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Vulnerability to Stress, Anxiety, and Development of Dementia in Old Age

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Abstract

Objective—To identify the components of the neuroticism trait most responsible for its association with cognitive decline and dementia in old age.

Design—Longitudinal clinical-pathologic cohort study.

Setting—Chicago metropolitan area.

Participants—785 older persons without dementia who completed standard self report measures of 6 components of neuroticism and then had annual clinical evaluations for a mean of 3.4 years and brain autopsy in the event of death.

Measurements—Incidence of clinically diagnosed Alzheimer's disease, change in global and specific cognitive functions, and postmortem measures of plaques and tangles, cerebral infarction, and Lewy bodies.

Results—During follow-up, 94 individuals developed Alzheimer's disease. Higher levels of anxiety and vulnerability to stress were associated with increased risk of Alzheimer's disease and more rapid decline in global cognition with no effects for the other four trait components. In analyses of specific cognitive systems, neuroticism subscales were related to decline in episodic memory, working memory, and perceptual speed but not semantic memory or visuospatial ability. No component of neuroticism was related to the neuropathologic lesions most commonly associated with late life dementia.

Conclusions—Neuroticism's association with late life dementia mainly reflects vulnerability to stress and anxiety and their correlation with decline in the ability to process and retain new information.

Keywords

Neuroticism; Anxiety; Stress; Alzheimer's disease; Cognitive decline

In old age, higher level of the personality trait of neuroticism has been associated with lower level of cognitive function [1], more rapid cognitive decline [2-4] and increased risk of developing mild cognitive impairment [5] and dementia [2,4,6]. Neuroticism is a broadly defined trait, however, that includes a number of more narrowly specified components or facets such as anxiety, depression, self consciousness, and impulsiveness [7]. It is uncertain

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which dimensions of neuroticism are primarily responsible for its association with late life dementia.

In this article, we examined the relation of different facets of neuroticism to risk of developing Alzheimer's disease (AD). Data are from the Rush Memory and Aging Project, a longitudinal clinical-pathologic study of risk factors for common chronic conditions of old age. Older persons without dementia completed standard self report measures of 6 facets of neuroticism: anxiety, angry hostility, depression, self-consciousness, impulsiveness, and vulnerability to stress. Participants were followed at annual intervals with uniform clinical evaluations that involved detailed cognitive testing and diagnosis of dementia and AD. At death, there was a uniform neuropathological examination. In analyses, we assessed the relation of neuroticism's facets to incidence of clinically diagnosed AD, rate of cognitive decline, and presence of common neuropathologic lesions traditionally associated with dementia.

Methods

Participants

All subjects are from the Rush Memory and Aging Project [8]. The project entails annual clinical evaluations and brain donation at death. It was approved by the Institutional Review Board of Rush University Medical Center.

Participants were recruited from retirement communities, Section 8 and Section 202 housing subsidized by the Department of Housing and Urban Development, social service agencies, and churches in and around Chicago. Discussions with administrators and staff, and sometimes with resident councils, were followed by a 60 to 90 minute presentation for interested residents. After the meeting, persons rated how interested they were in the study on a 3-point scale (i.e., a little, somewhat, very) and were given information packets and encouraged to discuss participation with family and friends. Those who were somewhat or very interested were subsequently contacted by study personnel who provided further information and obtained written consent.

Each participant underwent a uniform structured clinical evaluation that included a medical history, neurological examination, and assessment of cognitive function. Classification of dementia was done by experienced clinicians using the results of this evaluation plus an in-person examination and the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [9]. To minimize random variability in clinical classification across clinicians and time, we developed algorithms to guide clinical decisions about cognitive impairment, dementia, and AD [10,11]. Dementia required a history of cognitive decline and impairment in at least two domains of cognition, one of which had to be memory to meet criteria for AD, as previously described [2,4,6,8,12]. Persons who met AD criteria and were judged to have another condition contributing to cognitive dysfunction were included in analyses of incident AD. Of 921 otherwise eligible persons, 50 met criteria for dementia and were excluded. Of remaining 871 who were eligible at baseline, 28 died before first follow-up and 23 had not yet reached the date of first follow-up at the time of analyses. This left 820 people eligible for follow-up and follow-up data were available on 785 people (95.7% of those eligible). They had a mean age of 80.7 years (SD=7.4), a mean of 14.5 years of schooling (SD=3.1), and a mean score of 28.0 on the Mini-Mental State Examination (SD=2.1); 76.3% were women and 89.6% were white and non-Hispanic.

