2003 In search of the emotional self: an FMRI study using positive and negative emotional words. *Am. J. Psychiatry* 160, 1938–1945. 10.1176/appi.ajp.160.11.1938 [PubMed: 14594739]
- Fu CHY, Steiner H, Costafreda SG, 2013 Predictive neural biomarkers of clinical response in depression: A meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. *Neurobiol. Dis* 52, 75–83. 10.1016/j.nbd.2012.05.008 [PubMed: 22659303]
- Geerlings MI, Brickman AM, Schupf N, Devanand DP, Luchsinger JA, Mayeux R, Small SA, 2012 Depressive symptoms, antidepressant use, and brain volumes on MRI in a population-based cohort of old persons without dementia. *J. Alzheimer's Dis* 30, 75–82. 10.3233/JAD-2012-112009 [PubMed: 22377782]
- Gerber AJ, Posner J, Gorman D, Colibazzi T, Yu S, Wang Z, Kangarlou A, Zhu H, Russell J, Peterson BS, 2008 An affective circumplex model of neural systems subserving valence, arousal, and cognitive overlay during the appraisal of emotional faces. *Neuropsychologia* 46, 2129–2139. 10.1016/j.neuropsychologia.2008.02.032 [PubMed: 18440572]
- Gotlib IH, Krasnoperova E, Yue DN, Joormann J, 2004 Attentional Biases for Negative Interpersonal Stimuli in Clinical Depression. *J. Abnorm. Psychol* 113, 127–135. 10.1037/0021-843X.113.1.121
- Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG, 2013 Emotional valence modulates brain functional abnormalities in depression: Evidence from a meta-analysis of fMRI studies. *Neurosci. Biobehav. Rev* 37, 152–163. 10.1016/j.neubiorev.2012.11.015 [PubMed: 23206667]
- Groenewold NA, Roest AM, Renken RJ, Opmeer EM, Veltman DJ, van der Wee NJA, de Jonge P, Aleman A, Harmer CJ, 2014 Cognitive vulnerability and implicit emotional processing: imbalance in frontolimbic brain areas? *Cogn. Affect. Behav. Neurosci* 15, 69–79. 10.3758/s13415-014-0316-5
- Gunning-Dixon FM, Brickman AM, Cheng JC, Alexopoulos GS, 2009 Aging of cerebral white matter: a review of MRI findings. *Int. J. Geriatr. Psychiatry* 24, 109–117. 10.1002/gps [PubMed: 18637641]
- Gunning-Dixon FM, Walton M, Cheng J, Acuna J, Klimstra S, Zimmerman ME, Brickman AM, Hoptman MJ, Young RC, Alexopoulos GS, 2010 MRI signal hyperintensities and treatment remission of geriatric depression. *J. Affect. Disord* 126, 395–401. 10.1016/j.jad.2010.04.004 [PubMed: 20452031]
- Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH, 2012 Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. *Am. J. Psychiatry* 169, 693–703. 10.1176/appi.ajp.2012.11071105 [PubMed: 22535198]
- Hamilton JP, Furman DJ, Chang C, Thomason ME, Dennis E, Gotlib IH, 2011 Default-mode and task-positive network activity in major depressive disorder: Implications for adaptive and maladaptive rumination. *Biol. Psychiatry* 70, 327–333. 10.1016/j.biopsych.2011.02.003 [PubMed: 21459364]
- Hamilton M, 1960 A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23, 56–62. 10.1136/jnnp.23.1.56 [PubMed: 14399272]
- Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, Goodwin GM, Cowen PJ, 2009 Effect of acute antidepressant administration on negative affective bias in depressed patients. *Am. J. Psychiatry* 166, 1178–1184. 10.1176/appi.ajp.2009.09020149 [PubMed: 19755572]
- Hau J, Sarubbo S, Houde JC, Corsini F, Girard G, Deledalle C, Crivello F, Zago L, Mellet E, Jobard G, Joliot M, Mazoyer B, Tzourio-Mazoyer N, Descoteaux M, Petit L, 2017 Revisiting the human uncinate fasciculus, its subcomponents and asymmetries with stem-based tractography and microdissection validation. *Brain Struct. Funct* 222, 1645–1662. 10.1007/s00429-016-1298-6 [PubMed: 27581617]
- Hilimire MR, Mayberg HS, Holtzheimer PE, Broadway JM, Parks NA, DeVylder JE, Corballis PM, 2015 Effects of subcallosal cingulate deep brain stimulation on negative self-bias in patients with treatment-resistant depression. *Brain Stimul* 8, 185–191. 10.1016/j.brs.2014.11.010 [PubMed: 25499035]

