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

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Abstract

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 three 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

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individual traits are associated with different neurobiological substrates and clinical characteristics of LLD.

Keywords

depression; elderly; neuroticism; cognition

Objective

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 (1). Variability in the cognitive presentation of LLD is also common. Mild cognitive weaknesses in processing speed and executive functioning are ubiquitous cross-sectional findings in LLD (2, 3), yet prospective evidence also suggests major depression increases the probability of subsequent cognitive decline (4), as well as disability (5), hospitalization (6), and mortality (7). 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 (8). 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) (9). Total neuroticism is associated with increased risk of depression (10) and cognitive decline (11, 12) in non-depressed 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 non-depressed adults correlate with volume loss and hyper-metabolism in the ventromedial prefrontal cortex, amygdala, and hippocampus (13, 14). 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 (15), and 2) contribute to a chronic stress response that induces neuronal dysfunction increasing susceptibility to cognitive decline and dementia (16). Neuroticism is frequently elevated in LLD (17), 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 one-year antidepressant treatment response and a two-year decline in global cognitive functioning in LLD (18, 19). Elsewhere, increased VS and anxiety were the only neuroticism traits associated with global cognitive decline in non-depressed older adults followed over three years (11). We therefore hypothesized that LLD patients with high VS would be associated with worse illness course and cognitive decline over time. We extended our preliminary investigations into the association between

neuroticism and one-year illness course (19) and two- year global cognitive functioning (18) 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.

Methods

Participants

Participants age 60 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 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for a current episode of major depressive disorder. Patients were assessed by a geriatric psychiatrist at intake and thereafter at least every three 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 dementia, other neurological illnesses were excluded, such as Parkinson's disease, multiple sclerosis, and seizure disorder. All participants provided informed consent before beginning any study procedures. The NCODE study was approved by the Duke University Health System Institutional Review Board.

Measurements

Neuroticism. Participants completed the 240-item NEO PI-R which derives five factors of personality including neuroticism, extraversion, openness, conscientiousness, and agreeableness. The focus of the current study was on the total neuroticism score and its six individual traits (anxiety, anger-hostility, depression, social anxiety, impulsiveness, and VS). Trait raw scores (range 0-32) were converted to gender-adjusted T scores using normative data (9). Whereas there are no scientifically validated thresholds for personality scales, we selected a T-score of 55 to define high neuroticism traits. The T-score 55 is consistent with a T 56 (based on gender-combined norms) used to identify “risky” traits in the

Baltimore Longitudinal Study of Aging (20). Both T-scores and raw scores were used in the analyses as described in detail below.

Depression Severity. Depressed patients were monitored using the MADRS, a clinician-rated instrument designed to measure depression severity among patients diagnosed with depression and to be sensitive to changes due to treatment. It has been found to have high interrater reliability ranging from 0.89 to 0.97. It provides a rating of depression severity on a scale from 0 to 60, with scores from 0 to 6 indicating remitted depression, 7-19 mild depression, 20-34 moderate depression, and 35-60 severe depression.

Cognition. Participants completed the Mini-Mental State Examination (MMSE(21); used only for descriptive purposes in the current study) and the Consortium to Establish a Registry in Alzheimer's Disease (CERAD) neuropsychological battery (22), a collection of measures with normative standards for the elderly and established utility in longitudinal studies of cognitive impairment (23). The CERAD measures are tallied to create a composite measure of global cognitive functioning (maximum score=100). Normative standards suggest healthy elderly typically perform around 79 whereas patients with mild cognitive impairment and dementia exhibit average scores of 68 and 49, respectively (24). The CERAD battery was supplemented by other neuropsychological measures sensitive to cognitive domains thought to be commonly disrupted in LLD and/or predementia cognitive changes. Measures include: 1) recall of verbal information following an extended delay measured using the Logical Memory subtest of the Wechsler Memory Scale-Revised (maximum score=50) (25), 2) graphomotor processing speed measured using the Symbol Digit Modalities Test (maximum score=110) (26), and 3) cognitive flexibility measured using the Trail Making Test Part B (score in seconds to complete test) (27)

Demographics. Self-reported demographic characteristics used as covariates in this study included sex, age, race, and years of education.

Longitudinal Assessment

The NCODE study operates in a naturalistic treatment milieu using treatment guidelines established by the Duke Affective Disorders Program. Treatment modalities available include antidepressant medications, electro-convulsive therapy, and individual and group cognitive-behavioral psychotherapy. Treatment was monitored to ensure that clinical guidelines are followed appropriately. As indicated above, patients were evaluated when clinically indicated, and at least every three months while they were in the study. The protocol recommends that patients receive continuation treatment for at least one to two years (some indefinitely) once they achieve remission. Each patient was thus assured to receive the most appropriate care we were able to provide. The current study includes all depressed participants' assessment within 10 years from enrollment.

