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Trait Neuroticism, Depression, and Cognitive Function in Older Primary Care Patients

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Abstract

Objective—Prior studies on the association of trait neuroticism and cognitive function in older adults have yielded mixed findings. We tested hypotheses that neuroticism is associated with measures of cognition and that depression moderates these relationships.

Design—Cross-sectional observational study.

Setting—Primary care offices.

Participants—Primary care patients age ≥65 years.

Measurements—Trait neuroticism was assessed by the NEO-Five Factor Inventory. Major and minor depression (MDD, MinD) were determined by the Structured Clinical Interview for DSM-IV, and depressive symptom severity by the Hamilton Depression Rating Scale (Ham-D). Cognitive measures included the Mini-Mental State Examination (MMSE), Initiation-Perseveration subscale of the Mattis Dementia Rating Scale, and Trail-Making Tests A and B.

Results—In multiple regression analyses, neuroticism was associated with MMSE score independent of depression diagnosis ($\beta = -0.04$, $\chi^2 = 14.2$, df = 1, p = 0.0002, 95% CI = −0.07, −0.02) and Ham-D score ($\beta = -0.04$, $\chi^2 = 8.97$, df = 1, p = 0.003, 95% CI = −0.06, −0.01). Interactions between neuroticism and depression diagnosis ($\chi^2 = 7.21$, df = 2, p = 0.03) and Ham-D scores ($\chi^2 = 0.55$, df = 1, p = 0.46) failed to lend strong support to the moderation hypothesis.

Conclusion—Neuroticism is associated with lower MMSE scores. Findings do not confirm a moderating role for depression, but suggest that depression diagnosis may confer additional risk for poorer global cognitive function in patients with high neuroticism. Further study is necessary.

Keywords

Personality; Late Life Depression; Cognition

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Cognitive impairment is an increasingly significant public health concern with the growth of the older population. Age is one established risk factor for cognitive impairment (1). Identification of other risks would facilitate earlier clinical diagnosis and interventions, potentially conferring benefits such as improved quality of life, decreased medical comorbidity, and improved functioning and independence for a growing population.

Neuroticism, a personality trait that is characterized by chronic negative affect and susceptibility to stress, may be a risk factor for cognitive dysfunction (2–4). In one proposed model, neuroticism is associated with longstanding heightened hypothalamic-pituitary-adrenal axis activity, in turn causing changes to hippocampus and other brain regions that support memory (2,4–7). Some evidence suggests that neuroticism is correlated with poorer cognitive functioning with older men scoring lower on the Mini-Mental State Examination (MMSE) and on measures of fluid intelligence and episodic memory and with older women performing slower on a measure of reaction time (5). Low neuroticism has been associated with better episodic memory (8), while high neuroticism has been associated with poorer episodic memory (6). Higher levels of neuroticism also convey increased risk for global cognitive decline using a composite cognitive measure incorporating MMSE scores (3) and dementia (2,4) in community-dwelling older adults. However, not all studies found an association between neuroticism and cognitive function (9–11). Methodological differences may account for these disparate findings, including the use of different measures to assess neuroticism and cognitive function and the study of different samples with varied ages, educational levels, racial heterogeneity and inclusion criteria.

Additionally, neuroticism has been associated with depression (12–14). Late life depression represents a potentially treatable (15) risk factor for cognitive impairment. Previous studies have demonstrated that late life depression amplifies risk of cognitive impairment (16–19). Therefore, older adults who have high levels of neuroticism may experience enhanced cognitive dysfunction when clinically depressed. Yet depression's role as a potential moderator of the neuroticism-cognition relationship has received little study. One suggestive study of community-dwelling seniors found that low neuroticism weakened the association between cognitive impairment and depression in men (20). To our knowledge, no prior work has examined these relationships in a primary care cohort, even though older patients are more likely to receive treatment for depression in primary care rather than mental health specialty settings (21).

