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Methodology and preliminary results from the Neurobiology of Late-life Depression study

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Abstract

Background—We sought to investigate the relationship between neuroticism and depression in an elderly cohort. In this paper, we describe the methods of an NIMH-supported study and present findings among the cohort enrolled to date.

Methods—We used the NEO Personality Inventory to assess neuroticism, and we employed several cognitive neuroscience-based measures to examine emotional control.

Results—Compared with a group of 27 non-depressed older control subjects, 33 older depressed subjects scored higher on measures of state and trait anxiety and neuroticism. On our experimental neuroscience-based measures, depressed subjects endorsed more negative words compared with controls on an emotional characterization test. In addition, we found a significant group-by-congruency effect on an emotional interference test where subjects were asked to identify the face's emotional expression while ignoring the words "fear" or "happy" labeled across the face.

Conclusion—Thus, in this preliminary work, we found significant differences in measures of neuroticism and emotional controls among older adults with and without depression.

Keywords

depression; elderly; neuroticism; neuroscience

Introduction

The links between depression and personality pathology are complex and generally have been understudied in older adults. The personality construct of neuroticism has been associated with increased risk of depression across the lifespan, including older age (Kendler

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Conflict of Interest

None

Description of authors' roles

D. Steffens designed and obtained funding for the study and wrote the article. K. Manning interpreted the results from neuroscience-based measures and assisted in writing the article. R. Wu and J. Grady performed statistical analyses and assisted in writing the article. R. Fortinsky H. Tennen interpreted results of measures of resilience and optimism and assisted in writing the article.

et al., 2006). Whereas the term "neurotic" is used loosely by clinicians and the lay public, personality theorists have sought to provide clarity and definition to the term. For example, the Eysenck Personality Questionnaire includes a Neuroticism/Stability factor (Eysenck and Eysenck, 1975). Costa and McCrae, as they studied personality and aging, developed the NEO-Personality Inventory (NEO-PI), with five personality factors, including neuroticism (Costa and McCrae, 1985). These assessments capture clinical characteristics such as a tendency to experience anxiety and negative mood states, particularly in the context of stress. This tendency to experience fluctuating negative mood states, such as depression, is separable from the experience of a more enduring syndromal depression.

Subsequent studies have documented the reliability and validity of the NEO-PI (McCrae and Costa, 1983; Cano-García *et al.*, 2005). Within the NEO-PI, neuroticism as a construct was developed to identify individuals prone to psychological distress, and its "facets" (i.e., component subscales) consist of 1) Anxiety: level of free floating anxiety; 2) Angry Hostility: tendency to experience anger and related states, e.g., frustration and bitterness; 3) Depression: tendency to experience feelings of guilt, sadness, despondency and loneliness; 4) Self Consciousness: shyness or social anxiety; 5) Impulsiveness: tendency to act on cravings and urges rather than reining them in and delaying gratification; and 6) Vulnerability: general susceptibility to stress. Although neuroticism has been shown to decrease as we age (Costa and McCrae, 2006), it clearly has public health importance, as it limits quality of life and longevity (Lahey, 2009).

Limited research has examined the effects of neuroticism on the course of enduring syndromal depression and on brain structure and function. Neuroticism has been associated with worse mood outcomes in both non-geriatric depression (Bock *et al.*, 2010) and late-life depression (Canuto *et al.*, 2009; Steffens *et al.*, 2013), although there are negative studies (Petersen *et al.*, 2002). Beyond mood outcomes, neuroticism is associated with worse cognitive outcomes in older adults in some studies (Wilson *et al.*, 2005; Steffens *et al.*, 2013), though not in others (Wetherell *et al.*, 2002; Jelicic *et al.*, 2003). In addition, imaging studies have found links between neuroticism and structural brain changes, specifically in the anterior cingulate cortex (ACC), the orbital frontal cortex (OFC), the middle frontal gyrus (MFG), the dorsomedial prefrontal cortex (PFC), hippocampus and the amygdala (DeYoung *et al.*, 2010; Omura *et al.*, 2005; Wright *et al.*, 2006) and altered frontotemporal connectivity (Fruhholz *et al.*, 2010; Cremers *et al.*, 2010), particularly with altered left amygdala-ACC connectivity (Cremers *et al.*, 2010). Despite these interesting studies, there remain significant gaps in our knowledge of the mood and cognitive outcomes and the structural and functional correlates of neuroticism, particularly in the elderly. One intriguing inference from prior studies is a putative bidirectionality between neuroticism and brain changes in the elderly, with underlying structural and functional brain changes increasing risk of expressing a neurotic style, and neuroticism, possibly through increased susceptibility to stress, being associated with subsequent alterations in brain structure and function.

Given these knowledge gaps, we received support from the National Institute of Mental Health (NIMH) to further understand the relationships among depression, neuroticism and neuroimaging changes in older adults (age 60 or older). Our specific aims include: 1) determining acute response to standardized antidepressant medication treatment among

older depressed adults with and without high neuroticism scores; 2): ascertaining differences in functional connectivity seen on functional magnetic resonance imaging (fMRI) between depressed and non-depressed subjects with high neuroticism scores, and between depressed subjects with and without high neuroticism scores; and 3) assessing two-year cognitive trajectories of depressed older adults scoring low and high on measures of neuroticism. In this paper, we present the methodology of the study, known as Neurobiology of Late-life Depression (NBOLD), as well as preliminary findings among two groups recruited to date: those with current major depression and a group of never-depressed control subjects scoring low on neuroticism measures. To characterize our sample, we employed both standard and less well studied clinical and cognitive assessments, the latter including experimental paradigms focused on emotional processing. For our baseline measures, we hypothesized that, compared with control subjects, the depressed group would score higher on measures of neuroticism and state and trait anxiety, score lower on measures of resilience and optimism, and report more childhood adverse experiences. We also hypothesized that subjects with late-life depression would exhibit a pattern of emotional processing performance distinct from non-depressed subjects.

