

# Neuroticism Traits Selectively Impact Long Term Illness Course and Cognitive Decline in Late-Life Depression

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**Objectives:** *Neuroticism is a broad construct that conveys a predisposition to experience psychological distress and negative mood states. Vulnerability to stress (VS) is one neuroticism trait that has been linked to worse mood and cognitive outcomes in older adults. We hypothesized that elevated VS would be associated with worse illness course and cognitive decline in older adults with late-life major depression (LLD).* **Design:** *Participants were enrolled in the Neurocognitive Outcomes of Depression in the Elderly (NCODE), a longitudinal investigation of the predictors of poor illness course and cognitive decline in LLD. Participants were followed upwards of 10 years.* **Setting:** *NCODE operates in a naturalistic treatment milieu.* **Participants:** *112 participants aged 60 and older with a current diagnosis of major depressive disorder.* **Measurements:** *Treatment response was assessed at least every 3 months and more often if clinically needed. Participants also completed the NEO Personality Inventory-Revised (NEO PI-R) and an annual cognitive examination. Neuroticism traits from the NEO PI-R included anxiety, depression, anger-hostility, self-consciousness, impulsivity, and VS.* **Results:** *Higher neuroticism traits of VS, impulsivity, anger-hostility, and anxiety were associated with worse treatment response over time. High VS was the only neuroticism trait significantly associated with cognitive functioning. High VS negatively influenced the rate of global cognitive decline over time.* **Conclusions:** *Individual personality traits within the neuroticism dimension are associated with treatment resistance and cognitive impairment in LLD. It remains to be seen whether these individual traits are associated with different neurobiological substrates and clinical characteristics of LLD.* (Am J Geriatr Psychiatry 2016; ■■■:■■■-■■■)

**Key Words:** Depression, elderly, neuroticism, cognition

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Major depression in older adults is a heterogeneous syndrome with a diverse illness course and cognitive profile. Older adults with late-life depression (LLD) exhibit considerable variability in

their response to antidepressants, with over 50% of patients failing to respond to initial psychopharmacological treatment.<sup>1</sup> Variability in the cognitive presentation of LLD is also common. Mild cognitive

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*Neuroticism in LLD and Longitudinal Clinical Change*

weaknesses in processing speed and executive functioning are ubiquitous cross-sectional findings in LLD,<sup>2,3</sup> yet prospective evidence also suggests major depression increases the probability of subsequent cognitive decline,<sup>4</sup> as well as disability,<sup>5</sup> hospitalization,<sup>6</sup> and mortality.<sup>7</sup> Thus, identifying factors that increase the risk for poor illness course and cognitive decline in LLD has important individualized treatment and public health implications. Neuroticism has received increasing attention as an indicator of worse cognitive and mood outcomes in older adults with and without major depression.

Neuroticism is a multidimensional personality characteristic conveying a predisposition to experience psychological distress and negative mood states.<sup>8</sup> Facets or traits of neuroticism on the Revised NEO Personality Inventory (NEO PI-R) include anxiety, anger-hostility, depression, self-consciousness, impulsiveness, and vulnerability to stress (VS).<sup>9</sup> Total neuroticism is associated with increased risk of depression<sup>10</sup> and cognitive decline<sup>11,12</sup> in nondepressed older adults, and is associated with structural and functional abnormalities in brain regions responsible for threat perception, emotional regulation, and memory. Higher neuroticism scores in nondepressed adults correlate with volume loss and hyper-metabolism in the ventromedial prefrontal cortex, amygdala, and hippocampus.<sup>13,14</sup> Overall, this body of evidence suggests elevated neuroticism in older adults may therefore: 1) predispose or perpetuate acute episodes of major depression via underlying chronic limbic overactivity,<sup>15</sup> and 2) contribute to a chronic stress response that induces neuronal dysfunction increasing susceptibility to cognitive decline and dementia.<sup>16</sup> Neuroticism is frequently elevated in LLD,<sup>17</sup> yet the long-term clinical trajectory of acute major depression superimposed on neuroticism in older adults is not well understood.

Neuroticism may exacerbate treatment resistance and cognitive impairment in LLD. Our preliminary evidence indicated high total neuroticism and the VS trait were the only neuroticism scores associated with both a worse 1-year antidepressant treatment response and a 2-year decline in global cognitive functioning in LLD.<sup>18,19</sup> Elsewhere, increased VS and anxiety were the only neuroticism traits associated with global cognitive decline in nondepressed older adults followed over 3 years.<sup>11</sup> We therefore hypothesized that LLD patients with high VS would be associated with worse illness course and cognitive decline over time. We ex-

tended our preliminary investigations into the association between neuroticism and 1-year illness course<sup>19</sup> and 2-year global cognitive functioning<sup>18</sup> by including participants followed upwards of 10 years. We also measured multiple cognitive domains as opposed to just global functioning and investigated the association between long-term outcomes and all six neuroticism traits in order to understand individual differences within neuroticism that influence cognition and treatment.

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## METHODS

### Participants

Participants aged 60 years and older were enrolled in the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study at Duke University Medical Center, a longitudinal investigation of the predictors of poor illness course and cognitive decline in LLD. The present study includes a subset of participants who agreed to participate in an ancillary study of personality between February 1998 and February 2001. These participants were initially enrolled in the NCODE study between December 1994 and June 2000. Thus, depending on when each participant entered the study and when they completed the NEO PI-R, depression and cognitive data predate personality assessment by between 0 and 63 months. Neuroticism is therefore treated as a retrospective measure in this study and is used in the analysis of depression severity and cognitive functioning data collected earlier.

Participants were recruited from among inpatients and outpatients from the Duke Psychiatric Service meeting DSM-IV criteria for a current episode of major depressive disorder. Patients were assessed by a geriatric psychiatrist at intake and thereafter at least every 3 months (or more frequently depending on clinical need) using the Montgomery-Asberg Depression Rating Scale (MADRS). Exclusion criteria included the presence of another major psychiatric illness such as schizophrenia, schizoaffective disorder, bipolar disorder, and lifetime alcohol or substance dependence. Dementia at baseline was an exclusionary criterion. Patients with psychotic depression were included, as were those with comorbid anxiety disorders, as long as major depression was deemed by the study psychiatrist to be the primary psychiatric disorder. In addition to de-

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