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Personality and resilience to Alzheimer's disease neuropathology: a prospective autopsy study

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ABSTRACT

Alzheimer's disease (AD) neuropathology is found at autopsy in approximately 30% of cognitively normal older individuals. We examined whether personality traits are associated with such resilience to clinical dementia in individuals with AD neuropathology. Broad factors and specific facets of personality were assessed up to 28 years (mean 11 ± 7 years) before onset of dementia and up to 30 years (mean 15 ± 7 years) before death in a cohort ($n = 111$) evaluated for AD neuropathology at autopsy. Individuals with higher baseline scores on vulnerability to stress, anxiety, and depression (neuroticism: odds ratio, 2.0; 95% confidence interval, 1.2–3.5), or lower scores on order and competence (conscientiousness: odds ratio, 0.4; 95% confidence interval, 0.2–0.9) were less likely to remain asymptomatic in the presence of AD neuropathology. Neuroticism ($r = 0.26$), low agreeableness ($r = -0.34$), and some facets were also significantly associated with advanced stages of neurofibrillary tangles, but the associations between personality traits and risk of clinical dementia were mostly unchanged by controlling for the extent of neurofibrillary tangles and Aβ neuritic plaques. In sum, a resilient personality profile is associated with lower risk or delay of clinical dementia even in persons with AD neuropathology.

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1. Introduction

Among cognitively normal individuals older than 75 years, approximately a third have sufficient Aβ neuritic plaques and neurofibrillary tangles at autopsy to meet criteria for Alzheimer's disease (AD) (Arriagada et al., 1992; Bennett et al., 2006a; Driscoll and Troncoso 2011). These cases, referred to as asymptomatic AD (ASYMAD) or high pathology controls, can be informative to understand the progression of the disease and to help identify factors that promote cognitive resilience, or cognitive reserve (Bennett et al., 2006b; Craik et al., 2010; Fratiglioni et al., 2004; Iacono et al., 2009; Tucker and Stern 2011).

In this study, we investigate whether personality traits contribute to the cognitive resilience of ASYMAD compared with those with both clinical dementia and corresponding AD pathology at autopsy. A number of studies indicate that those who score higher on conscientiousness and lower on neuroticism engage in fewer health-risk behaviors and have healthier metabolic, cardiovascular, and inflammatory risk profiles (Chapman et al., 2011; Courneya and Hellsten 1998; Deary et al., 2010; Sutin et al., 2010a, 2010b, 2011; Terracciano and Costa 2004; Terracciano et al., 2008; Wilson et al., 2004). Prospective studies indicate that cognitively normal older adults who score higher on conscientiousness or lower on neuroticism have a lower risk of developing clinical symptoms of AD (Duberstein et al., 2011; Wilson et al., 2003, 2005, 2007). These traits were unrelated to the extent of neuropathologic damage at autopsy (Wilson et al., 2003, 2007), which suggests that personality traits may offset the effects of AD-like brain pathology. We test this hypothesis by examining whether personality traits

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predict who is cognitively resilient (ASYMAD) and who is not (AD) in the face of AD neuropathology found at autopsy. Thus, we specifically compare the preclinical personality traits of those who subsequently developed clinical dementia with those who subsequently died cognitively normal, but with AD neuropathology at autopsy. We also examine whether personality traits are associated with semiquantitative measures of neuritic plaques and neurofibrillary tangles.

2. Methods

2.1. BLSA study and autopsy program

Subjects were participants in the autopsy program of the Baltimore Longitudinal Study of Aging (BLSA). The BLSA is a prospective study of physical and psychological aging (Shock et al., 1984). To date, 519 participants have enrolled into the autopsy component of the study, of which 267 died and 224 were examined at autopsy and had complete clinical and neuropathology data. The interval between the last clinical evaluation and autopsy was mean 0.95 ± 1.04 years. Personality data were missing for 16 participants that died or developed dementia before they had a chance to complete the questionnaire, and an additional 12 cases were excluded because personality was assessed in the year of dementia's onset or after. Although we included all available cases in secondary analyses, we excluded 85 participants from the primary analyses according to the criteria described below. The primary analyses were thus based on up to 111 participants who completed the personality inventory at least once before onset of cognitive impairment. The larger proportion of males (75 men, 68%) in the sample reflects the composition of the BLSA cohort, which was limited to men until 1978. All participants analyzed in this study were of European ancestry.

Participants agreed to serial follow-ups until their death, gave written informed consent prior to each assessment, and assented to autopsy. Final autopsy consent was obtained from the next-of-kin or legally designated individual. The local institutional review board and the National Institute on Aging approved all BLSA protocols and the associated autopsy program.