Using data collected as part of a larger study of older adults in primary care, we tested the following *a priori* hypotheses: 1) Neuroticism is associated with cognitive function, with higher neuroticism associated with poorer global cognitive and executive functioning; and 2) depression moderates these relationships, such that subjects with high trait neuroticism who also meet criteria for a depressive disorder or who have elevated levels of depressive symptoms will have lower scores on tests of global cognitive and executive functioning. Selected measures for executive function were chosen because of executive function's association with late life depression (22).

METHODS

Study procedures have been reported elsewhere (23). Briefly, patients aged 65 years and older from private and hospital-affiliated internal medicine, geriatric, and family medicine practices in greater Rochester, New York who could provide written informed consent using procedures approved by the University of Rochester Research Subjects Review Board were eligible to participate. Enrolled subjects underwent semistructured interviews, administered by trained raters who also reviewed each subject's primary care chart.

The Structured Clinical Interview for *DSM-IV* (SCID) (24) was used to assign subjects to diagnostic groups, defined as follows: 1) current or partially remitted major depression; 2) current or partially remitted minor depression (based on *DSM-IV* appendix criteria); or 3) nondepressed (all others). Trait neuroticism was assessed by the NEO-Five Factor Inventory (NEO-FFI), a 60-item self-report questionnaire (25). The subjects received the NEO-FFI forms, along with addressed postage-paid envelopes, to complete and return to study personnel. The 24-item Hamilton Rating Scale for Depression (Ham-D) was used to assess depression symptom severity (26). In our research group, interrater reliability has been high, e.g., an intraclass correlation coefficient of 0.93 for the Ham-D (based on six raters and five subjects), and kappa coefficients for the diagnoses of mood disorders ranging from 0.66–0.86 (based on six raters and three subjects). Medical illness burden, covaried in analyses given its known association with cognitive functioning, was assessed with the Cumulative Illness Rating Scale (CIRS) (27). The CIRS score was based on a physician-investigator's (JML) review of each patient's primary care chart and all other available records and was completed blind to the SCID interview data, although not blinded to any mention of depression in the medical records.

Cognitive function measures included the MMSE (28), a widely employed measure of global cognitive function. Measures of executive function included the Mattis Dementia Rating Scale (Mattis-IP) (29) and the Trail-making tests A (Trails A) and B (Trails B) (30). The Mattis-IP evaluates category fluency and alternating verbal and psychomotor tasks. The Trails B characterizes mental set shifting and response inhibition, and was administered along with the Trails A which measures sustained attention, sequencing, and information processing/motor speed. Trails A and B were analyzed based on completion time in seconds. The study raters administered the cognitive measures according to procedures developed under the supervision of a neuropsychologist.

Linear models, with continuous variables centered, examined the associations between the NEO-FFI neuroticism score independent of depression and each of the four dependent variables (MMSE, Mattis-IP, Trails A, Trails B) controlling for age, gender, years of education, and CIRS score. These covariates were chosen because they might affect cognition (the dependent variable) and partly to allow comparability with other studies. To increase robustness of the study findings, inference for the linear regression model was carried out using the estimating equations approach, which does not require the normal distribution assumption for the dependent variable (31). Multi-collinearity was evaluated using condition indices and the variance inflation ratio (VIF) (32). Possible bias of subjects who completed the demographic, CIRS, depressive measures and MMSE but had missing neuroticism scores was evaluated with a logistic regression of NEO-FFI completion status on age, gender, years of education, CIRS score, depression, MMSE and completion of Mattis-IP, Trails A, and Trails B.

A moderator role for depression was inferred by regressing each cognitive measure on a neuroticism by depression interaction term. For analyses involving the trichotomous variable depression diagnosis, non-depressed subjects served as the reference group.

To examine the robustness of the findings, additional analyses were conducted by focusing on: 1) major depression vs. non-depressed, i.e., excluding the minor depression group; 2) late-onset (age $\geq$65 years) major or minor depression vs. non-depressed, i.e., excluding all depressed subjects with age of onset <65 years; and 3) current major or minor depression vs. non-depressed, i.e., excluding partially-remitted major or minor depression group.