Assessment of Neuroticism Facets

Neuroticism, which refers to an enduring tendency to experience negative emotion, was assessed with the 48-item Neuroticism scale from the NEO Personality Inventory-Revised [6], as previously described [13]. Each item consisted of a statement (e.g., I am easily frightened) with which participants rated agreement on a five-point scale. Item scores ranged from 0 to 4 with higher scores indicating higher levels of the trait. The scale consists of six subscales, or facets, each based on 8 items (score range: 0 to 32): anxiety, angry hostility, depression, self-consciousness, impulsiveness, and vulnerability to stress.

Assessment of Cognitive Function

Nineteen cognitive tests were administered in an approximately one hour session as part of the initial clinical evaluation. Detailed information on the individual tests is published elsewhere [8,14,15]. One test, the Mini-Mental State Examination, was used for descriptive purposes but not in analyses. The other 18 tests included seven episodic memory measures: immediate and delayed recall of the East Boston Story and story A from Logical Memory and Word List Memory, Word List Recall, and Word List Recognition which involve immediate recall, delayed recall, and delayed recognition of a 10-word list. There were three semantic memory tests: Verbal Fluency, a 15-item version of the Boston Naming Test, and a 15-item reading test. Working memory was measured with Digit Span Forward and Digit Span Backward plus Digit Ordering. There were four measures of perceptual speed: the oral version of the Symbol Digit Modalities Test, Number Comparison, and two measures from a modified Stroop Neuropsychological Screening Test: number of correctly read color names in 30 seconds minus the number incorrect and number of correctly named colors in 30 seconds minus the number incorrect. Visuospatial ability was evaluated with a 15-item version of Judgment of Line Orientation and 16-item form of Standard Progressive Matrices.

To minimize random variability, composite cognitive measures based on two or more individual tests were used in analyses. All 18 tests were used to form a measure of global cognition, and tests were clustered into five specific functional domains, based in part on a previous factor analyses [14,15]: episodic memory (7 tests), semantic memory (3 tests), working memory (3 tests), perceptual speed (4 tests), and visuospatial ability (2 tests). For each composite measure, raw test scores were converted to z scores, using the mean and standard deviation for the entire cohort, and averaged to yield the composite score.

Neuropathological Examination

Brains were removed in a standard fashion and cut coronally into 1 cm slabs that were visually inspected and photographed. After slabs were fixed in 4% paraformaldehyde for 3-21 days, they were dissected into blocks that were embedded in paraffin and cut into 6μm sections. Bielschowsky silver stain was used to visualize neuritic plaques, diffuse plaques, and neurofibrillary tangles in 5 brain regions: midfrontal gyrus, superior temporal gyrus, inferior parietal gyrus, entorhinal cortex, and the CA1 sector of the hippocampus. A summary index of these 3 pathologic lesion in 5 brain regions was derived as previously described [16]. Because scores were skewed, a square root transformation was used.

The 1 cm slabs were visually inspected for evidence of gross cerebral infarction [16]. The age, volume, and location of infarctions visible to the naked eye were noted. Lewy bodies were identified with antibodies to alpha-synuclein, as described elsewhere [16]. In analyses, cerebral infarctions and Lewy bodies were treated as present or absent.

Data Analysis

Cox proportional hazards models [17] were used to assess the relation of each neuroticism facet to subsequent risk of developing clinical AD. These and all subsequent analyses controlled for age, sex, and education.

We used mixed-effects regression models [18] to assess individual paths of change in cognitive function and the relation of trait scores to these paths. A strong advantage of this approach is that it allows simultaneous estimation of initial level of cognitive function and rate of cognitive change (and relation of trait score to each) while controlling for individual differences in baseline cognitive ability and its rate of change [18,19]. Each model included terms for time (in years since baseline), to estimate the mean annual rate of cognitive change; trait score, to control for the association of the trait score with baseline level of cognition; and the interaction of trait score with time to test the relation of trait score to annual rate of cognitive change. Terms for age, sex, education, and their interaction with time were also included. Initial analyses with a composite measure of global cognition were subsequently repeated with composite measure of specific cognitive functions.

