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The Relation Between Personality and Biomarkers in Sensitivity and Conversion to Alzheimer Type Dementia

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Abstract

Objectives: The present study explored relationships among personality, Alzheimer's disease (AD) biomarkers and Dementia by addressing the following questions: (1) Does personality discriminate healthy aging and earliest detectable stage of AD? (2) Does personality predict conversion from healthy aging to early stage AD? (3) Do AD biomarkers mediate any observed relationships between personality and dementia status/conversion?

Methods: Both self- and informant ratings of personality were obtained in a large well-characterized longitudinal sample of cognitively normal older adults (N = 436) and individuals with early stage dementia (N = 74). Biomarkers included amyloid imaging, hippocampal volume, CSF Aβ42, and CSF tau.

Results: Higher neuroticism, lower conscientiousness, along with all four biomarkers strongly discriminated cognitively normal controls from early stage AD individuals. The direct effects of neuroticism and conscientiousness were only mediated by hippocampal volume. Conscientiousness along with all biomarkers predicted conversion from healthy aging to early stage AD; however, none of the biomarkers mediated the relationship between conscientiousness and conversion. Conscientiousness predicted conversion as strongly as the biomarkers, with the exception of hippocampal volume.

Conclusions: Conscientiousness, and to a lesser extent neuroticism, serve as important independent behavioral markers for AD risk.

Keywords

Alzheimer disease; personality; biomarkers; dementia; aging; older adults

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Introduction

There has been considerable effort devoted to developing sensitive, noninvasive behavioral markers for the earliest detectable onset of Alzheimer's disease (AD). It is well known that the pathological changes associated with AD are present a decade or more before the behavioral symptoms are apparent (Bateman et al., 2012; Price et al, 2009; Sperling et al., 2011). Thus, it is important to identify preclinical behavioral markers in individuals who appear cognitively normal but are at increased risk for developing the disease.

Although much of the past work has focused on cognitive markers, specific personality traits have also been identified as behavioral risk factors that appear to be sensitive to the early detection of AD. For example, in an early cross-sectional study, Duchek, Balota, Storandt and Larsen (2007) found that individuals with very mild AD had higher scores on neuroticism and lower scores on conscientiousness, compared to cognitively normal controls. Interestingly, neuroticism and conscientiousness scores discriminated these two groups as well as a highly sensitive composite measure of episodic memory performance.

More recently, there have been large-scale longitudinal studies that indicate high neuroticism and low conscientiousness may place individuals at a greater risk for developing AD. Several studies have reported a link between baseline neuroticism and conscientiousness and subsequent onset of dementia (Crowe et al., 2006; Duberstein et al., 2011; Terracciano et al., 2014; Wilson et al., 2003; 2007). In a recent large-scale study, Terracciano et al (2017) reported high neuroticism and low conscientiousness were independently associated with increased risk of cognitive impairment and dementia, and also low conscientiousness predicted conversion from mild cognitive impairment without dementia to a clinical diagnosis of dementia.

It is interesting to note that relative to the other traits in the Big Five model of personality (i.e., extraversion, openness, agreeableness), neuroticism and conscientiousness are the two traits that consistently have been related to AD risk. A priori, one might expect neuroticism to be predictive of disease onset given the well-established link between chronic stress and dysregulation in the hypothalamic-pituitary adrenal (HPA) axis (e.g., Zobel et al., 2004), which, in turn, has been associated with changes in hippocampal structure and function (e.g., Baker & Kim, 2002; McEwen & Magarinos, 2001). Moreover, there is substantial evidence that hippocampal volume mediates memory performance (e.g., Fjell & Walhovd, 2010; Head et al., 2008; Squire, 1987) and neuropathological changes in hippocampal structures accompany AD onset (e.g., Price et al.,1991). In this light, Wilson et al (2003; 2007) have argued that exposure to chronic stress (as exhibited in individuals high in neuroticism) over time may produce changes in the hippocampal formation, thereby rendering an individual more susceptible to lower levels of overall neuropathology.