Given the relatively large sample size and the number of comparisons, statistical significance was set at $p < 0.01$ to be conservative. All analyses were carried out using SAS 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Of 1415 subjects approached for study enrollment, 709 (50.l %) completed intake assessments. As reported elsewhere (23), while complete information on non-enrolled subjects was not available due to the Health Insurance Portability Accountability Act, enrolled subjects did not differ from non-enrolled patients on age, gender, or 15-item Geriatric Depression Scale (33) score based on available data. Of 709 enrollees, 499 returned completed NEO-FFI forms. Of these 499, 488 completed the cognitive and depressive measures and were included in this study; the remaining 221 were excluded. To assess sub-sample representativeness, a logistic regression compared subjects with demographic, CIRS, depressive measures and MMSE who completed the NEO-FFI versus those who did not. Only MMSE score ($\beta = 0.16$, Wald $\chi^2 = 13.18$, df = 1, $p = 0.0003$) and completion of Trails A and Trails B ($\beta = 1.17$, Wald $\chi^2 = 17.13$, df = 1, $p < 0.0001$) were associated with group membership: subjects with completed NEO-FFI had higher MMSE scores (28.2 (±1.6) vs. 27.8 (±1.9)) and subjects who completed the Trails A and Trails B were more likely to have completed the NEO-FFI (OR = 3.23, 95%CI = 1.85, 5.62).

Descriptive data are reported in Table 1. Of the 80 subjects with major depression, 23 had current and 57 partially remitted major depression; of 79 with minor depression, 32 had current and 47 a partially remitted disorder. Twenty-nine (37%) of the patients with major depressive disorder had late-onset depression, while 52 (68%) of the patients with minor depression had late-onset depression.

Table 2 shows the results of the multivariate analyses where the p-values are reported for the associated χ^2 tests subsequent to the estimating equations analysis. Multi-collinearity was not detected in any of the models since the VIF for all models were less than 3, much smaller than the recommended threshold of 10 (32). Testing the first hypothesis in the overall sample, neuroticism was significantly associated with MMSE score, but not with the measures representing executive function. Neither depression diagnosis ($\chi^2 = 0.97$, df = 2, $p = 0.62$; represented by two vectors, one which compared the major depression disorder group and non-depressed group and the second which compared the minor depression disorder group with the non-depressed group) nor depressive symptoms were associated with MMSE scores. Also, depression was not associated with the other cognitive measures in the overall sample.

Turning to the analyses to test the second hypothesis of the moderating effects of depression (not shown in Table 2) the neuroticism by depression diagnosis interaction term suggests an association with MMSE scores, using a more conventional $p < 0.05$, although it was not statistically significant by the more conservative $p < 0.01$ ($\chi^2 = 7.21$, df = 2, $p = 0.03$). The major component contributing to the interaction was the minor depression group ($\beta = -0.08$, $\chi^2 = 6.94$, df = 1, p=0.008, 95%CI = −0.14, −0.02), while for the major depression group ($\beta = -0.03$, $\chi^2 = 1.48$, df = 1, $p = 0.22$, 95%CI = −0.09, 0.02) and the non-depressed group ($\beta = -0.02$, $\chi^2 = 2.08$, df = 1, $p = 0.15$, 95%CI = −0.05, 0.01) interactions did not achieve significance. For participants who scored one standard deviation above the mean NEO-FFI score for neuroticism, MMSE scores dropped by 0.23 in those with major depression and by 0.62 in those with minor depression. The neuroticism by depression diagnosis interaction term was not associated with executive function. The neuroticism by Ham-D interaction term was not associated with MMSE score ($\beta = -0.001$, $\chi^2 = 0.55$, df = 1, $p = 0.46$, 95% CI = −0.004, 0.002) or any of the cognitive measures.

In the sensitivity analyses that compared subjects with major depression versus nondepressed (excluding minor depression, not shown in Table 2), neuroticism's association with MMSE was strongly suggestive independent of depression diagnosis ($\beta = -0.03$, $\chi^2 = 5.13$, df = 1, $p = 0.02$, 95% CI = −0.06, −0.004) but not independent of Ham-D scores ($\beta = -0.02$, $\chi^2 = 3.24$, df

= 1, p = 0.07, 95% CI = −0.05, 0.002). Depression diagnosis, although not significant, had a suggestive association with scores on both Trails A (β = 7.27, χ^2 = 4.07, df = 1, p = 0.04, 95% CI = 0.19, 14.36) and Trails B (β = 16.17, χ^2 = 4.29, df = 1, p = 0.04, 95% CI = 0.83, 31.52). The neuroticism by depression diagnosis and neuroticism by Ham-D scores interaction terms were not associated with any of the cognitive measures.