Statistical Analyses

Separate generalized linear mixed models (GLMM) were used to examine the relationships between neuroticism (total score and each of the six neuroticism trait scores) and each of the five outcomes (MADRS, CERAD, Logical Memory, Symbol Digit Modalities, and Trail Making Part B) over time after adjusting for potential baseline confounders. All models

included neuroticism main effect, time (since first evaluation in years) main effect as well as neuroticism by time interaction to investigate how level of neuroticism affects rate of illness course and cognitive decline for up to 10 years. Both the intercept and rate of change with respect to time were treated as random. Analyses were initially conducted with high and low neuroticism scores (based upon a T cut-score of 55) and then repeated with continuous raw scores to ensure findings were not biased as a result of dichotomization or gender-normalization. The illness course outcome (MADRS) exhibited a positively skewed distribution and hence it was modeled by negative binomial GLMM controlling for gender and baseline age. Normal GLMMs were used to model the four cognitive outcomes given gender, race, and baseline age and education level. The raw CERAD score distribution was negatively skewed, and hence it was transformed to square-root of (100 minus CERAD score) prior to model fitting. SAS 9.4 was used for all analyses.

Results

Baseline characteristics of the sample are shown in Table 1. The majority of the sample were white women with an average age of 67.8 and 13.9 years of education. Five percent of the sample identified as Black, five percent as mixed race, and one percent as Asian. Average baseline global cognitive functioning was within normal limits based on the MMSE and CERAD. In terms of longitudinal data, 112 participants were administered an average of 27.3 (SD = 12.5) MADRS assessments over a mean of 6.8 years (SD = 2.3). Cognitive assessments were available for a subset of 76 participants who underwent an average of 5.2 annual cognitive batteries (SD = 3.8). Participants were administered their initial MADRS an average of 19.6 months (SD = 14.5) before completing the NEO PI-R, with 50% of participants completing the MADRS between six and 30 months. Participants completed the cognitive examination within an average of 5.5 months (SD = 28.4) of the NEO PI-R, with 50% of participants completing cognitive testing between six months prior and seven months after the NEO PI-R.

Illness Course

Using a high / low neuroticism dichotomization, several neuroticism traits were associated with baseline MADRS scores. Subjects who scored high on anxiety, depression, VS, self-consciousness, and total neuroticism experienced more severe depression at baseline. By contrast, only VS, impulsivity, and total neuroticism influenced progression of depression over time, with participants who scored high in these traits experiencing a slower treatment response after controlling for age and gender (see Table 2). For example, fitting the estimates from Table 2 (as well as the median sample age and female as the imputed sex) revealed that, compared to low VS subjects, high VS participants scored an average of 5.0, 3.5, and 2.0 MADRS points higher at baseline, year five, and year 10, respectively (data not graphically represented).

When these negative binomial generalized mixed models were repeated using continuous raw neuroticism scores, the direction and statistical significance of findings remained largely unchanged, with the exception that the interaction between time and anxiety ($t = 2.03$, $df = 2834$, $b (SE) = 0.008 (0.004)$, $p = 0.04$) and time and anger-hostility ($t = 2.11$, $df = 2834$, b

(SE) = 0.010 (0.005), $p = .03$) were now statistically significant (other data using continuous raw scores are not shown). Participants who scored high in these traits experienced a slower treatment response after controlling for age and gender.

Cognitive Decline

Using a high / low neuroticism dichotomization, vulnerability to stress was associated with an accelerated rate of global cognitive decline using the CERAD after controlling for age, gender, race, and education (see Table 3). No other significant associations between neuroticism and cognitive functioning were found. Figure 1 provides an illustrated example of the association between high / low VS and global cognitive functioning over time. Despite roughly equivalent CERAD scores at baseline, LLD patients who exhibited high scores in VS declined over time whereas low VS subjects remained cognitively stable; the difference in CERAD scores was 10 points at 10 years. When these generalized linear models were repeated using continuous raw neuroticism scores, there was a statistically significant main effect of vulnerability to stress on global cognition using the CERAD ($t = 2.10$, $df = 248$, b (SE) = 0.038 (0.018), $p = 0.03$) whereas the interaction between time and vulnerability to stress was no longer significant ($t = 0.46$, $df = 248$, b (SE) = 0.001 (0.002), $p = 0.64$). The direction and statistical significance of other findings remained unchanged (data using continuous raw scores are not shown).