There are also reasons why conscientiousness may be an important behavioral marker of AD. Conscientiousness is defined as being dependable, reliable, goal directed, self-disciplined, and in control of impulses (Costa & McCrae, 1992). Conscientiousness has been linked to a myriad of outcomes (see Bogg & Roberts, 2013, for a review), including health outcomes (Bogg & Roberts, 2004), depressive symptoms (Kendler et al., 2006),

occupational and educational attainment (Lodi-Smith et al., 2010) and even mortality (Friedman et al., 1993; Wilson et al., 2004). Hence, it is quite possible that individuals high in conscientiousness are more likely to engage in health and lifestyle behaviors that may serve to protect against the accumulation of AD neuropathology and hence reduce risk for AD onset (e.g., Bogg & Roberts, 2013 Chapman et al., 2011; Terracciano et al., 2013; Terracciano & Sutin, 2019; Wilson et al., 2007).

Given that neuropathology consistent with AD is present in the brains of cognitively normal older individuals decades before the onset of the disease (e.g., Bateman et al., 2012; Price et al., 2009), there also has been interest in identifying how biomarkers for the disease may influence the relationship between personality and behavioral symptoms of dementia. For example, Jackson, Balota, and Head (2011) have reported that high neuroticism and low conscientiousness are associated with reduced volume in prefrontal and medial temporal areas. Dar-Nimrod et al (2012) have argued that the risk for cognitive decline as a function of APOE status is modulated by neuroticism (i.e., APOE 4 risk for cognitive decline is greater for individuals high in neuroticism). In an autopsy study, Terracciano et al (2013) found that individuals low in neuroticism and high in conscientiousness were more likely to remain asymptomatic in the presence of AD neuropathology, suggesting these personality characteristics may afford cognitive resilience in the face of accumulating brain pathology. Finally, in a recent study of healthy controls and individuals with mild cognitive impairment or mild AD, Tautvydaite et al (2017) reported that retrospective informant ratings of neuroticism and conscientiousness accompanied by abnormal levels of CSF biomarkers predicted cognition as defined by CDR sum of box scores (Morris 1993). Thus, there is an emerging literature that the personality traits of neuroticism and conscientiousness may be related to biomarkers that predict risk for the onset of AD.

The present study further explores this relationship in a large well-characterized longitudinal sample, with a rich set of AD related biomarkers, and estimates of personality from both self and informant reports. In this light, we have three major goals. First, we further explore the relationship between conscientiousness and neuroticism in the discrimination between healthy aging and the earliest detectable stage of AD, via cross-sectional analyses. Second, we further examine the extent to which baseline neuroticism and conscientiousness predicts conversion from healthy aging to early stage AD, utilizing longitudinal data. Third, and most critically, we examine the role of biomarkers in mediating any observed relationship between neuroticism/conscientiousness and dementia status/conversion to early stage AD observed in the first two goals.

The present project adds to the available literature in the following three ways. First, previous studies have utilized either baseline self-report (e.g., Duberstein et al., Terracciano et al., 2014; Wilson et al., 2003; 2007) or retrospective informant report (e.g., Tautvydaite et al., 2017) and have not examined the *convergence of self and informant* reports of personality in predicting dementia status or conversion to dementia. Second, we examine the *relative* predictive power of well-established biomarkers compared to personality in discriminating healthy aging from earliest stages of AD, and longitudinal conversion from healthy aging to dementia. Third, this rich dataset affords an examination of any potential *mediating effects* of a wide range of multiple well-established AD biomarkers (amyloid

imaging, hippocampal volume, cerebral spinal fluid (CSF) Aβ42, CSF tau) in understanding any observed relationship between personality and dementia status (CDR 0 vs CDR 0.5) or conversion from healthy aging to dementia (CDR 0 to CDR 0.5 or greater).