Methods

Subjects

All subjects were enrolled in NBOLD, an NIMH funded R01 grant entitled “Neurobiology and Adverse Outcomes of Neuroticism in Late-life Depression” (MH096725) at the University of Connecticut Health Center (UCHC) and the Olin Neuropsychiatry Research Center at the Institute of Living at Hartford Hospital. The study was approved by the Institutional Review Boards of UCHC and Hartford Hospital. All subjects were provided information about the study, including a review of the consent form, and then provided written, informed consent to participate.

Depressed subjects have been recruited from clinic referrals, newspaper advertisements and community presentations. Non-depressed comparison subjects were recruited from a volunteer registry list housed in the Center on Aging at UCHC as well as newspaper advertisements and community presentations. Our recruitment strategy included monitoring for sufficient numbers of depressed and non-depressed subjects likely to score high in neuroticism; details are provided below.

Inclusion criteria for all subjects were age 60 or above, ability to read and write English, Mini-Mental State Examination (MMSE, (Folstein *et al.*, 1975)) score 25 or greater. In addition, depressed subjects met criteria for major depression, single episode or recurrent.

Exclusion criteria for the study were: lifetime alcohol or drug dependence; conditions associated with MRI abnormalities such as hydrocephalus, benign and cancerous brain tumors, epilepsy, Parkinson’s disease, Huntington’s chorea, dementia, and demyelinating diseases; endocrine disorder other than diabetes mellitus; any physical or intellectual disability that may affect completion of self-rating instruments; established clinical diagnosis of dementia; other primary psychiatric disorders, e.g., panic disorder, social phobia, obsessive compulsive disorder, schizoaffective disorder, schizophrenia, bipolar

disorder; and any metal or pacemaker in the body that might preclude MRI. In addition, current treatment with fluoxetine was an exclusion for the depressed group given its long wash-out period.

All participants were screened for depression using the Center for Epidemiologic Studies-Depression (CES-D) scale, using a score of 16 or greater as a cut-off for depression (Weissman *et al.*, 1977). To screen for neuroticism, we used the DS-14, a measure of tendency toward Negative Affectivity (NA, 7 items) and social inhibition (7 items) (Denollet, 2005). NA correlated positively with NEO-PI neuroticism ($r = 0.68$), and scale-level factor analysis confirmed the construct validity of the DS14 NA scale against the NEO-PI (Denollet, 2005). Based on our preliminary analyses, a cutoff of 10 or greater identified individuals high in NA. For the present study, we used the 7-item NA subscale of the DS-14, planning to oversample for those with the ≥10 cutoff among both depressed and non-depressed in order to ensure adequate numbers of individuals likely to score high in neuroticism. Oversampling has proven to be unnecessary among the depressed group, so we are currently only oversampling among the non-depressed controls. Our preliminary data showed that we likely would need to screen 500 control subjects in order to identify 25 controls meeting our criterion for neuroticism.

Upon enrollment and completion of baseline assessments, each participant was paid $100 for their time completing the MRI, cognitive test battery and experimental computerized measures (described below).

Baseline Assessments

Trained clinical research assistants administered the Duke Depression Evaluation Schedule (DDES, (Landerman *et al.*, 1989)) to each participant. The DDES contains items covering demographic data, life events, social support and coping, activities of daily living, self-rated depression severity, age of depression onset, and the Diagnostic Interview Schedule (DIS) sections for depression, mania, generalized anxiety disorder, somatization symptoms, and alcohol use (Robins *et al.*, 1981). The DDES takes 1–2 hours to administer. When necessary for the comfort of the patient, it is administered in more than one session. The DDES is completed in close temporal proximity to cognitive testing and neuroimaging studies, so that the psychometric and sociometric data contained within the DDES is considered contemporary with clinical, cognitive and imaging data. We administer the DDES using a specially programmed computer to ensure all items are covered, and that correct skip patterns are followed.

At study entry, each subject was interviewed by a study geriatric psychiatrist to establish a clinical diagnosis of major depression (for depressed subjects) or rule out history of mental illness (for comparison subjects). During the visit, the following assessments are completed: Montgomery-Ásberg Depression Rating Scale (MADRS, Montgomery and Asberg, 1979), 17-item Hamilton Depression Rating Scale (Hamilton, 1960), the Clinical Global Impression severity scale, the Antidepressant Treatment History Form (Keller *et al.*, 1987; Sackeim *et al.*, 1990), and the Cumulative Illness Rating Scale (CIRS) (Linn *et al.*, 1988), as modified for geriatric patients (Miller *et al.*, 1992). The MADRS will be our primary depression outcome measure.

Each subject completed several self-report measures, including the State-Trait Anxiety Inventory (Spielberger *et al.*, 1983); the NEO-PI (Costa and McCrae, 1985) as a measure of neuroticism and other personality factors (Extraversion, Openness to Experience, Agreeableness, and Conscientiousness); the Carroll Depression Scale – Revised (Carroll *et al.*, 1981; Carroll, 1998); the Adverse Childhood Experiences Scale (ACES, (Anda *et al.*, 2010)); the Brief Resilience Scale (BRS) (Smith *et al.*, 2008); and a measure of optimism/pessimism, the Life Orientation Test – Revised (LOT-R) (Scheier *et al.*, 1994).