A last set of analyses examined the relation of postmortem pathological measures to trait scores. Each neuroticism facet was regressed on each postmortem measure in a series of linear regression analyses.

Results

Facets of Neuroticism

Scores on the neuroticism facet scales could range from 0 to 32, with higher values indicating more of the trait component. Facet scores were approximately normally distributed and had adequate levels of internal consistency, with coefficient alpha values ranging from .71 to .82 (Table 1). The facets were moderately intercorrelated (range: .37-.70), negatively associated with education, and weakly related to age.

Neuroticism Facets and Incidence of Alzheimer's disease

During a mean of 3.4 years of annual observation (SD=1.4), 94 people developed AD. We excluded 10 persons who developed other forms of dementia from analyses of incident AD. Those with AD were older (84.8 [SD=6.0] vs 80.1 [SD=7.4], t [134.9]=6.9, p<.001) than unaffected persons but did not differ in education (14.6 [SD=2.6]vs 14.5 [SD=3.2], t[132.3]=0.3, p=.742) or gender (72.3% vs 76.9%, χ^2 [1]=0.9,p=.335). We examined the association of each neuroticism facet with risk of AD in separate proportional hazards models adjusted for age, education, and sex. As shown in Table 2, risk of developing AD increased by about 5% for each point on the anxiety scale and by about 6% for each point on the vulnerability to stress scale. For purposes of comparison, the effect of each additional scale point on risk approximated the effect of being 6 months older. To visually examine the results of these analyses, we plotted the cumulative risk of AD predicted for high versus low scores. The upper right panel of Figure 1 shows that risk of AD was increased by 84% with a high anxiety score (19, 90th percentile, dashed line) compared to a low score (6, 10th percentile, dotted line) and by 79% with a high vulnerability score (15, 90th percentile, dashed line) compared to a low score (5, 10th percentile, solid line).

Neuroticism Facets and Cognitive Decline

To ensure that results were not due to diagnostic imprecision, we examined the relation of the facets to cognitive decline, the principal clinical manifestation of AD. To make use of all available cognitive data, initial analyses focused on the composite measure of global cognition. At baseline, scores ranged from a low of -1.65 to a high of 1.42 (mean=0.17,

SD=0.51). We constructed separate mixed-effects models to characterize change in global cognition and to test the relation of each facet to initial level of function and rate of change (Table 3). In the first analysis, each additional point on the anxiety scale was associated with a decrease of 0.009-unit in baseline level of global cognition, as shown by the term for anxiety, and with an increase of 0.003-unit in annual rate of global cognitive decline, as indicated by the interaction of anxiety with time. Of the remaining facets, only vulnerability to stress was related to global cognitive decline. To visualize these effects, we plotted the 5-year paths of change in cognitive function predicted for high versus low trait scores. The lower left panel of Figure 1 shows that global cognitive function declined about 67% faster in those with high anxiety (score = 19, 90^{th} percentile, dashed line) compared to those with low anxiety (score =6, 10^{th} percentile, solid line). The lower right panel of Figure 1 shows that those with high vulnerability (score = 15, 90^{th} percentile, dashed line) declined about 71% faster than those with low vulnerability (score =5, 10^{th} percentile, solid line).

Because prior research has suggested that neuroticism's association with cognitive decline varies across functional domains [2,4,5], we conducted separate analyses of change in 5 specific cognitive systems. As shown in Table 4, higher neuroticism facet scores were related to more rapid decline in 3 cognitive domains (i.e., episodic memory, working memory, perceptual speed) with no effect in the remaining 2 domains (i.e., semantic memory, visuospatial ability). These effects were seen not only for anxiety and vulnerability but also for depression, impulsiveness, and angry hostility. Self-consciousness was not related to change in any cognitive domain.

Neuroticism Facets and Neurodegenerative Lesions

During the observation period, 191 people died and 156 (81.7%) underwent brain autopsy. Neuropathologic data were collected in a uniform examination of each brain that was in progress or pending in some cases. Those with completed neuropathologic examinations did not differ on any trait or cognitive variable from those with incomplete examinations. At the time of these analyses, data on plaques and tangles were available from 109 individuals with a mean age at death of 88.2 (SD=5.9) and a mean of 14.2 years of education (SD=2.6); 75.2% were women. Data on the presence of chronic gross cerebral infarction and Lewy bodies were available in 71 of the 109. In separate linear regression models adjusted for age at death, education, and sex, none of the 6 neuroticism facets was related to a composite measure of plaques and tangles or to the presence of cerebral infarction or Lewy bodies.