Conclusions

The principal finding of this study is that older adults with major depression with high VS experienced a slower rate of treatment response and greater cognitive decline compared with low VS LLD participants over an average of 5-6 years. Elevations in impulsivity and anger-hostility / anxiety also predicted worse illness course over time. Higher total neuroticism was associated with a slower rate of treatment response, but was not correlated with cognitive functioning. To our knowledge, this is the first study to identify a long-term association between neuroticism and treatment response and cognitive decline in LLD.

The present findings replicate and extend existing evidence for the impact of neuroticism, and VS specifically, on both treatment response and cognitive decline in LLD (18, 19). The current findings demonstrate a clinically meaningful 10-point difference in global cognition between high and low VS LLD subjects at 10 years. The magnitude of this effect is roughly equivalent to one standard deviation on the CERAD according to the current sample and published normative data (24). Of note, the extent of cognitive decline in the high VS group approaches that of the normative mild cognitive impairment range (24), whereas the global cognitive functioning of the low VS group remained stable over the same 10 year period. These findings call attention to high VS as a risk factor for cognitive decline in LLD and raise speculation as to whether interventions targeting VS could stabilize cognitive decline in LLD (28). The effect size of high VS and the traits of impulsivity, anger-hostility, anxiety on worse depression course could also be considered clinically significant in the context of evidence suggesting there is no absolute MADRS threshold that must be reached for predicting depression relapse and, thus, any decline in MADRS score (even one point) is associated with a lower risk of relapse over time (29).

Biopsychological processes may explain the mechanisms by which elevated VS is an indicator of poor clinical outcome in LLD. Individuals high in VS are described as becoming dependent, hopeless, or panicked when facing trying situations (9), and such maladaptive coping in the presence of psychosocial stressors might perpetuate mood disturbance in LLD (30). Less is known about the neurobiological response to stress in older adults. In children, neuroendocrine markers of stress and adversity at baseline (i.e., high cortisol) are predictive of smaller amygdala and hippocampal volumes and cognitive functioning (31, 32). The neurological sequelae of chronic stress is considered diffuse (33), consistent with the present and prior findings where high VS resulted in greater decline in global cognitive functioning and more than doubled the risk of clinical and neuropathological confirmed dementia (34). There may also be a threshold to which VS must cross to influence cognitive decline in LLD. High VS, when based upon a gender-adjusted T score ≥ 55 , was associated with cognitive decline in the current sample, yet a similar interaction with time was not found when the analysis included raw scores. It remains to be seen if VS increases the risk of Alzheimer's disease diagnosis in LLD or whether biological indicators of stress and inflammation, such as cortisol reactivity and cytokines, correlate with VS and subsequent cognitive impairment and volume loss in LLD.

Neuroticism traits of anxiety, anger-hostility, and impulsivity were also associated with worse treatment response over time. The current findings are consistent with evidence that anxiety superimposed on LLD is associated with worse treatment outcome compared to LLD alone (35). Hostility and treatment response in LLD has not been well studied. This is despite the high prevalence estimates of anger-hostility in middle aged adults with major depression (36) and the association between anger-hostility and cerebrovascular disease in this cohort (37). Of note, MDD participants prone to anger-hostility exhibit increased activity between the ventromedial prefrontal cortex and amygdala during anger induction (38), and functional connectivity among these and surrounding regions correlates with white matter integrity of the uncinate fasciculus in LLD (39). Thus, cerebrovascular disease, particularly white matter disruption between the VMPFC and amygdala, may contribute to the association between anger-hostility and illness course in LLD. This requires further investigation.

Impulsivity was also associated with worse treatment response over time. Impulsivity is an umbrella construct that refers to poorly conceived or prematurely expressed actions that are either inappropriate or risky for a particular situation (40). The NEO PI-R impulsivity subscale is thought to be synonymous with the construct of urgency, or rash action in response to negative emotion (41). Urgency correlates with emotional regulation and reward regions in healthy adults (42) and is correlated with impulsive behavior and addiction in younger adults (43). Whereas urgency has not been previously investigated in LLD, a prior study found no association between reward related decision making and antidepressant treatment response over three months in older adults with major depression (44). Investigation into the neurophysiology of impulsivity constructs in LLD may elucidate the selective findings with treatment response and cognitive outcome.