Several experimental computerized measures were administered by a trained research assistant. These included a modification of the classic color-word Stroop test developed by Egner *et al.* (Egner *et al.*, 2008) to measure cognitive and emotional attentional control. Specifically, subjects completed two versions of a task in which they were presented with faces depicting negative emotional expressions (fear) and positive emotional expressions (happiness). In version one, the cognitive interference task, subjects were asked to identify the gender of the face while ignoring the words “male” or “female” labeled across the face. Word and face parings were both congruent (e.g., the word male overlaid on a man’s face) and incongruent (e.g., the word female overlaid on a man’s face). In version two, the emotional interference task, subjects were asked to identify the face’s emotional expression while ignoring the words “fear” or “happy” labeled across the face. Word and face parings were again both congruent (e.g., the word fear overlaid on a fearful face) and incongruent (e.g., the word fear overlaid on a happy face). Using these two versions enables the comparison of whether attention to task is selectively interfered with by either cognitive or emotional distractions. Subjects completed 80 trials (where faces were displayed for 1250 ms) of each version. Faces were identical during each version and gender and facial expressions were counterbalanced across trials. Mean reaction times were computed across congruent and incongruent trials for each version. Late-life depression is commonly associated with abnormalities in cognitive control and emotional regulation compared with age-matched controls. Deficits in simple motoric response speed are less often observed (Lockwood *et al.*, 2002). We therefore posited that both cognitive and emotional incongruent trials (requiring cognitive controls and emotional regulation) would result in slower reaction times for the depressed cohort but not controls, and no group reaction time differences would be evident in either version when trials were congruent (i.e., simple response speed in the absence of distraction).

Negative response bias was recorded on an emotional categorization test. All subjects were shown 60 personality characteristics deemed either to be either likable or dislikeable and were asked to categorize themselves according to each characteristic. Total number of positive and negative words endorsed was recorded. Preliminary evidence suggests neuroticism is correlated with anterior cingulate functioning during emotional categorization and this effect is independent that of major depression (Chan *et al.*, 2008). Thus, while not reported here, future analyses will examine shared neuroantomical correlates of major depression and neuroticism in older adults.

Subjects also were administered a standardized cognitive assessment that is comprised of the Consortium to Establish a Registry in Alzheimer’s Disease (CERAD) neuropsychological battery (Morris *et al.*, 1989), a collection of neuropsychological measures with normative

standards for the elderly and established utility in longitudinal studies of cognitive impairment. (Welsh *et al.*, 1994). The CERAD measures include the MMSE; language tasks consisting of category fluency (animal naming) and object naming (Kaplan *et al.*, 1983); constructional praxis and visual memory, requiring copy of 4 geometric designs, with delayed recall and delayed recognition procedures; and verbal learning and memory, consisting of immediate recall of 3 learning trials of a 10-item word list, delayed recall of the list, and recognition/discrimination of target words from nontarget foils. The CERAD measures (minus the MMSE) are tallied to create a composite measure of global cognitive functioning (maximum score=100). The CERAD battery is supplemented by other common neuropsychological measures used in clinical practice for assessing (1) immediate and delayed verbal memory (Logical Memory subtest of the Wechsler Memory Scale–Revised (Wechsler, 1987)), (2) visual immediate memory (Benton Visual Retention Test) (Benton, 1974), (3) verbal initiation/lexical fluency (Controlled Oral Word Association Test from the Multilingual Aphasia Examination) (Benton *et al.*, 1983), (4) attentional/executive functions (Trail Making Test, (Reitan, 1992), Symbol Digit Modalites Test (Smith, 1982), Digit Span subtest of the Wechsler Adult Intelligence Scale–Revised (Wechsler, 1987), and a separate ascending Digit Span task modeled after the Digit Ordering Test) (Hoppe *et al.*, 2000), and (5) premorbid verbal ability (Shipley Vocabulary Test) (Zachary, 1991). The current preliminary analyses included measures of global cognitive functioning (MMSE and CERAD Total Score). Considering late-life depression is usually characterized by mild deficits in executive functioning and processing speed (Sheline *et al.*, 2006; Lockwood *et al.*, 2002), we did not expect to see significant group differences on these measures, but presently include them to better characterize our sample.

Laboratory Assessment

On a separate day, each subject returned for fasting bloodwork that includes blood chemistry, complete blood count, lipid profile, serum homocysteine, serum folate and B12, and thyroid stimulating hormone. Blood is also stored for later DNA testing.

Neuroimaging

Following blood work, the subject is transported to the Olin Neuropsychiatry Research Center at the Institute of Living at Hartford Hospital for a brain magnetic resonance imaging scan. Future studies will describe the protocols related to structural and functional imaging acquisition, data processing and analysis.

Clinical Follow-up of Depressed Subjects

Depressed subjects will be followed by a study psychiatrist every two weeks for 12 weeks. Once they have achieved remission (MADRS score<10) and are stable on medications, they will be followed monthly for three months and then every three months. Otherwise, at the 12 week visit they will continue to be followed every two weeks until they achieve remission and are stable on medications. Subjects are initially offered treatment with sertraline 50 mg daily (25 mg daily for individuals 80 and older), with dosing increases every two weeks if needed, up to a maximum daily dose of 200 mg. At 12 weeks, subjects in remission will continue their dose of sertraline for up to two years. If not, there are options to add

bupropion SR or switch to desvenlafaxine. Those individuals started on bupropion are administered 150mg daily, which can be increased to 300mg daily at 4 weeks and can be further increased to 400mg at 8 weeks. Subjects are followed on bupropion SR for at least 12 weeks. If the choice is to switch to desvenlafaxine, subjects will be tapered off sertraline, with doses reduced by 50mg every 3–4 days. This taper can be extended for concerns about discontinuation syndrome. After the taper, subjects will receive desvenlafaxine 50mg every-other-day for at least 4 days then 50mg a day. Assuming tolerability, this dose will be maintained for the 12-week period. At this second 12-week phase, subjects in remission are continued on their medication(s) for two years.