In the sensitivity analyses focusing on the effects of late-onset depression (not shown in Table 2), an association between neuroticism and MMSE score (β = −0.03, χ^2 = 5.37, df = 1, p = 0.02, 95% CI = −0.06, −0.005) was observed independent of depression diagnosis, but the neuroticism by depression diagnosis interaction term was not statistically significant. The interaction of neuroticism by depression diagnosis group was suggestive (χ^2 = 6.60, df = 2, p = 0.04) for Trails A (β = 0.66, χ^2 = 1.47, df = 1, p = 0.23, 95% CI = −0.41, 1.73 for the major depression group, β = −0.96, χ^2 = 4.40, df = 1, p = 0.04, 95% CI = −1.85, −0.06 for the minor depression group, β = 0.28, χ^2 = 2.06, df = 1, p = 0.15, 95% CI = −0.10, 0.65 for the non-depressed group) but not significant for Trails B or the Mattis-IP. When controlling for Ham-D scores, neither neuroticism nor the neuroticism by Ham-D interaction term were statistically significant for performance on MMSE in those with late-onset depression vs. those who were nondepressed. Ham-D scores' association with Trails A scores was suggestive (β = 0.48, χ^2 = 3.89, df = 1, p = 0.05, 95% CI = 0.002, 0.97), but not with other cognitive measures. None of the neuroticism by Ham-D interaction terms were associated with Mattis-IP or Trails A or B scores.

In the sensitivity analyses that compared subjects with current major and minor depression versus nondepressed (excluding partially-remitted major or minor depression, not shown in Table 2), neuroticism's association with MMSE was strongly suggestive independent of depression diagnosis (β = −0.03, χ^2 =4.83, df = 1, p = 0.03, 95% CI = −0.06, −0.003) but not independent of Ham-D scores. The neuroticism by depression diagnosis and neuroticism by Ham-D scores interaction terms were not associated with any of the cognitive measures.

CONCLUSIONS

The results partially support our first hypothesis, as higher neuroticism was associated with poorer scores on the MMSE. However, neuroticism was not independently associated with the executive function measures. To our knowledge this was the first study to test the hypothesis that depression moderates the relationship between neuroticism and cognitive function in a sample of primary care elders. Regarding this second hypothesis, Ham-D scores did not moderate any neuroticism-cognition relationship. We found modest evidence that depression diagnosis' moderator effect on the relationship between neuroticism and cognition did not attain statistical significance using a conservative $p < 0.01$, suggesting the need for further study of this important question.

The finding that neuroticism was associated with global cognitive function, consistent with prior work (2–5), might reflect the effects of chronic experience of emotional stress, as stress-associated glucocorticoid activity may result in atrophy of the hippocampus, important for learning and memory (2,4–7). In support for the hypothesized associations between chronic stress exposure and cognition, "distress proneness" or trait neuroticism has been associated with performance on measures of episodic memory (2,4,6,8). We conceptualize trait neuroticism as an indicator of chronic stress exposure that has implications for cognitive function. Such mechanisms may be independent of brain pathology reflecting Alzheimer's disease or other age-related neuropathology (2,4,34). Effects on cognitive and brain function of neuroticism are probably specific to particular tasks and brain regions. Neuroticism does not appear to be related to executive function, suggesting that potential mechanisms through which neuroticism impacts cognitive functioning are not related to changes involving the

frontal cortex and basal ganglia and thalamus connections (35). We acknowledge that in this study we did not examine the NEO-FFI personality traits other than neuroticism. We focused on neuroticism because of the prior literature, but future work could explore whether the other four personality traits (i.e., agreeableness, conscientiousness, extraversion, and openness to experience) are associated with cognitive function in an older primary care patient sample.