2.2. Clinical and neuropsychological evaluations of the BLSA

Baseline evaluations for each participant enrolled into the BLSA autopsy study were performed by a neurologist to document history of cerebrovascular disease, focal neurological abnormalities, and impairment of cognitive or behavioral functions because of secondary causes or medical treatments. Follow-up evaluations included a neuropsychological battery, neurological examination, medication review, and informant/subject structured interview. The latter was based on the Clinical Dementia Rating (Morris, 1997) scale after 1998 and the Dementia Questionnaire (Kawas et al., 1994) before 1998. All subjects were reviewed at a diagnostic consensus conference if their Blessed Information Memory Concentration score (Blessed et al., 1968) was greater than or equal to 4, if their informant or subject Clinical Dementia Rating score was greater than or equal to 0.5, or if their Dementia Questionnaire was abnormal. All subjects, regardless of the screening tests, were evaluated at a diagnostic conference at the time of entry into the autopsy program and at withdrawal or death. Personality data were not considered at the diagnostic conference, where the full panel of neuropsychological diagnostic tests and clinical data were available for review. Diagnosis of dementia was based on *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* criteria and diagnosis of AD was based on the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984).

2.3. Personality traits assessment

Personality traits were assessed in 1980 and 1986 using the NEO Personality Inventory (NEO-PI) and from 1989 using the Revised NEO Personality Inventory (NEO-PI-R) (Costa and McCrae 1992). The NEO-PI-R is a 240-item questionnaire that assesses 30 facets, 6 for each of the 5 major dimensions of personality—neuroticism, extraversion, openness, conscientiousness, and agreeableness. The NEO-PI did not assess the conscientiousness and agreeableness domains; therefore the analyses for these 2 domains were based on the subsample tested with the full NEO-PI-R. The neuroticism, extraversion, and openness domains were measured with essentially identical scales in the NEO-PI and NEO-PI-R. Raw scores were standardized using combined sex norms (Costa and McCrae, 1992). The NEO instruments have been extensively validated in the BLSA and other samples. In the BLSA sample, the NEO-PI-R factor structure shows high congruence with the normative structure (Tucker's φ, 0.97–0.99) and the internal consistencies for the 5 dimensions range from 0.87 to 0.92. As reported elsewhere (Terracciano et al., 2006), over an average interval of 19 years the test-retest correlations between the 1980 NEO-PI and later NEO-PI-R assessments were 0.73, 0.74, and 0.77 for neuroticism, extraversion, and openness, respectively. These dimensions are thus highly reliable and stable (Terracciano et al., 2006).

2.4. Neuropathology methods and diagnostic criteria

All brains were examined at the Alzheimer's Disease Research Center of the Johns Hopkins University. After weighing and external examination, the right hemibrain was cut in 1-cm coronal slabs and frozen at −80 °C. The left hemibrain was fixed in 10% buffered formaldehyde for at least 2 weeks and then cut coronally. For diagnostic purposes, tissue blocks were dissected from middle frontal gyrus, superior and middle temporal gyri, inferior parietal cortex, occipital cortex, entorhinal cortex, amygdala, thalamus, basal ganglia, and cerebellum. Tissue blocks were processed and embedded in paraffin, cut at 10 μm, and stained with hematoxylin-eosin and Hirano-silver method (Yamamoto and Hirano, 1986) for diagnostic purposes. The severity of neuritic plaques was assigned a semiquantitative score of 0 for none, A or 1 for rare, B or 2 for moderate, and C or 3 for frequent, according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria (Mirra et al., 1991), except we did not adjust for age. The neurofibrillary tangles stage was assigned a score (0–6) according to Braak and Braak (1991, 1998). Vascular lesions (infarcts, lacunes, and hemorrhages) were evaluated on all hematoxylin-eosin-stained sections.

Because of the small sample sizes of subjects with mild cognitive impairment because of AD, we excluded these individuals from analyses. Similarly, we excluded dementia cases with other primary neuropathological processes, including vascular disease, frontotemporal dementia, Lewy body dementia, and cases in which clinical dementia assessment might have been compromised by psychiatric or other pathologies, including intraparenchymal hemorrhages and primary or metastatic brain tumors. Lewy body disease was determined on immunostain findings of α-synuclein lesions (Lewy bodies or neurites; anti-α-synuclein antibody from BD Transduction Laboratories, Biosciences, Palo Alto, CA, USA; dilution 1:500) in brain stem or cerebral cortex and tauopathies were determined by anti-phosphorylated tau (PHF-1 clone; a gift of Dr P. Davies, Albert Einstein College of Medicine, Bronx, NY, USA; dilution 1:100).

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