If, after this initial 24-week standardized treatment phase, a subject is not in remission, the subject is offered naturalistic antidepressant treatment using treatment guidelines previously established, including switching to another standard antidepressant and augmentation strategies (Steffens *et al.*, 2002). They will be followed at clinically indicated intervals. Subjects may also be referred for psychotherapy at this phase.

Follow-up Cognitive Testing

Each subject will be administered annually the entire cognitive battery listed above. Those subjects with clear impairment on testing, and those for whom the study geriatric psychiatrist suspects clinically significant cognitive decline will be referred to the Memory Disorders Clinic at UCHC.

Sample Size and Recruitment

In our grant submission, we conducted power analyses to determine our sample size targets. Given three groups, we set an alpha of 0.05 divided by 3 = 0.01667. Setting power at 0.80, based on preliminary data, our per-group target was 50. Herein we present data on the initial cohort recruited to date. Recruitment began in April 2013 and is expected to continue through April 2016.

$$\text{T- score} = \frac{(\text{Raw Score} - \text{Mean of Standard population})}{\text{SD of Standard population}} * 10 + 50$$

Statistical Analyses

Participants recruited to date include those with current major depression (n=33), a group of never-depressed control subjects scoring low in neuroticism measures (n=27), and a group of never-depressed control subjects scoring high in neuroticism measures (n=3). For the latter group, we will only present summary characteristics given the small sample recruited to date.

We prepared the NEO PI-R data as follows. The NEO PI-R profile contains 5 domains: Neuroticism (N), Extraversion (E), Openness to Experience (O), Agreeableness (A) and Conscientiousness (C). The raw score of each domain was obtained by summing up all the scores of its component items. Each raw score was further converted into standardized T-score based on gender-specific norm, by following the formula:

The gender-specific means and standard deviations, derived from a normative group of 500 men and 500 women, were provided in the manual by Costa and McCrae (Costa and McCrae, 1992). A T-score ≥55 was used to identify control subjects scoring high in neuroticism (Costa and McCrae, 1985).

Analyses for this manuscript focus on contrasting depressed vs. non-neurotic controls. Pearson Chi-square tests are used to assess associations between categorical variables. If the data are sparse and the expected cell counts are <5, exact *p*-values (e.g., Fisher's Exact Test) are reported. For numerical data, group comparisons are assessed using a two-sample t-test, after the distributions were found to be approximately normal and group sizes >25. For future analyses, with data that do not meet the normality assumptions for t-tests, have extreme values, or have limited distributions such as Likert scales, the appropriate non-parametric alternative (e.g. Wilcoxon Rank Sum Test) will be used. A two-sided alpha level of significance of 0.05 was used to evaluate statistical significance. All analyses were conducted using SAS version 9.4 (SAS, Inc., Cary, NC).

Results

Baseline characteristics of the sample are shown in Table 1. Here, we present data on the depressed group as a whole, while the non-depressed comparison group was divided into "neurotic" versus "non-neurotic" based on their Neuroticism score on the NEO-PI. Overall, the sample was about 72 years old, predominantly white and female. This cohort had a high degree of educational achievement, with about 63% of controls and 70% of depressed participants had at least a college degree. Global cognitive functioning was similarly high (mean above 29) in both groups.

The depressed group had significantly higher scores on the MADRS, STAI-state anxiety, STAI-trait anxiety and the CIRS (see Table 1). In respect to personality characteristics, compared to controls the depressed group scored significantly higher on the NEO domain of Neuroticism, significantly lower on the domains of Extraversion, Agreeableness, and Conscientiousness, and equivalently on the domain of Openness to Experience. In addition, depressed individuals reported a mean of 2.0 adverse childhood experiences compared with a mean of 1.2 for the non-neurotic controls ($p = 0.18$).

Depressed and control subjects were not significantly different on the CERAD neuropsychological composite measure. By contrast, significant group differences were observed on experimental "neuroscience" measures (see Table 2). Depressed subjects endorsed more negative words compared to controls on the emotional characterization test. Elsewhere, when compared with controls, depressed adults exhibited slower responding on a cognitive interference test requiring the identification of fearful or happy faces as male or female while ignoring the words "male" or "female" labeled across the face. In this small sample, no group by congruency effect was observed on this test. That is, depressed older adults exhibited slower processing speed compared with non-depressed subjects regardless of whether trials were congruent (e.g., the word male overlaid on a man's face) or incongruent (e.g., the word female overlaid on a man's face). By contrast, a group by congruency effect was observed on the emotional interference test where subjects were

asked to identify the face's emotional expression while ignoring the words "fear" or "happy" labeled across the face. Response times were equivalent for controls and depressed subjects when tasked with identifying the emotional expressions of faces overlaid with congruent written emotions (e.g., the word fear overlaid on a fearful face). Yet, when the pairing between words and faces was incongruent (e.g., the word fear overlaid on a happy face), older adults with major depression were significantly slower than controls in identifying the face's emotion.

In analyses not shown, we found no differences between the depression and control groups on laboratory measures of TSH, homocysteine, or folate.

Discussion

In this preliminary report from the NBOLD study, we report our methods for initial clinical and cognitive assessment, as well as our baseline assessments of neuroticism and other personality characteristics, resilience, and life orientation. We also report preliminary evidence describing behavioral results from experimental "neuroscience" measures of emotional processing.