Our study examined whether depression acts as a moderator, defined as a "variable that affects the direction and/or strength of the relation between an independent or predictor variable and a dependent or criterion variable," (36) of the relationship between neuroticism and cognitive function. Our findings leave open the possibility that current or partially-remitted major or minor depression may have a moderating role in the relationship between neuroticism and MMSE scores, albeit the effect size was small in magnitude. If future studies provide additional support for a moderating role of depression, this would indicate that patients with an already-heightened vulnerability to cognitive dysfunction on account of lifelong vulnerability to negative mood states and stress may have further cognitive worsening when they become clinically depressed. Our finding, that minor depression, compared with major depression, had a more robust effect on the relationship between neuroticism and MMSE scores is puzzling and cause for more research. However, if future studies do not support depression as a moderator of the neuroticism-cognitive function relationship, this would signify that neuroticism itself may be a risk factor for cognitive dysfunction and a target for intervention. Our cross-sectional findings cannot establish whether these associations reflect the causal relationships of true risk factors (37), or whether they are in effect risk markers of a common underlying disease process.

The mixed findings from studies examining the association between neuroticism and cognitive function are unlikely to reflect different approaches to the measurement of trait neuroticism, as neuroticism measures are highly correlated (38,39). One also must consider the potential confounding by neuroticism and depression. Although questions persist about the reliability of assessing personality during acute depressive episodes (40), the vast majority of our study's sample was not depressed. A strength of our study is the inclusion of depression diagnoses using the SCID, while other studies relied on depressive symptom scales (2–5,10–11,20).

The MMSE was chosen as a global measure of cognitive functioning due to its widespread use; previous studies have also used the MMSE (3,5,10,20). We had limited measures to characterize specific aspects of memory, including episodic memory. Our use of the MMSE as a measure of global cognition could not inform whether neuroticism was associated with specific cognitive domains (2,4–6,10–11,20,34).

Interpretation of study findings should be tempered by recognition of other potential limitations. Subjects were largely white, had relatively high levels of education and overall cognitive functioning, and were able to complete and return the NEO-FFI questionnaire. Subjects with completed NEO-FFI had slightly higher MMSE scores. Subjects who completed the Trails A and Trails B were more than three times as likely to have completed the NEO-FFI. These differences point to potential sample bias; however, there was no association between completion of the Mattis-IP and completion of the NEO-FFI. Our use of the MMSE as a proxy for cognitive functioning may be limited by a ceiling effect in this relatively well-educated and cognitively intact sample. Repeating these analyses in a sample with more cognitive variability would be helpful to further elucidate depression's role in the relationship between neuroticism and cognition. That depression's moderating effect was less suggestive after restricting the analyses to only those with major depression, to those with late onset depression, or alternatively to those with current depression, may reflect the relative lack of variability in MMSE scores across the depressive groups or that the role of depression as a

moderator in the relationship between neuroticism and cognition is not robust. Findings may not generalize to other populations.

Our results highlight the need to better understand the role of neuroticism in the pathogenesis of cognitive disorders in older primary care adults; such insights may assist primary care doctors and other providers to identify particularly vulnerable populations of older adults and inform targeted interventions. Such work should examine the relative roles of minor as well as major depression. Clinicians should recognize that older patients with elevated levels of trait neuroticism may be at risk for poorer cognitive functioning. Cognitive functioning may be disturbed further with depression and warrants further evaluation and monitoring. Future studies should examine the longitudinal relationships among personality, depression, and cognitive outcomes over time, to better inform models of pathogenesis as well as to identify those at greatest risk of cognitive decline.