Discussion

In a prospective study of more than 700 old persons, we examined the relation of different dimensions of the neuroticism trait to risk of developing AD. The results suggest that neuroticism's association with AD risk primarily reflects two dimensions: vulnerability to stress and anxiety.

Vulnerability to stress has not been extensively studied, but a related construct, perceived stress, has been associated with a variety of adverse health outcomes ranging from the common cold [20] to cardiovascular disease [21]. We are not aware of prior research on perceived stress and risk of dementia or AD. The association of perceived vulnerability to stress with AD risk in these data is consistent, however, with previous data linking stressful life events [22] and reactivity to stress [23] with late life dementia or cognitive decline. These observations suggest that chronically feeling overwhelmed and unable to cope is associated with late life loss of cognition.

There is a recent evidence linking anxiety with late life loss of cognition. One population-based study found, like the present study, that higher anxiety predicted higher risk of

developing dementia and more rapid cognitive decline [24]. A similar association between anxiety and cognitive decline was observed in the longitudinal Aging Study of Amsterdam [25]. Studies of small groups (i.e. <300) from clinical settings have had inconsistent results [26-28], however, possibly due to limited statistical power. Further research on anxiety and late life cognitive function is needed.

The neurobiologic basis of the association between these neuroticism facets and dementia is uncertain. In this study, none of the neuroticism facets was associated with plaques, tangles, infarcts, or Lewy bodies. This finding is consistent with previous research using global measures of the neuroticism trait [2,4,29]. This make it unlikely that higher trait scores are a consequence of the pathology underlying dementia or a reaction to the symptoms caused by that pathology, and suggests the involvement of mechanisms other than those traditionally associated with late life dementia. High perceived stress has been associated with reduced hippocampal volume [30], and a recent clinical-pathologic study found high trait anxiety to be associated with decreased density of dendrites and spines in the CA3 region of the hippocampus [31], a characteristic finding in animal models of chronic stress. These observations suggest that chronic feelings of perceived stress and anxiety in humans may eventually damage selective circuits supporting stress-related behavior thereby contributing to cognitive impairment and making it more likely that other common age-related neurodegenerative changes (i.e., plaques, tangles, infarcts, and Lewy bodies) will result in dementia. The inverse association of neuroticism with baseline level of cognition is consistent with this idea.

We used rate of cognitive decline as a complementary outcome. That anxiety and vulnerability to stress also predicted rate of global cognitive decline makes it unlikely that their association with AD incidence was due to diagnostic bias or imprecision. Consistent with prior research [2,4,5], neuroticism's association with cognitive decline was relatively selective, mainly affecting systems involved in processing (i.e., working memory, perceptual speed) and retaining (i.e., episodic memory) information. Within these more sensitive cognitive domains, neuroticism's relation to decline was less specific, with effects observed for two additional neuroticism facets: depression and impulsiveness.

These findings have important strengths and limitations. Clinical classification of dementia and AD was based on uniform evaluations and accepted criteria applied by experienced clinicians, minimizing the likelihood of diagnostic error. Analyses of cognitive decline and incident AD yielded similar findings, making it unlikely that results were affected by any diagnostic error that did occur. Neuroticism facets and cognitive function were assessed with previously established psychometrically sound scales. High rates of participation in follow-up and autopsy make it unlikely that selective attrition affected results. The main limitation is that participants were selected which could affect the generalizability of the results.

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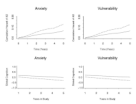

Figure 1.
Model-based estimates of risk of incident Alzheimer's disease (upper panels) and rate of global cognitive decline (lower panels) associated with high (dashed line) or low (solid line) levels of anxiety (left side) and vulnerability to stress (right side), adjusted for age, sex, and education.