These findings need to be interpreted within the context of some limitations. First, neuroticism is treated as a retrospective measure and therefore assumed to remain relatively

stable from the time cognition and mood were first assessed and the time the NEO-PI-R was added to the NCODE protocol, consistent with neuroticism's general stability following treatment of major depression (45) and high test-retest reliability when the retest interval spans an average of 10 years (.78) (46). However, considering there is a dearth of evidence on the short-term stability of the NEO-PI-R, and the potential negative implications of increased neuroticism in the oldest old (age 80+) (47), investigation into the longitudinal course of the NEO PI-R in LLD is planned (18). Second, individual neuroticism traits are not orthogonal and modestly to moderately overlap in shared variance. Yet, by showing neuroticism traits vary in the strength of their relationships with clinical outcomes, our findings are consistent with prior evidence of discriminant validity among the six neuroticism traits and support the examination these individual differences within the domain of neuroticism. Third, the sample size of participants who completed the cognitive evaluation was on the smaller size, and may have contributed to the lack of significant findings between cognition and neuroticism traits. We are currently recruiting a larger sample of LLD and healthy control subjects who undergo a cognitive evaluation and complete the NEO-PI-R (18). There was also a large number of hypothesis tests done without correction for multiple comparisons. Our primary focus was on the association between depression, cognition, and VS. Other analyses warrant replication and further exploration. Finally, potential moderators and mediators influencing the association between neuroticism and clinical outcome in LLD (e.g., early and recent life stressors; cerebrovascular disease) were not included in the present study but will be investigated in future analyses.

In conclusion, VS, as well as anger-hostility, anxiety, and impulsivity, are useful prognostic indicators for subsequent long-term clinical outcomes in LLD. Assessment of neuroticism in the clinic may be a feasible way to identify patients who are at risk for poor response to depression treatment and cognitive decline.

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Note. Dashed lines represent 95% Confidence Intervals. High / Low VS determination based upon a T cut-score of 55. Model fitted using the most representative characteristics of the sample in terms of age, race, education, and gender.

Figure 1.
High / Low Vulnerability to Stress (VS) and Global Cognitive Functioning Over Time.

Table 1

Baseline Demographics and Clinical Characteristics (n=112)

Variable	Mean (SD)
Age	67.8 (6.1)
Education	13.9 (2.7)
Gender	62% Female
Race	89% White
NEO-PI-R T scores [% > 55]	Mean (SD)
Anxiety	53.8 (10.7) [46%]
Anger-Hostility	50.5 (9.7) [21%]
Depression	56.0 (11.5) [48%]
Self-Consciousness	51.2 (11.5) [34%]
Impulsiveness	51.6 (9.6) [35%]
Vulnerability to Stress	57.9 (14.0) [52%]
Total Neuroticism	54.7 (11.7) [44%]
MADRS (SD) [Range]	26.9 (6.9) [13-50]
Cognitive Examination	Mean (SD) [Range]
Mini-Mental State Exam (MMSE)	28.2 (2.6) [11-30]
CERAD Global Score	74.1 (11.6) [43 – 94]
Symbol Digit Modalities Test	37.7 (11.0) [12 – 57]
Trail Making Part B	135.6 (82.2) [42 – 300]
Logical Memory Delayed Recall	20.6 (9.0) [0 – 37]

Note. CERAD = Consortium to Establish a Registry in Alzheimer's Disease. MADRS = Montgomery-Asberg Depression Rating Scale. n=76 participants completed the cognitive evaluation at baseline.

Associations Between Neuroticism Components and Montgomery-Asberg Depression Rating Scale (MADRS) Over Time

Table 2

Component	Anxiety		Anger-Hostility		Depression		Self-Consciousness		Impulsiveness		Vulnerability to Stress		Total Neuroticism	
	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>
Neuroticism	0.291 (0.110)	0.008	0.129 (0.138)	0.353	0.458 (0.103)	< 0.001	0.326 (0.116)	0.005	0.126 (0.118)	0.285	0.378 (0.101)	< 0.001	0.422 (0.105)	< 0.001
Time	−0.256 (0.033)	< 0.001	−0.246 (0.027)	< 0.001	−0.260 (0.034)	< 0.001	−0.215 (0.030)	< 0.001	−0.265 (0.030)	< 0.001	−0.279 (0.035)	< 0.001	−0.272 (0.032)	< 0.001
Neuroticism*Time	0.063 (0.048)	0.189	0.103 (0.058)	0.077	0.067 (0.048)	0.162	−0.034 (0.051)	0.507	0.111 (0.049)	0.023	0.099 (0.048)	0.038	0.102 (0.048)	0.032

Notes. All models control for age and gender. 112 subjects, 3059 evaluations (up to 10 years of follow-ups since first MADRS assessment). Analyses included negative binomial generalized linear mixed models on raw MADRS score with random intercept and time (since first ever NCODE study assessment); t-test statistic = *b*/*SE* (unstandardized estimated regression coefficient/standard error); t-test *df* = 2834 for both the neuroticism main and time by neuroticism interaction, *df* = 111 for linear time