Depressed participants not surprisingly scored higher on clinical measures of depression and anxiety. We also included several measures not normally part of most geriatric depression studies related to constructs of personality, adverse childhood experiences, optimism, and resilience. The depressed group scored quite differently than the control group on several personality domains, with older depressed adults showing higher scores on Neuroticism and lower scores on Extraversion, Agreeableness and Conscientiousness. The depressed cohort also showed less resilience and optimism as measured on the Brief Resilience Scale and the Life Orientation Test. To our knowledge this represents the first use of these instruments in this population; in the case of resilience, these cross-sectional findings suggest that depression might have a dampening effect on resilience, or that resilience might operate as a protective mechanism against developing depression and coping with other chronic illnesses in middle and later life (Fortinsky *et al.*, 2013). Likewise, we found a non-significant trend for more adverse childhood experiences in the depressed group using the ACES, an instrument that is also underutilized in geriatric depression research.

The present findings of higher levels of increased neuroticism and less extraversion, agreeableness, and conscientiousness are consistent with prior studies of older depressed adults (Steffens *et al.*, 2013; Weber *et al.*, 2013). The interconnections among neuroticism, depression, and anxiety in older adults are complex and warrant ongoing investigation. Our preliminary evidence suggests higher levels of neuroticism in older adults with major depression are associated with reduced treatment response over time (Hayward *et al.*, 2013). Thus, the presence of neuroticism may mediate symptom severity in late-life depression. However, an alternative theory is that comorbid anxiety (especially rumination and worry) may moderate the association between neuroticism and depression (Roelofs *et al.*, 2008). This theory is consistent with the notion of neuroticism as a primary manifestation of sensitivity to threat and punishment (DeYoung *et al.*, 2010). In future analyses, we will be in

a position to examine the complex relationships among depression, anxiety, neuroticism, and other personality factors.

Findings from experimental neuroscience measures were mixed in respect to the expected interaction between group and distracter stimulus (congruent or incongruent) across cognitive and emotional interference tests. Contrary to our hypothesis, depressed subjects responded slower on the cognitive interference test requiring gender identification of faces regardless of whether extraneous distracters (the words “male” or “female” overlaid on the face) were congruent or incongruent. Overall slower cognitive processing speed in the depressed cohort may explain the lack of congruency effect on this task. However, the expected congruency effect was observed during the emotional distraction test, in that depressed subjects were slower to identify faces as fearful or happy, but only under the incongruent condition (e.g., the word fear overlaid on a happy face). This latter finding is consistent with prior evidence that resistance to emotional distraction is enabled by top-down inhibition of the amygdala from the rostral anterior cingulate cortex (rACC) (Egner *et al.*, 2008). Therefore, disrupted connectivity between the rACC and amygdala (representing a failure of amygdala inhibition) (Etkin *et al.*, 2006) may explain slower response times in depressed compared to control subjects specifically during emotional interference (incongruent trials) but not emotionally neutral (congruent) conditions. Our future analyses will examine these behavioral paradigms in greater detail and provide corroborating evidence of functional connectivity.

We did not find significant cross-sectional differences between older adults with major depression and controls on a composite measure of cognitive functioning. This is consistent with evidence showing the vast majority of older adults with major depression do not experience global cognitive impairment (Morimoto *et al.*, 2015). Instead, the cognitive profile of late-life depression is usually characterized by mild deficits in executive functioning and processing speed (Sheline *et al.*, 2006; Lockwood *et al.*, 2002). While major depression may be a risk factor for later cognitive decline (Diniz *et al.*, 2013), only a minority of older adults with major depression eventually develop dementia (Potter *et al.*, 2013). However, the combination of neuroticism and major depression may be especially detrimental to the cognitive wellbeing of older adults. Higher neuroticism, and the vulnerability to stress component in particular, was associated with a two-year decline in global cognitive functioning in older adults with major depression (Steffens *et al.*, 2013). Moreover, vulnerability to stress and trait anxiety were the only neuroticism components associated with the risk of Alzheimer’s disease in non-depressed older adults (Wilson *et al.*, 2011). Longstanding stress and anxiety may reduce hippocampal volume via glucocorticoid secretion thereby increasing susceptibility to cognitive decline and dementia (Mah *et al.*, 2015; Tschanz *et al.*, 2013; Zannas *et al.*, 2013).

There are some limitations of our method that are worth mentioning. First, our recruitment strategy, in which we monitor our depressed and non-depressed samples to ensure adequate numbers of subjects likely to score high in neuroticism, may lead to populations of older depressed and non-depressed adults that are not representative of the general population. Another limitation is that, lthough we initially administer a standardized six month treatment regimen, subjects not in remission at six months are offered naturalistic treatment. That is,

the decision for treatment is made between psychiatrist and patient and may vary considerable from one patient to the next. In addition, we have not instituted guidelines for treatment of cognitive disorders although we suspect the prevalence of medications to treat cognitive symptoms (e.g., cholinesterase inhibitors) will be low. Finally, the evaluation period is currently limited to two years. Although this initially may seem a relatively short period to detect meaningful cognitive change in this cohort, our preliminary data revealed cognitive differences at two year interval (Steffens *et al.*, 2013).

The aim of the NBOLD study is to examine the relationships among depression, neuroticism, and neuroimaging changes in older adults. This study will primarily serve to elucidate: 1) the potential synergistic effect of neuroticism and major depression on treatment response and cognitive decline in older adults, and 2) the functional connectivity amongst limbic and frontal regions involved in emotional and cognitive processing. Ventromedial (VMPFC) behavioral dysfunction is not well understood in late-life depression (Manning *et al.*, 2014), and we hope to clarify the association between VMPFC connectivity, neuroticism components (e.g., impulsivity, hostility), and clinical outcomes. Finally, by including resilience and life orientation, we will better understand how these protective factors may influence the experience of depression, neuroticism, and cognitive decline in late-life. Thus, this study will be well positioned to characterize the course of clinical outcomes associated with neuroticism and depression in late-life.