- Huang H, Movellan J, Paulus MP, Harlé KM, 2015 The influence of depression on cognitive control: Disambiguating approach and avoidance tendencies. *PLoS One* 10, 1–13. 10.1371/journal.pone.0143714
- Jenkins LM, Barba A, Campbell M, Lamar M, Shankman SA, Leow AD, Ajilore O, Langenecker SA, 2016 Shared white matter alterations across emotional disorders: A voxel-based meta-analysis of fractional anisotropy. *NeuroImage Clin* 12, 1022–1034. 10.1016/j.nicl.2016.09.001 [PubMed: 27995068]
- Jones NP, Siegle GJ, Thase ME, 2008 Effects of rumination and initial severity on remission to cognitive therapy for depression. *Cognit. Ther. Res* 32, 591–604. 10.1007/s10608-008-9191-0
- Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA, 2015 Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. *JAMA Psychiatry* 72, 603–611. 10.1001/jamapsychiatry.2015.0071 [PubMed: 25785575]
- Karim HT, Andreescu C, Tudorascu D, Smagula SF, Butters MA, Karp JF, Reynolds C, Aizenstein HJ, 2017 Intrinsic functional connectivity in late-life depression: Trajectories over the course of pharmacotherapy in remitters and non-remitters. *Mol. Psychiatry* 22, 450–457. 10.1038/mp.2016.55 [PubMed: 27090303]
- Kochunov P, Thompson PM, Lancaster JL, Bartzokis G, Smith S, Coyle T, Royall DR, Laird A, Fox PT, 2007 Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: Tract-based spatial statistics study of aging. *Neuroimage* 35, 478–487. 10.1016/j.neuroimage.2006.12.021 [PubMed: 17292629]
- Koster EHW, De Lissnyder E, Derakshan N, De Raedt R, 2011 Understanding depressive rumination from a cognitive science perspective: The impaired disengagement hypothesis. *Clin. Psychol. Rev* 31, 138–145. 10.1016/j.cpr.2010.08.005 [PubMed: 20817334]
- Landa A, Wang Z, Russell JA, Posner J, Duan Y, Kangarlou A, Huo Y, Fallon BA, Peterson BS, 2013 Distinct neural circuits subserve interpersonal and non-interpersonal emotions. *Soc. Neurosci* 8, 474–488. 10.1080/17470919.2013.833984 [PubMed: 24028312]
- Langenecker SA, Jacobs RH, Passarotti AM, 2014 Current Neural and Behavioral Dimensional Constructs Across Mood Disorders. *Curr. Behav. Neurosci. Reports* 1, 144–153. 10.1007/s40473-014-0018-x
- Lemogne C, Delaveau P, Freton M, Guionnet S, Fossati P, 2012 Medial prefrontal cortex and the self in major depression. *J. Affect. Disord* 136, e1–e11. 10.1016/j.jad.2010.11.034 [PubMed: 21185083]
- LeMoult J, Kircanski K, Prasad G, Gotlib IH, 2017 Negative Self-Referential Processing Predicts the Recurrence of Major Depressive Episodes. *Clin. Psychol. Sci* 5, 174–181. 10.1177/2167702616654898 [PubMed: 28286705]
- Marchetti I, Koster EHW, Sonuga-Barke EJ, De Raedt R, 2012 The Default Mode Network and recurrent depression: A neurobiological model of cognitive risk factors. *Neuropsychol. Rev* 22, 229–251. 10.1007/s11065-012-9199-9 [PubMed: 22569771]
- Marques PCG, Soares JMM, Magalhães RJ da S, Santos NC, Sousa NJC, 2016 Macro- and micro-structural white matter differences correlate with cognitive performance in healthy aging. *Brain Imaging Behav* 10, 168–181. 10.1007/s11682-015-9378-4 [PubMed: 25824621]
- Mattis S, 1988 Dementia Rating Scale: DRS. Odessa, FL Prof. Assess. Resour.
- McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallagher LA, Kudlow P, Alsuwaidan M, Baskaran A, 2013 Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. *Depress. Anxiety* 30, 515–527. 10.1002/da.22063 [PubMed: 23468126]
- Mennin DS, Fresco DM, 2013 What, me worry and ruminate about dsm-5 and rdoc? The importance of targeting negative self-referential processing. *Clin. Psychol. Sci. Pract* 20, 258–267. 10.1111/cpsp.12038
- Meyer MM, Lieberman MD, 2018 Why people are always thinking about themselves: medial prefrontal cortex activity during rest primes self-referential processing. *J. Cogn. Neurosci* 30, 714–721. 10.1162/jocn [PubMed: 29308983]
- Michalak J, Hölz A, Teismann T, 2011 Rumination as a predictor of relapse in mindfulness-based cognitive therapy for depression. *Psychol. Psychother. Theory, Res. Pract* 84, 230–236. 10.1348/147608310X520166