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TABLE 1

Demographics and Descriptive Data

	All		Major Depression (n=80)		Minor Depression (n=79)		Non-depressed (n=329)	
Variable	**n**	**Mean (SD), Range**	**n**	**Mean (SD), Range**	**n**	**Mean (SD), Range**	**n**	**Mean (SD), Range**
Age (y)	488	75.0 (6.5), 65–95	80	72.9 (5.7), 65–88	79	75.9 (6.2), 65–94	329	75.3 (6.7), 65–95
Education(y)	488	14.3 (2.4), 4–17	80	14.1 (2.3), 8–17	79	14.0 (2.7), 4–17	329	14.4 (2.3), 6–17
Female:Male	304:184		60:20		64:15		180:149	
CIRS	488	7.4 (2.9), 1–19	80	8.2 (2.9), 3–16	79	8.4 (3.4), 3–19	329	7.0 (2.7), 1–16
Ham-D	488	8.7 (6.3), 0–37	80	16.3 (7.7), 0–37	79	11.6 (5.4), 2–26	329	6.1 (3.8), 0–26
N	488	15.2 (7.8), 0–42	80	23.1 (7.9), 3–42	79	17.3 (7.2), 6–35	329	12.7 (6.4), 0–33
MMSE	488	28.0 (1.9), 17–30	80	28.0 (1.8), 21–30	79	28.0 (1.9), 21–30	329	28.0 (1.9), 17–30
Mattis-IP	480	35.5 (3.0), 10–37	80	35.1 (3.6), 21–37	77	35.8 (2.5), 20–37	323	35.5 (3.0), 10–37
Trails A (sec)	482	53.7 (26.2), 13–300	80	58.0 (39.7), 22–300	79	55.6 (26.5), 21–170	323	52.1 (21.5), 13–173
Trails B (sec)	453	117.2 (54.4), 27–300	71	130.3 (56.5), 30–300	75	121.7 (59.4), 35–300	307	113.1 (52.2), 27–298

Note: CIRS: Cumulative Illness Rating Scale; Ham-D: Hamilton Rating Scale for Depression; N: Neuroticism; MMSE: Mini-Mental State Examination; Mattis-IP: Mattis Dementia Rating Scale; Trails A: Trail-making test A; Trails B: Trail-making test B.

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TABLE 2

Predictors of Cognition: Neuroticism and Depression

	Dependent Variables											
	MMSE			Mattis-IP			Trails A			Trails B		
Independent Variables	**β (χ^2)**	**95%CI**	**p**	**β (χ^2)**	**95%CI**	**p**	**β (χ^2)**	**95%CI**	**P**	**β (χ^2)**	**95%CI**	**p**
Neuroticism	−0.04 (14.2)	−0.07, −0.02	**0.0002**	−0.03 (2.11)	−0.07, 0.01	0.15	0.09 (0.28)	−0.24, 0.42	0.60	0.40 (1.26)	−0.30, 1.11	0.26
Dep Dx MDD	0.21 (0.71)	−0.28, 0.69	0.40	−0.19 (0.20)	−1.03, 0.65	0.65	7.86 (5.04)	0.99, 14.73	0.02	16.20 (4.54)	1.27, 31.14	0.03
MinD	0.16 (0.55)	−0.27, 0.60	0.46	0.45 (1.34)	−0.31, 1.22	0.25	1.91 (0.36)	−4.29, 8.11	0.55	0.37 (0.00)	−12.84, 13.59	0.96
Neuroticism	−0.04 (8.97)	−0.06, −0.01	**0.003**	−0.02 (1.32)	−0.07, 0.02	0.25	0.12 (0.48)	−0.23, 0.47	0.49	0.38 (1.00)	−0.37, 1.13	0.32
Ham-D	−0.01 (0.13)	−0.04, 0.03	0.72	−0.02 (0.42)	−0.07, 0.04	0.52	0.33 (2.14)	−0.11, 0.76	0.14	0.83 (3.03)	−0.11, 1.77	0.08

Note: All analyses covaried age, gender, years of education, and Cumulative Illness Rating Scale score. For depression diagnosis β reported for major depression (MDD) and minor depression (MinD), respectively. All analyses shown have one degree of freedom (df). P-values are reported for the associated Wald χ^2 tests. MMSE: Mini-Mental State Examination; Mattis-IP: Mattis Dementia Rating Scale; Trails A: Trail-making test A; Trails B: Trail-making test B; N: Neuroticism; Dep Dx: Depression Diagnosis (MDD, MinD versus reference non-depressed group); Ham-D: Hamilton Rating Scale for Depression