Table 3

Associations Between Neuroticism Components and Cognitive Performance Over Time

Component	Anxiety		Anger-Hostility		Depression		Self-Consciousness		Impulsiveness		Vulnerability to Stress		Total Neuroticism	
	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>	<i>b</i> (<i>SE</i>)	<i>p</i>
CERAD Total [‡]														
Neuroticism	−0.063 (0.219)	0.775	−0.185 (0.259)	0.475	0.066 (0.215)	0.757	0.066 (0.230)	0.774	−0.293 (0.228)	0.200	0.349 (0.212)	0.101	0.042 (0.220)	0.850
Time	0.014 (0.024)	0.547	0.016 (0.019)	0.404	0.019 (0.025)	0.456	0.011 (0.019)	0.580	0.015 (0.022)	0.509	−0.010 (0.023)	0.659	0.008 (0.023)	0.735
Neuroticism*Time	0.018 (0.033)	0.583	0.034 (0.038)	0.380	0.009 (0.034)	0.790	0.047 (0.036)	0.197	0.024 (0.034)	0.480	0.064 (0.032)	0.048	0.033 (0.033)	0.317
SDMT														
Neuroticism	−1.772 (2.311)	0.444	1.036 (2.727)	0.705	−1.570 (2.246)	0.485	0.671 (2.479)	0.787	3.513 (2.425)	0.149	−2.941 (2.252)	0.193	0.103 (2.328)	0.965
Time	−0.869 (0.215)	<0.001	−0.778 (0.168)	<0.001	−1.058 (0.220)	<0.001	−0.730 (0.168)	<0.001	−0.802 (0.196)	<0.001	−0.601 (0.198)	0.004	−0.848 (0.204)	<0.001
Neuroticism*Time	0.048 (0.297)	0.872	−0.276 (0.336)	0.412	0.377 (0.295)	0.202	−0.429 (0.322)	0.185	−0.125 (0.298)	0.674	−0.471 (0.283)	0.098	0.0004 (0.297)	0.999
Trail Making B														
Neuroticism	24.974 (15.590)	0.111	1.763 (18.608)	0.925	−1.609 (15.678)	0.918	19.871 (16.545)	0.231	−10.372 (16.551)	0.532	5.138 (15.489)	0.740	11.493 (15.844)	0.469
Time	5.444 (1.729)	0.003	4.893 (1.377)	<0.001	4.836 (1.802)	0.009	5.026 (1.399)	<0.001	4.699 (1.592)	0.004	2.719 (1.564)	0.087	5.286 (1.659)	0.002
Neuroticism*Time	−1.048 (2.362)	0.658	0.233 (2.705)	0.932	0.212 (2.393)	0.930	−0.174 (2.658)	0.948	0.648 (2.383)	0.786	4.216 (2.218)	0.059	−0.733 (2.381)	0.758
LM Delay Recall														
Neuroticism	1.460 (1.858)	0.433	−0.063 (2.210)	0.977	1.620 (1.825)	0.376	0.231 (1.972)	0.907	−0.021 (1.985)	0.992	−2.251 (1.814)	0.216	−0.552 (1.878)	0.769
Time	0.193 (0.220)	0.382	0.222 (0.175)	0.208	0.089 (0.231)	0.701	0.194 (0.180)	0.285	−0.005 (0.201)	0.982	0.453 (0.209)	0.034	0.239 (0.210)	0.260
Neuroticism*Time	−0.094 (0.307)	0.760	−0.280 (0.351)	0.425	0.103 (0.310)	0.740	−0.156 (0.340)	0.646	0.364 (0.310)	0.242	−0.540 (0.291)	0.065	−0.177 (0.306)	0.563

Notes. CERAD = Consortium to Establish a Registry for Alzheimer's Disease; SDMT = Symbol Digit Modalities Test; LM = Logical Memory. All models control for age, race, education, and gender. 76 subjects, 397 evaluations (up to 10 years of follow-ups since first cognitive performance evaluation). Analyses included generalized linear models on transformed/raw scores score with random intercept and time (since first ever NCODE study assessment); t-test statistic = b/SE (unstandardized estimated regression coefficient/standard error); neuroticism main and time by neuroticism interaction t-test df = 248 for CERAD, 289 for SDMT, 223 for Trail Making B, and 244 for LM Delay Recall; linear time df = 70 for CERAD, 69 for SDMT, 66 for Trail Making B, and 67 for LM Delay Recall

[‡]Transformed CERAD: sqrt(100 – CERAD score)