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Research paper

White matter abnormalities predict residual negative self-referential thinking following treatment of late-life depression with escitalopram: A preliminary study

Lindsay W. Victoria[a,*], George S. Alexopoulos[a], Irena Ilieva[a], Aliza T. Stein[b], Matthew J. Hoptman[c,d], Naib Chowdhury[a], Matteo Respino[a], Sarah Shizuko Morimoto[e], Dora Kanellopoulos[a], Jimmy N. Avari[a], Faith M. Gunning[a]

[a] Weill Cornell Institute of Geriatric Psychiatry, Department of Psychiatry, Weill Cornell Medicine, 21 Bloomingdale Road, White Plains, NY, United States
[b] Department of Psychology, University of Texas at Austin, Austin, TX, United States
[c] Schizophrenia Research Division, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, United States
[d] Department of Psychiatry, New York University School of Medicine, New York, NY, United States
[e] Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT, United States

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 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.

1. 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; Stuhrmann 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.

* Corresponding author.
E-mail address: liv3002@med.cornell.edu (L.W. Victoria).

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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; Simplico 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; Stuhrmann 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, 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 associate 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.

2. Methods

2.1. 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 infraction, or stroke within three months proceeding 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, claustrophia; (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.

2.2. 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.

2.3. 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.