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References

Anda RF, Butchart A, Felitti VJ, Brown DW. Building a framework for global surveillance of the public health implications of adverse childhood experiences. American Journal of Preventive Medicine. 2010; 39:93–98. [PubMed: 20547282]

Benton, A. Revised Visual Retention Test. 4. New York: The Psychological Corporation; 1974.

Benton, AL.; Hamsher, K.; Varney, N.; Spreen, O. Contributions to Neuropsychological Assessment. New York: Oxford University Press; 1983.

Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. The influence of comorbid personality disorder and neuroticism on treatment outcome in first episode depression. Psychopathology. 2010; 43:197–204. [PubMed: 20375542]

Cano-García FJ, Padilla-Muñoz EM, Carrasco-Ortiz MA. Personality and contextual variables in teacher burnout. Personality and Individual Differences. 2005; 38:929–940.

Canuto A, Giannakopoulos P, Meiler-Mititelu C, Delaloye C, Herrmann FR, Weber K. Personality traits influence clinical outcome in day hospital-treated elderly depressed patients. American Journal of Geriatric Psychiatry. 2009; 17:335–343. [PubMed: 19307862]

Carroll, BJ. Carroll Depression Scales-Revised (CDS-R): Technical Manual. Toronto: Multi-Health Systems; 1998.

Carroll BJ, Feinberg M, Smouse PE, Rawson SG, Greden JF. The Carroll rating scale for depression. I. Development, reliability and validation. British Journal of Psychiatry. 1981; 138:194–200. [PubMed: 7272609]

Chan SW, Harmer CJ, Goodwin GM, Norbury R. Risk for depression is associated with neural biases in emotional categorisation. Neuropsychologia. 2008; 46:2896–2903. [PubMed: 18601940]

Costa PT Jr, McCrae RR. Age changes in personality and their origins: comment on Roberts, Walton, and Viechtbauer (2006). Psychological Bulletin. 2006; 132:26–28. [PubMed: 16435955]

Costa, PT.; McCrae, RR. The NEO personality inventory manual. Odessa, FL: Psychological Assessment Resources; 1985.

Costa, PT.; McCrae, RR. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) professional manual. Odessa, FL: Psychological Assessment Resources; 1992.

Cremers HR, et al. Neuroticism modulates amygdala-prefrontal connectivity in response to negative emotional facial expressions. Neuroimage. 2010; 49:963–970. [PubMed: 19683585]

Denollet J. DS14: standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosomatic Medicine. 2005; 67:89–97. [PubMed: 15673629]

DeYoung CG, Hirsh JB, Shane MS, Papademetris X, Rajeevan N, Gray JR. Testing predictions from personality neuroscience. Brain structure and the big five. Psychological Science. 2010; 21:820–828. [PubMed: 20435951]

Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF 3RD. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. British Journal of Psychiatry. 2013; 202:329–335. [PubMed: 23637108]

Egner T, Elkin A, Gale S, Hirsch J. Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. Cerebral Cortex. 2008; 18:1475–1484. [PubMed: 17940084]

Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. Neuron. 2006; 51:871–882. [PubMed: 16982430]

Eysenck, HJ.; Eysenck, SBG. Manual of the Eysenck Personality Questionnaire. London: Hodder and Stoughton; 1975.

Folstein MF, Folstein SE, McHugh PR. Mini-Mental state. A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975; 12:189–198. [PubMed: 1202204]

Fortinsky RH, Tennen H, Steffens DC. Resilience in the face of chronic illness and family caregiving in middle and later life. Psychiatric Annals. 2013; 43:549–554.

Fruhholz S, Prinz M, Herrmann M. Affect-related personality traits and contextual interference processing during perception of facial affect. Neuroscience Letters. 2010; 469:260–264. [PubMed: 20005920]

Hamilton M. A rating scale for depression. Journal of Neurology, Neurosurgery, and Psychiatry. 1960; 23:55–61.

Hayward RD, Taylor WD, Smoski MJ, Steffens DC, Payne ME. Association of five-factor model personality domains and facets with presence, onset, and treatment outcomes of major depression in older adults. American Journal of Geriatric Psychiatry. 2013; 21:88–96. [PubMed: 23290206]

Hoppe CD, Muller UD, Werheid KD, Thone AD, von Cramon YD. Digit Ordering Test: clinical, psychometric, and experimental evaluation of a verbal working memory test. The Clinical Neuropsychologist. 2000; 14:38–55. [PubMed: 10855058]

Jelicic M, Bosma H, Ponds RW, van Boxtel MP, Houx PJ, Jolles J. Neuroticism does not affect cognitive functioning in later life. Experimental Aging Research. 2003; 29:73–78. [PubMed: 12744220]

Kaplan, EF.; Goodlass, H.; Weintraub, S. The Boston Naming Test. 2. Philadephia: Lea and Febiger; 1983.

Keller MB, et al. The Longitudinal Interval Follow-up Evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. Archives of General Psychiatry. 1987; 44:540–548. [PubMed: 3579500]

Kendler KS, Gatz M, Gardner CO, Pedersen NL. Personality and major depression: a Swedish longitudinal, population-based twin study. Archives of General Psychiatry. 2006; 63:1113–1120. [PubMed: 17015813]

Lahey BB. Public health significance of neuroticism. American Psychologist. 2009; 64:241–256. [PubMed: 19449983]

Landerman R, George LK, Campbell RT, Blazer DG. Alternative models of the stress buffering hypothesis. American Journal of Community Psychology. 1989; 17:626–642.