- Montgomery SA, Asberg M, 1979 Scale Designed to be Sensitive to Change. *Br. J. Psychiatry* 134, 382–389. [PubMed: 444788]
- Nejad AB, Fossati P, Lemogne C, 2013 Self-referential processing, rumination, and cortical midline structures in major depression. *Front. Hum. Neurosci* 7, 666 10.3389/fnhum.2013.00666 [PubMed: 24124416]
- Northoff G, Bermpohl F, 2004 Cortical midline structures and the self. *Trends Cogn. Sci* 8, 102–107. 10.1016/j.tics.2004.01.004 [PubMed: 15301749]
- Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J, 2006 Self-referential processing in our brain-A meta-analysis of imaging studies on the self. *Neuroimage* 31, 440–457. 10.1016/j.neuroimage.2005.12.002 [PubMed: 16466680]
- O'Neill PK, Gore F, Salzman CD, 2018 Basolateral amygdala circuitry in positive and negative valence. *Curr. Opin. Neurobiol* 49, 175–183. 10.1016/j.conb.2018.02.012 [PubMed: 29525574]
- Oishi K, Faria AV, Hsu J, Tippet D, Mori S, Hillis AE, 2015 Critical role of the right uncinate fasciculus in emotional empathy. *Ann. Neurol* 77, 68–74. 10.1002/ana.24300 [PubMed: 25377694]
- Olatunji BO, Naragon-Gainey K, Wolitzky-Taylor KB, 2013 Specificity of rumination in anxiety and depression: A multimodal meta-analysis. *Clin. Psychol. Sci. Pract* 20, 225–257. 10.1111/cpsp.12037
- Olson IR, McCoy D, Klobusicky E, Ross LA, 2013 Social cognition and the anterior temporal lobes: A review and theoretical framework. *Soc. Cogn. Affect. Neurosci* 8, 123–133. 10.1093/scan/nss119 [PubMed: 23051902]
- Osoba A, Hänggi J, Li M, Horn DI, Metzger C, Eckert U, Kaufmann J, Zierhut K, Steiner J, Schiltz K, Heinze HJ, Bogerts B, Walter M, 2013 Disease severity is correlated to tract specific changes of fractional anisotropy in MD and CM thalamus - A DTI study in major depressive disorder. *J. Affect. Disord* 149, 116–128. 10.1016/j.jad.2012.12.026 [PubMed: 23489404]
- Phillips ML, Chase HW, Sheline YI, Etkin A, Almeida JRC, Deckersbach T, Trivedi MH, 2015 Identifying predictors, moderators, and mediators of antidepressant response in major depressive disorder: Neuroimaging approaches. *Am. J. Psychiatry* 172, 124–138. 10.1176/appi.ajp.2014.14010076 [PubMed: 25640931]
- Pizzagalli DA, 2011 Frontocingulate dysfunction in depression: Toward biomarkers of treatment response. *Neuropsychopharmacology* 36, 183–206. 10.1038/npp.2010.166 [PubMed: 20861828]
- Renner F, Siep N, Lobbestael J, Arntz A, Peeters FPML, Huibers MJH, 2015 Neural correlates of self-referential processing and implicit self-associations in chronic depression. *J. Affect. Disord* 186, 40–47. 10.1016/j.jad.2015.07.008 [PubMed: 26226432]
- Rizk MM, Rubin-Falcone H, Keilp J, Miller JM, Sublette ME, Burke A, Oquendo MA, Kamal AM, Abdelhameed MA, Mann JJ, 2017 White matter correlates of impaired attention control in major depressive disorder and healthy volunteers. *J. Affect. Disord* 222, 103–111. 10.1016/j.jad.2017.06.066 [PubMed: 28688263]
- Salat DH, Tuch DS, Hevelone ND, Fischl B, Corkin S, Rosas HD, Dale AM, 2005 Age-related changes in prefrontal white matter measured by diffusion tensor imaging. *Ann. N. Y. Acad. Sci* 1064, 37–49. 10.1196/annals.1340.009 [PubMed: 16394146]
- Salomon R, Levy DR, Malach R, 2014 Deconstructing the default: Cortical subdivision of the default mode/intrinsic system during self-related processing. *Hum. Brain Mapp* 35, 1491–1502. 10.1002/hbm.22268 [PubMed: 23568328]
- Schmaling KB, Dimidjian S, Katon W, Sullivan M, 2002 Response Styles Among Patients With Minor Depression and Dysthymia in Primary Care. *J. Abnorm. Psychol* 111, 350–356. 10.1037//0021-843X.111.2.350 [PubMed: 12003456]
- Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, Mintun MA, Wang S, Coalson RS, Raichle ME, 2009 The default mode network and self-referential processes in depression. *Proc. Natl. Acad. Sci. U. S. A* 106, 1942–1947. 10.1073/pnas.0812686106 [PubMed: 19171889]
- Shenhav A, Cohen JD, Botvinick MM, 2016 Dorsal anterior cingulate cortex and the value of control. *Nat. Neurosci* 19, 1286–1291. 10.1038/nn.4382 [PubMed: 27669989]
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TEJ, 2006 Tract based spatial statistics:

- voxelwise analysis of multi-subjects diffusion data. *Neuroimage* 31, 1487–1505. 10.1016/j.neuroimage.2006.02.024 [PubMed: 16624579]
- Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH, 2002 Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17, 1429–1436. 10.1006/nimg.2002.1267 [PubMed: 12414282]
- Steffens DC, Taylor WD, Denny KL, Bergman SR, Wang L, 2011 Structural integrity of the uncinate fasciculus and resting state functional connectivity of the ventral prefrontal cortex in late life depression. *PLoS One* 6 10.1371/journal.pone.0022697
- Stuhrmann A, Dohm K, Kugel H, Zwanzger P, Redlich R, Grotegerd D, Rauch AV, Arolt V, Heindel W, Suslow T, Zwieterlood P, Dannlowski U, 2013 Mood-congruent amygdala responses to subliminally presented facial expressions in major depression: Associations with anhedonia. *J. Psychiatry Neurosci* 38, 249–258. 10.1503/jpn.120060 [PubMed: 23171695]
- Taylor WD, Boyd B, McQuoid DR, Kudra K, Saleh A, MacFall JR, 2015 Widespread white matter but focal gray matter alterations in depressed individuals with thoughts of death. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 62, 22–28. 10.1016/j.pnpbp.2015.05.001
- Taylor WD, Kuchibhatla M, Payne ME, MacFall JR, Sheline YI, Krishnan KR, Doraiswamy PM, 2008 Frontal white matter anisotropy and antidepressant remission in late-life depression. *PLoS One* 3, 1–6. 10.1371/journal.pone.0003267
- Taylor WD, MacFall JR, Boyd B, Payne ME, Sheline YI, Krishnan RR, Doraiswamy PM, 2011 One-year change in anterior cingulate cortex white matter microstructure: Relationship with late-life depression outcomes. *Am. J. Geriatr. Psychiatry* 19, 43–52. 10.1097/JGP.0b013e3181e70cec [PubMed: 20808126]
- Thomas AJ, O'Brien JT, Barber R, McMeekin W, Perry R, 2003 A neuropathological study of periventricular white matter hyperintensities in major depression. *J. Affect. Disord* 76, 49–54. 10.1016/S0165-0327(02)00064-2 [PubMed: 12943933]
- Von Der Heide RJ, Skipper LM, Klobusicky E, Olson IR, 2013 Dissecting the uncinate fasciculus: Disorders, controversies and a hypothesis. *Brain* 136, 1692–1707. 10.1093/brain/awt094 [PubMed: 23649697]
- Wagner G, Schachtzabel C, Peikert G, Bär KJ, 2015 The neural basis of the abnormal self-referential processing and its impact on cognitive control in depressed patients. *Hum. Brain Mapp* 36, 2781–2794. 10.1002/hbm.22807 [PubMed: 25872899]
- Wilkinson PO, Croudace TJ, Goodyer IM, 2013 Rumination, anxiety, depressive symptoms and subsequent depression in adolescents at risk for psychopathology: A longitudinal cohort study. *BMC Psychiatry* 13, 250 10.1186/1471-244X-13-250 [PubMed: 24103296]
- Wu M, Aizenstein HJ, 2017 The Multi-Faceted Relationship between White Matter Lesions and Late-Life Depression. *Am. J. Geriatr. Psychiatry* 25, 1322–1325. 10.1016/j.jagp.2017.09.017 [PubMed: 29050911]
- Wu M, Andreescu C, Butters MA, Tamburo R, Reynolds CF, Aizenstein H, 2011 Default-mode network connectivity and white matter burden in late-life depression. *Psychiatry Res. - Neuroimaging* 194, 39–46. 10.1016/j.psychres.2011.04.003
- Zhang A, Leow A, Ajilore O, Lamar M, Yang S, Joseph J, Medina J, Zhan L, Kumar A, 2012 Quantitative tract-specific measures of uncinate and cingulum in major depression using diffusion tensor imaging. *Neuropsychopharmacology* 37, 959–967. 10.1038/npp.2011.279 [PubMed: 22089322]

