Journal of Affective Disorders 166 (2014) 179–186

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research Report

Neuroanatomical correlates of apathy in late-life depression and antidepressant treatment response

Genevieve S. Yuen [a,*], Faith M. Gunning [a], Eric Woods [a], Sibel A. Klimstra [a], Matthew J. Hoptman [b,c], George S. Alexopoulos [a]

[a] Weill Medical College of Cornell University, Weill Cornell Institute of Geriatric Psychiatry, NY, USA
[b] Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA
[c] New York University School of Medicine, New York, NY, USA

ARTICLE INFO

Article history:
Received 1 December 2013
Received in revised form
6 May 2014
Accepted 6 May 2014
Available online 22 May 2014

Keywords:
Apathy
Depression
Geriatric
SSRI
Cingulate
Uncinate

ABSTRACT

Background: Apathy is a prominent feature of geriatric depression that predicts poor clinical outcomes and hinders depression treatment. Yet little is known about the neurobiology and treatment of apathy in late-life depression. This study examined apathy prevalence in a clinical sample of depressed elderly, response of apathy to selective serotonin reuptake inhibitor (SSRI) treatment, and neuroanatomical correlates that distinguished responders from non-responders and healthy controls.

Methods: Participants included 45 non-demented, elderly with major depression and 43 elderly comparison individuals. After a 2-week single-blind placebo period, depressed participants received escitalopram 10 mg daily for 12 weeks. The Apathy Evaluation Scale (AES) and 24-item Hamilton Depression Rating Scale (HDRS) were administered at baseline and 12 weeks. MRI scans were acquired at baseline for concurrent structural and diffusion tensor imaging of anterior cingulate gray matter and associated white matter tracts.

Results: 35.5% of depressed patients suffered from apathy. This declined to 15.6% ($p < 0.1$) following treatment, but 43% of initial sufferers continued to report significant apathy. Improvement of apathy with SSRI was independent of change in depression but correlated with larger left posterior subgenual cingulate volumes and greater fractional anisotropy of left uncinate fasciculi.

Limitations: Modest sample size, no placebo control, post-hoc secondary analysis, use of 1.5T MRI scanner

Conclusions: While prevalent in geriatric depression, apathy is separable from depression with regards to medication response. Structural abnormalities of the posterior subgenual cingulate and uncinate fasciculus may perpetuate apathetic states by interfering with prefrontal cortical recruitment of limbic activity essential to motivated behavior.

1. Introduction

Apathy is a common feature of late-life depression (Chase, 2011; Krishnan et al., 1995; Mehta et al., 2008). It afflicts 19–88% of those suffering from major depression, and is most prevalent in depressed older adults (Forsell et al., 1993; Lampe and Heeren, 2004; Mehta et al., 2008). The syndrome of apathy is defined as a primary motivational impairment that in depression results in diminished goal-oriented behavior, lack of intellectual interest, and indifference or flattening of affect (Marin, 1990). These clinical signs often translate into apathetic, depressed patients being poorly engaged in treatment, posing a greater burden to caregivers, and having increased risk of future functional and cognitive impairment(Holtta et al., 2012). Further, apathy is a predictor of poor response to antidepressants(Chaturvedi and Sarmukaddam, 1986; Levkovitz et al., 2011), and chronicity of depression (Lavretsky et al., 1999).

While selective serotonin reuptake inhibitors (SSRIs) are prescribed first-line for depression, apathy response to SSRIs is variable. Several case reports and case-control studies argue that SSRIs may actually cause or exacerbate apathy when used in the treatment of depression (Bolling and Kohlenberg, 2004; Fava, 2006; Hoehn-Saric et al., 1990; Kodela and Venkata, 2010; Padala et al., 2012; Sato and Asada, 2011; Wongpakaran et al., 2007). It is unclear to what extent apathy represents an SSRI side effect, a

* Correspondence to: Weill Cornell Institute of Geriatric Psychiatry, New York-Presbyterian Hospital – Westchester Division, 21 Bloomingdale Road, New York, NY 10605-1596, USA. Tel.: +1 914 997 4047, +1 646 232 3464; fax: +1 914 682 6979.
E-mail address: gsyuen@med.cornell.edu (G.S. Yuen).

http://dx.doi.org/10.1016/j.jad.2014.05.008
0165-0327/

residual symptom not adequately treated by SSRIs alone, or both. To date, we lack an understanding of the neurobiology of apathy in depression and lack a consensus on its optimal treatment. As such, this study sought to investigate differences in neuroanatomical correlates that might explain the variable response of apathy to SSRI treatment in the context of depression.

Convergent findings from structural MRI, functional MRI, and neuropsychological studies implicate altered function of frontolimbic networks in late-life depression (Alexopoulos et al., 2012, 1997; Gunning-Dixon et al., 2009, 2008; Raz et al., 1997). Among the frontolimbic networks implicated in geriatric depression, the anterior cingulate cortex (ACC) plays a key role (Alexopoulos et al., 2008a). Based on cytoarchitecture and functional connectivity, the ACC is divided into dorsal (BA 24b′–c′ and 32′) and perigenual ACC (rostral BA 24a–c and 32 and subgenual BA 25 and 33) regions, which govern cognitive and emotional processes, respectively (Bush et al., 2000; Devinsky et al., 1995; Drevets et al., 2008; Vogt et al., 1992). While the dorsal ACC controls aspects of executive function (conflict detection, cognitive inhibition, and conflict resolution) (Carter et al., 1998; Carter and van Veen, 2007; Posner and DiGirolamo, 1998), the perigenual ACC assesses the salience of emotional input and regulates emotional responses (Devinsky et al., 1995; Etkin et al., 2006). In a previous analysis, our group described a pattern wherein smaller dorsal and rostral ACC volumes and decreased frontosubcortical white matter integrity predicted failure of depression to remit with SSRI treatment (Alexopoulos et al., 2010, 2002, 2008b; Gunning et al., 2009).