Table 1

Psychometric information on measures of neuroticism

					Correlations **						
Neuroticism facet	**Mean**	**SD**	**Range**	**Alpha***	**Ang. Hos.**	**Dep.**	**Self-cons.**	**Impuls.**	**Vuln.**	**Age**	**Educ.**
Anxiety	12.3	5.0	0-32	0.82	.55	.68	.52	.45	.70	.00	-.24
Angry Hostility	10.5	4.5	0-28	0.77		.53	.48	.47	.51	-.08	-.20
Depression	11.0	4.9	0-32	0.78			.66	.41	.67	.05	-.24
Self-consciousness	12.0	4.4	0-28	0.72				.37	.59	.04	-.20
Impulsiveness	13.3	4.4	0-28	0.71					.45	-.18	-.14
Vulnerability	9.9	4.1	0-30	0.80						.09	-.26

* Cronbach's coefficient alpha, a measure of internal consistency.

** p <0.05 for correlations with an absolute value of .07 or more.

Table 2

Relation of neuroticism measures to risk of developing Alzheimer's disease *

Neuroticism Facet	Hazard Ratio	(95% Confidence Interval)
Anxiety	1.05	1.01, 1.09
Angry hostility	1.00	0.96, 1.05
Depression	1.04	0.99, 1.08
Self-consciousness	1.03	0.98, 1.08
Impulsiveness	1.01	0.96, 1.06
Vulnerability	1.06	1.01, 1.12

* From separate proportional hazards models adjusted for age, sex, and education.

Table 3

Relation of neuroticism measures to baseline level of global cognition and rate of global cognitive decline *

Model Terms	Estimate	Standard Error	t	df	P
Anxiety	-0.009	0.003	-2.87	780	.004
Anxiety × time	-0.003	0.001	-2.59	2,680	.010
Angry hostility	-0.006	0.004	-1.63	780	.103
Angry hostility × time	-0.001	0.001	-0.89	2,680	.373
Depression	-0.015	0.003	-4.41	780	<.001
Depression × time	-0.002	0.001	-1.95	2,680	.052
Self-consciousness	-0.010	0.004	-2.60	780	.010
Self-consciousness × time	-0.001	0.001	-1.15	2,680	.250
Impulsiveness	-0.002	0.004	-0.67	780	.503
Impulsiveness × time	-0.001	0.001	-1.21	2,680	.228
Vulnerability	-0.014	0.004	-3.53	780	<.001
Vulnerability × time	-0.004	0.001	-2.76	2,680	.006

*From separate mixed-effects regression models adjusted for age, sex, and education. Results show the effect of a 1-unit change in trait score on the cognitive outcomes.

Table 4

Relation of neuroticism measures to annual rate of change in specific cognitive functions*

Neuroticism Facet	Episodic memory Estimate (SE) p	Semantic memory Estimate (SE) p	Working memory Estimate (SE) p	Perceptual speed Estimate (SE) p	Visuospatial Ability Estimate (SE) p
Anxiety	-0.002 (0.001) .119	-0.001 (0.001) .590	-0.004 (0.001) <.001	-0.005 (0.001) <.001	-0.000 (0.002) .853
Angry hostility	-0.001 (0.001) .436	-0.000 (0.001) .947	-0.002 (0.002) .271	-0.003 (0.001) .047	-0.001 (0.002) .703
Depression	-0.003 (0.001) .045	-0.000 (0.001) .751	-0.003 (0.001) .059	-0.003 (0.001) .019	0.001 (0.002) .353
Self-consciousness	-0.002 (0.002) .230	0.001 (0.001) .733	-0.003 (0.002) .060	-0.002 (0.002) .195	0.001 (0.002) .638
Impulsiveness	-0.002 (0.001) .237	-0.001 (0.001) .571	-0.003 (0.002) .035	-0.003 (0.001) .020	-0.001 (0.002) .570
Vulnerability	-0.004 (0.002) .029	-0.002 (0.002) .284	-0.005 (0.002) .006	-0.005 (0.002) .004	-0.001 (0.002) .763

*Estimates of the relation of each facet to change in each cognitive outcome from separate mixed-effects regression models adjusted for age, sex, and education. Results show the effect of a 1-unit change in trait score on annual rate of cognitive change. P-values are based on the t-distribution with degrees of freedom equal to 2,623 for analyses of episodic memory, 2,600 for semantic memory, 2,679 for working memory, 2,573 for perceptual speed, and 2,557 for visuospatial ability.