Linn BS, Linn MW, Gurel L. Cumulative Illness Rating Scale. Journal of the American Geriatrics Society. 1988; 16:622–626. [PubMed: 5646906]

Lockwood KA, Alexopoulos GS, van Gorp WG. Executive dysfunction in geriatric depression. American Journal of Psychiatry. 2002; 159:1119–1126. [PubMed: 12091189]

Mah L, Binns MA, Steffens DC. Anxiety symptoms in amnestic mild cognitive impairment are associated with medial temporal atrophy and predict conversion to Alzheimer disease. American Journal of Geriatric Psychiatry. 2015; 23:466–476. [PubMed: 25500120]

Manning KJ, Gunning FM, McGovern AR, Kotbi N, Alexopoulos GS. Ventromedial syndrome with normal cognitive functioning in vascular depression. American Journal of Psychiatry. 2014; 171:1337–1338. [PubMed: 25756772]

McCrae RR, Costa PT. Joint factors in self-reports and ratings: Neuroticism, extraversion and openness to experience. Personality and Individual Differences. 1983; 4:245–255.

Miller MD, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Research. 1992; 41:237–248. [PubMed: 1594710]

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. British Journal of Psychiatry. 1979; 134:382–389. [PubMed: 444788]

Morimoto SS, Kanellopoulos D, Manning KJ, Alexopoulos GS. Diagnosis and treatment of depression and cognitive impairment in late life. Annals of the New York Academy of Sciences. 2015; 1345:36–46. [PubMed: 25655026]

Morris JC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. 1989; 39:1159–1165. [PubMed: 2771064]

Omura K, Todd Constable R, Canli T. Amygdala gray matter concentration is associated with extraversion and neuroticism. Neuroreport. 2005; 16:1905–1908. [PubMed: 16272876]

Petersen T, et al. NEO-FFI factor scores as predictors of clinical response to fluoxetine in depressed outpatients. Psychiatry Res. 2002; 109:9–16. [PubMed: 11850046]

Potter GG, Wagner HR, Burke JR, Plassman BL, Welsh-Bohmer KA, Steffens DC. Neuropsychological predictors of dementia in late-life major depressive disorder. American Journal of Geriatric Psychiatry. 2013; 21:297–306. [PubMed: 23395197]

Reitan, RM. Trail Making Test: Manual for Administration and Scoring. Tucson: Reitan Neuropsychological Laboratory; 1992.

Robins N, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health diagnostic interview schedule. Archives of General Psychiatry. 1981; 38:381–389. [PubMed: 6260053]

Roelfers J, Huibers M, Peeters F, Arntz A, van Os J. Rumination and worrying as possible mediators in the relation between neuroticism and symptoms of depression and anxiety in clinically depressed individuals. Behaviour Research and Therapy. 2008; 46:1283–1289. [PubMed: 19006785]

Sackheim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. Journal of Clinical Psychopharmacology. 1990; 10:96–104. [PubMed: 2341598]

Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. Journal of Personality and Social Psychology. 1994; 67:1063–1078. [PubMed: 7815302]

Sheline YI, et al. Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. Biological Psychiatry. 2006; 60:58–65. [PubMed: 16414031]

Smith, A. Symbol Digit Modalities Test-Manual. Los Angeles: Western Psychological Services; 1982.

Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. International Journal of Behavioral Medicine. 2008; 15:194–200. [PubMed: 18696313]

Spielberger, CD.; Gorssuch, RL.; Lushene, PR.; Vagg, PR.; Jacobs, GA. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, Inc; 1983.

Steffens DC, McQuoid DR, Krishnan KR. The Duke Somatic Treatment Algorithm for Geriatric Depression (STAGED) approach. Psychopharmacology Bulletin. 2002; 36:58–68. [PubMed: 12397841]

Steffens DC, McQuoid DR, Smoski MJ, Potter GG. Clinical outcomes of older depressed patients with and without comorbid neuroticism. International Psychogeriatrics. 2013; 25:1985–90. [PubMed: 23941723]

Tschanz JT, Norton MC, Zandi PP, Lyketsos CG. The Cache County Study on Memory in Aging: factors affecting risk of Alzheimer's disease and its progression after onset. International Review of Psychiatry. 2013; 25:673–685. [PubMed: 24423221]

Weber K, et al. Stressful life events and neuroticism as predictors of late-life versus early-life depression. Psychogeriatrics. 2013; 13:221–228. [PubMed: 24289463]

Wechsler, D. Wechsler Memory Scale-Revised Manual. San Antonio: Psychological Corporation; 1987.

Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. American Journal of Epidemiology. 1977; 106:203–214. [PubMed: 900119]

Welsh KA, et al. The Consortium to Establish a Registry of Alzheimer's Disease (CERAD) Part V: A normative study of the neuropsychological battery. Neurology. 1994; 44:609–614. [PubMed: 8164812]

Wetherell JL, Reynolds CA, Gatz M, Pedersen NL. Anxiety, cognitive performance, and cognitive decline in normal aging. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 2002; 57:246–255.

Wilson RS, Begeny CT, Boyle PA, Schneider JA, Bennett DA. Vulnerability to stress, anxiety, and development of dementia in old age. American Journal of Geriatric Psychiatry. 2011; 19:327–334. [PubMed: 21427641]

Wilson RS, Bennett DA, Mendes de Leon CF, Bienias JL, Morris MC, Evans DA. Distress proneness and cognitive decline in a population of older persons. Psychoneuroendocrinology. 2005; 30:11–17. [PubMed: 15358438]

Wright CI, et al. Neuroanatomical correlates of extraversion and neuroticism. Cerebral Cortex. 2006; 16:1809–1819. [PubMed: 16421327]

Zachary, RA. Shipley Institute of Living Scale - Revised Manual. Los Angeles: Western Psychological Services; 1991.