Highlights

- Self-referential thinking improved with antidepressant treatment in older adults.
- White matter abnormalities predict residual negative self-referential thoughts.
- Networks of the negative valence system may inform potential treatment targets.

Figure 1.
Regions from which fractional anisotropy (FA) values were extracted.

Figure 2.

Mean Trait Adjective Task responses in participants with late-life depression at baseline and following 12 weeks of escitalopram treatment. (Error bars represent one standard error of the mean.)

* Significant difference between baseline and week 12 at the $p < 0.05$ level.

Figure 3. interaction of adjective response (endorsed vs. rejected) and valence (positive vs. negative) in participants with late-life depression at (a) baseline, (b) following 12 weeks of escitalopram treatment, and (c) change from baseline to week 12.

Table 1.

Demographic, Clinical, and Cognitive Characteristics in Participants with Late-Life Depression and Psychiatrically Normal Control Participants at Baseline

Variable	Depressed (<i>N</i> = 20)	Controls (<i>N</i> = 20)	<i>t</i> (df), <i>p</i>
	Mean (SD)	Mean (SD)	
<i>Age (years)</i>	70.40 (5.80)	72.45 (6.78)	−1.03 (38), 0.31
<i>Education (years)</i>	13.75 (2.20)	16.95 (1.96)	−4.86 (38), 0.001 *
<i>MADRS</i>	26.05 (5.06)	1.20 (1.51)	21.04 (38), < 0.001 *
<i>MMSE</i>	28.00 (1.81)	28.78 (1.06)	0.22 (38), 0.83
<i>DRS</i>	138.75 (4.42)	138.35 (6.95)	−1.60 (38), 0.12

Note. MADRS = Montgomery Asberg Depression Rating Scale; MMSE = Mini Mental State Exam; DRS = Mattis Dementia Rating Scale.

* Group difference is significant at the $p < 0.05$ level.

Table 2.

Trait Adjective Task Responses in Participants with Late-Life Depression and Psychiatrically Normal Control Participants at Baseline and Week 12

	Depressed (Baseline: <i>N</i> = 20) (Week 12: <i>N</i> = 12)	Controls (Baseline: <i>N</i> = 20) (Week 12: <i>N</i> = 20)	
Measure	Mean (SD)	Mean (SD)	<i>t</i> (df), <i>p</i>
Baseline			
<i>Endorsed Positive</i>	14.10 (4.36)	19.50 (3.10)	−4.51 (38), < 0.001 *
<i>Endorsed Negative</i>	9.90 (4.54)	3.55 (2.67)	5.39 (38), < 0.001 *
<i>Rejected Positive</i>	7.35 (3.82)	3.25 (2.67)	3.94 (38), < 0.001 *
<i>Rejected Negative</i>	12.10 (5.43)	19.10 (3.68)	−4.77 (38), < 0.001 *
Week 12			
<i>Endorsed Positive</i>	15.25 (4.14)	19.10 (3.57)	−2.79 (30), 0.01 *
<i>Endorsed Negative</i>	6.75 (3.82)	2.75 (2.49)	3.61 (30), 0.001 *
<i>Rejected Positive</i>	6.08 (3.55)	3.20 (2.86)	2.52 (30), 0.02 *
<i>Rejected Negative</i>	14.17 (4.67)	19.50 (2.95)	−3.98 (30), < 0.001 *

* Group difference is significant at the $p < 0.05$ level.

Table 3.