Given the association of apathy with poor depression response to antidepressants, we performed a post-hoc, secondary analysis to explore a potential relationship between structural characteristics of ACC and adjacent white matter tracts and apathy in late-life depression. Several clinical observations and neuroimaging studies support the notion that apathy may emerge from frontosubcortical network dysfunction and ACC abnormality. Apathy is common in elderly individuals with prominent vascular white matter lesions (Alves et al., 2009; Lavretsky et al., 2007) and focal frontal lobe and basal ganglia lesions (Chase, 2011; Levy and Dubois, 2006). Among various neurodegenerative diseases, apathy develops early and prominently in dementias with greater frontosubcortical pathology (Huntington's, Lewy Body, Parkinson's and HIV dementia) (Chase, 2011; Quaranta et al., 2012; Starkstein et al., 2006), and, in the case of Alzheimer's disease, apathy correlates with neurofibrillary tangle density in the ACC (Marshall et al., 2006) and reduced gray matter volume and metabolic activity of the ACC (Apostolova et al., 2007; Bruen et al., 2008; Marshall et al., 2007; Starkstein et al., 2009). In a prior study of late-life major depression, apathy was associated with reduced right ACC gray matter volumes (Lavretsky et al., 2007). Further dissecting the neural correlates of apathy in depression would afford an understanding of the brain circuitry underlying motivational states and thus inform future treatment approaches for apathetic depression.

The objectives of this study were to examine the prevalence and severity of apathy in a clinical sample of patients with late-life depression, to analyze the response of apathy to SSRI treatment, and to identify the neuroanatomical correlates that might explain the maintenance of an apathetic state. We included a non-depressed comparison group to examine the relative specificity of such neuroanatomical findings to apathetic versus depressed states. Guided by the above literature, this study focused on the role of ACC subregions and white matter tracts in the apathy of late-life depression. It hypothesized that depressed elders who suffer from persistent apathy despite SSRI treatment were more likely to possess structural abnormalities in perigenual, as opposed to dorsal, ACC and in white matter tracts connecting the perigenual ACC to structures related to mood regulation, such as the amygdala and ventral striatum.

2. Methods

2.1. Participants

We studied 45 non-demented, elderly (>60 years) patients with non-psychotic major depression and 43 elderly, psychiatrically healthy participants. Subjects were recruited through radio and print advertisement in community radio stations and newspapers. Participants signed written informed consent approved by the Institutional Review Boards of Weill-Cornell Medical College and of the Nathan Kline Institute.

The depressed group met DSM-IV-TR criteria for unipolar major depression and had a score of ≥ 18 on the 24-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Exclusion criteria for the depressed group were (1) major depression with psychotic features; (2) history of other axis I psychiatric disorders prior to the onset of depression; (3) history of substance abuse; (4) severe medical illness (i.e., metastatic cancer, brain tumors, unstable cardiac, hepatic, or renal disease, myocardial infarction, or stroke) within the 3 months preceding the study; (5) neurological disorders (i.e., dementia, delirium, history of head trauma, Parkinson's disease, and multiple sclerosis); (6) medical illnesses often associated with depression (i.e., endocrinopathies other than diabetes, lymphoma, and pancreatic cancer); (7) drugs causing depression (i.e., steroids, α-methyl-dopa, clonidine, reserpine, tamoxifen, and cimetidine); (8) Mini-Mental State Examination (MMSE) score <25 (Folstein et al., 1975); (9) Mild Cognitive Impairment according to criteria described by Petersen et al. (1999)and (10) contraindications to MRI scanning. Exclusion criteria for non-depressed participants were the same as above, while inclusion criteria included absence of history of any psychiatric illness, and a HDRS score lower than 7.

2.2. Assessment

Depressive symptoms were assessed using the HDRS. Apathy was quantified using the self-rated Apathy Evaluation Scale (AES), a psychometrically validated instrument in older normal individuals and psychiatric patients (Clarke et al., 2007; Marin et al., 1991). For healthy comparison participants, the AES was administered at baseline. For depressed participants, the AES was administered at baseline (after the 2-week placebo lead-in/drug washout period) and again at the end of escitalopram treatment. An AES ≤ 36.5 was considered clinically significant apathy (Clarke et al., 2007). Overall cognitive impairment was examined in a clinical interview and was rated with the MMSE (Folstein et al., 1975) and the Dementia Rating Scale (DRS) (Mattis, 1988). Memory was rated with the Hopkins Verbal Learning Test – Revised (Brandt and Benedict, 2001), response inhibition with the Stroop Color Word Test (Golden, 1978) and visual attention and task switching with Trails A and Trails B (Reitan and Wolfson, 1985).

2.3. Treatment

Depressed participants entering the study were informed that they would receive placebo at some point during their 14-week trial. They underwent a 2-week single-blind placebo lead-in and drug washout period in which patients were tapered off all antidepressant and anxiolytic medications, including benzodiazepines. Continued beta-blocker use was allowed. Participants who still met DSM-IV-TR criteria for major depression and had a HDRS ≥ 18 received treatment with escitalopram 10 mg every morning, daily for 12 weeks.

Depressed participants were assessed weekly throughout the treatment trial. Assessment consisted of a brief meeting with a research psychiatrist and ratings by a trained research assistant