Zannas AS, et al. Negative life stress and longitudinal hippocampal volume changes in older adults with and without depression. Journal of Psychiatric Research. 2013; 47:829–834. [PubMed: 23478048]

Table 1

Characteristics of the sample.

	Depressed group (N = 33)	Non-depressed, low neuroticism group (N = 27)	Non-depressed, high neuroticism group (N = 3)	Depressed vs non-depressed, low neuroticism
Demographic variables				
Age	71.3 (7.7)	73.7 (6.7)	74.0 (9.5)	0.20
Gender (% Female)	22 (66.7%)	23 (85.2%)	3 (100%)	0.14[a]
Race (% White)	30 (90.9%)	26 (96.3%)	3 (100%)	0.62[a]
Marital Status (%)				0.09[b]
Single	5 (15.2%)	3 (11.1%)	0 (0%)	
Married	13 (39.4%)	15 (55.6%)	2 (66.7%	
Divorced/Separated	12 (36.4%)	3 (11.1%)	0 (0%)	
Widowed	3 (9.1%)	6 (22.2%)	1 (33.3%)	
Educational level (%)				0.90[b]
Less than high school	1 (3.0%)	0 (0%)	0 (0%)	
High School diploma	3 (9.1%)	4 (14.8%)	1 (33.3%)	
Some college	6 (18.2%)	5 (18.5%)	1 (33.3%)	
College degree	3 (9.1%)	4 (14.8%)	0 (0%)	
Beyond college	20 (60.6%)	14 (51.9%)	1 (33.3%)	
Working status (%)				0.39[b]
Working	11 (33.3%)	5 (18.5%)	1 (33.3%)	
Retired	18 (54.5%)	16 (59.3%)	2 (66.7%)	
Semi-retired	2 (6.1%)	5 (18.5%)	0 (0%)	
Unemployed	2 (6.1%)	1 (3.7%)	0 (0%)	
Clinical Variables				
MADRS	19.2 (6.3)	0.2 (0.8)	2.7 (2.3)	<0.0001
STAI State Anxiety	38.3 (9.7)	26.7 (4.7)	32.0 (7.2)	<0.0001
STAI Trait Anxiety	49.6 (11.1)	30.1 (5.7)	43.0 (8.7)	<0.0001
MMSE	29.4 (1.1)	29.4 (1.0)	29.0 (1.7)	0.87
Cumulative Illness Rating Scale	4.1 (2.6)	1.9 (1.4)	2.7 (0.6)	<0.0001
Other measures				
DS 14 Negative Affect	15.7 (6.3)	4.2 (4.0)	14.0 (5.3)	<0.0001
DS 14 Social Inhibition	11.5 (6.6)	6.4 (6.5)	11.3 (4.9)	0.004
NEO Personality Domains				
Neuroticism	61.0 (10.7)	40.2 (8.4)	57.2 (2.9)	<0.0001
Extraversion	41.3 (9.9)	51.6 (10.2)	47.8 (13.2)	<0.0001
Openness to Experience	52.5 (12.1)	51.7 (9.5)	52.9 (15.1)	0.76
Agreeableness	50.6 (10.1)	57.0 (9.0)	45.0 (6.3)	0.013
Conscientiousness	42.8 (13.1)	53.9 (11.2)	54.1 (16.1)	0.001

	Depressed group (N = 33)	Non-depressed, low neuroticism group (N = 27)	Non-depressed, high neuroticism group (N = 3)	Depressed vs non-depressed, low neuroticism
Brief Resilience Scale	15.9 (4.4)	24.6 (3.6)	16.7 (3.5)	<0.0001
Life Orientation Test	12.1 (4.8)	19.3 (2.9)	14.7 (1.5)	<0.0001
Adverse Childhood Experiences	1.9 (2.1) (N=29)	1.2 (1.7) (N=25)	1.0 (0.00) (N=3)	0.18

Note. Values represent means and standard deviations, with *p*-values from two-sample t-tests unless otherwise noted.

[a] Fisher's Exact Test

[b] Exact *p*-values for Pearson Chi-square test

Table 2

Performance on cognitive and experimental measures.

	Depressed group (N = 33)	Non-depressed, low neuroticism group (N = 27)	Non-depressed, high neuroticism group (N = 3)	Depressed vs non-depressed, low neuroticism
Standard cognitive battery				
CERAD total score	80.9 (11.9)	82.6 (9.6)	82.3 (8.0)	0.57
Experimental measures				
Emotional Interference Task[a]				
Congruent	887.4 (163.8)	814.8 (121.1)	934.7 (142.0)	0.065
Incongruent	1015 (175.0)	925.3 (131.9)	991.9 (114.7)	0.034
Cognitive Interference Task				
Congruent	886.9 (204.6)	790.0 (119.0)	970.9 (124.6)	0.026
Incongruent	987.8 (233.1)	841.0 (123.1)	983.4 (108.6)	0.03
Emotion Categorization Test[b]				
No. of Positive Words	26.1 (3.6)	29.1 (1.6)	26.0 (3.6)	<0.0001
No. of Negative Words	6.0 (4.3)	1.9 (2.3)	5.0 (2.7)	<0.0001

Note. Values represent means and standard deviations, with *p*-values from two-sample t-tests

[a] N = 30 in the depressed group. Three participants missing due hardware malfunction (N = 2) and premature discontinuation of the test (N = 1).

[b] N = 26 in the non-depressed low neuroticism group as this measure was added to the study after data collection was initiated.