Correlations Between Baseline FA and Baseline and Week 12 Trait Adjective Task Responses in Participants with Late-Life Depression and Psychiatrically Normal Control Participants

	Depressed (Baseline: N = 20)	Depressed (Week 12: N = 12)	Controls (Baseline: N = 20)	Controls (Week 12: N = 20)
Measure	r (df), p		r (df), p	
<i>Endorsed Positive</i>				
<i>L DMPFC</i>	0.19 (18), 0.43	−0.07 (10), 0.82	−0.58 (18), 0.007 *	−0.48 (18), 0.03 *
<i>R DMPFC</i>	0.10 (18), 0.69	0.06 (10), 0.85	−0.56 (18), 0.01 *	−0.49 (18), 0.03 *
<i>L dACC</i>	0.18 (18), 0.45	0.11 (10), 0.73	−0.27 (18), 0.26	−0.15 (18), 0.52
<i>R dACC</i>	−0.16 (18), 0.50	0.09 (10), 0.77	−0.15 (18), 0.52	−0.03 (18), 0.91
<i>L Uncinate</i>	0.02 (18), 0.94	−0.60 (10), 0.04 *	−0.03 (18), 0.90	0.02 (18), 0.94
<i>R Uncinate</i>	−0.25 (18), 0.28	0.27 (10), 0.40	0.06 (18), 0.81	−0.17 (18), 0.47
<i>Endorsed Negative</i>				
<i>L DMPFC</i>	0.26 (18), 0.27	0.55 (10), 0.06	0.71 (18), 0.001 *	0.55 (18), 0.01 *
<i>R DMPFC</i>	0.03 (18), 0.91	0.53 (10), 0.07	0.62 (18), 0.004 *	0.50 (18), 0.03 *
<i>L dACC</i>	0.41 (18), 0.07	0.22 (10), 0.49	0.33 (18), 0.16	0.44 (18), 0.05 *
<i>R dACC</i>	−0.05 (18), 0.82	−0.77 (10), 0.003 *	0.12 (18), 0.63	0.39 (18), 0.09
<i>L Uncinate</i>	−0.15 (18), 0.54	0.08 (10), 0.80	−0.19 (18), 0.44	−0.41 (18), 0.08
<i>R Uncinate</i>	−0.13 (18), 0.58	−0.63 (10), 0.03 *	0.33 (18), 0.16	0.22 (18), 0.36
<i>Rejected Positive</i>				
<i>L DMPFC</i>	−0.20 (18), 0.40	−0.11 (10), 0.74	0.43 (18), 0.06	0.57 (18), 0.01 *
<i>R DMPFC</i>	−0.03 (18), 0.90	0.01 (10), 0.98	0.50 (18), 0.02 *	0.57 (18), 0.01 *
<i>L dACC</i>	−0.20 (18), 0.39	−0.09 (10), 0.77	0.19 (18), 0.43	0.35 (18), 0.14
<i>R dACC</i>	0.34 (18), 0.14	−0.11 (10), 0.73	0.11 (18), 0.63	0.23 (18), 0.33
<i>L Uncinate</i>	−0.05 (18), 0.83	0.18 (10), 0.57	0.09 (18), 0.70	0.04 (18), 0.88
<i>R Uncinate</i>	0.15 (18), 0.53	−0.49 (10), 0.11	0.02 (18), 0.93	0.26 (18), 0.32
<i>Rejected Negative</i>				
<i>L DMPFC</i>	−0.16 (18), 0.50	−0.68 (10), 0.02 *	−0.64 (18), 0.002 *	−0.36 (18), 0.12
<i>R DMPFC</i>	0.08 (18), 0.73	−0.53 (10), 0.08	−0.57 (18), 0.01 *	−0.38 (18), 0.10
<i>L dACC</i>	−0.38 (18), 0.10	−0.21 (10), 0.52	−0.33 (18), 0.16	−0.23 (18), 0.33
<i>R dACC</i>	0.12 (18), 0.61	0.61 (10), 0.04 *	−0.12 (18), 0.63	−0.10 (18), 0.68
<i>L Uncinate</i>	0.10 (18), 0.69	−0.37 (10), 0.24	−0.01 (18), 0.96	0.26 (18), 0.27
<i>R Uncinate</i>	−0.01 (18), 0.97	0.34 (10), 0.28	−0.32 (18), 0.17	−0.22 (18), 0.35

* Correlation is significant at the $p < 0.05$ level.