Methods

Participants

Five hundred and ten individuals participated in this study; 436 cognitively normal older adults (CDR 0; 57% female) and 74 individuals with very mild AD (CDR 0.5; 32% female)[1]. Participants were recruited from the Charles and Joanne F. Knight Alzheimer's Disease Research Center (ADRC) at Washington University in St. Louis, as part of an ongoing longitudinal research program on AD progression. All participants were originally screened for depression with the Geriartic Depression Scale (GDS short form, Yesavage et al., 1983), untreated hypertension, reversible dementias, and other disorders that could potentially produce cognitive impairment. The inclusionary and exclusionary criteria for AD are consistent with the criteria set forth by the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984). We staged the severity of dementia according to the Washington University Clinical Dementia Rating (CDR) scale (Morris, 1993). The CDR is based on a 90-min clinical interview that assesses both the participant and relies on information from an informant concerning the participant without reference to neuropsychological test performance. According to this scale, CDR scores of 0, 0.5, 1, 2, and 3 represent no dementia, very mild dementia, mild dementia, moderate dementia, and severe dementia, respectively. We focus here on the CDR scores of 0 and 0.5 to examine the earliest detectable stages of symptomatic dementia. It should be noted that we refer to this earliest stage as very mild AD (CDR 0.5), rather than MCI. In a longitudinal study, Storandt at al. (2006) found that individuals who were CDR 0.5 who met criteria for MCI progressed *faster* than individuals who were CDR 0.5 but were not yet impaired enough to meet MCI criteria, thus suggesting that a CDR of 0.5 represents an earlier stage of AD than MCI because the CDR relies upon information regarding intraindividual change rather than group norms. Both the reliability of the CDR (Burke et al., 1988) and the validation of the diagnosis of AD (based upon autopsy) have previously been shown to be excellent (Berg et al., 1998; Storandt et al, 2006). The Washington University in St. Louis Institutional Review Board approved this study.

Materials and Procedure

All participants and their informant (i.e., typically a spouse or adult child) filled out the NEO Five-Factor Inventory (NEO-FFI; Costa & McCrae, 1992). The NEO-FFI measures the five factors of neuroticism, extraversion, openness, agreeableness, and conscientiousness. Based on the extant literature reviewed above, we focus on the traits of neuroticism and conscientiousness in this study. Participants and informants filled out the form at the time of

[1]It is important to note that some of the participants rated as CDR 0.5 also had an 'uncertain' status (n = 35) indicating the clinician was not entirely sure the observed cognitive impairment was due only to AD. We have included such individuals in our sample in order to maximize power in our study. Importantly, all statistical results remained unchanged when excluding these individuals from analyses.

the participants' clinical visit. There is relatively good agreement between self- and informant report ratings for individuals with very mild AD (Duchek et al., 2007; Rankin, Baldwin, Pace-Savitsky, Kramer, & Miller, 2005). In the present study, the correlations between self and informant report across all participants were as follows: Neuroticism r = .46, Conscientiousness r = .44, (all p's < .001), after controlling for age.

Participant characteristics including MMSE, GDS, neuropsychological test scores, and biomarkers scores for the CDR 0s and 0.5s, along with the raw scores for neuroticism and conscientiousness for self and informant report are presented in Table 1. It is important to note that although there were missing values for some informant reports, the overall response rate was very high (86%). In this sample, 35% and 62% were APOE+ for the CDR 0 and CDR 0.5 groups, respectively.

Biomarkers

To address the mediating effects of biomarkers on personality and dementia status and dementia conversion, we selected subsamples of our CDR 0 and CDR 0.5 participants with NEO self-report data who also had amyloid imaging (CDR 0, N = 393; CDR 0.5, N = 38), hippocampal volumetric estimates, CSF Aβ42, and CSF tau (CDR 0, N = 436; CDR 0.5, N = 74) data available. We selected four years as the cutoff interval between the baseline NEO assessment and biomarker assessment. The average interval between MRI and NEO was 295 days (SD = 363) and lumbar puncture and NEO was 162 days (SD = 248).

Amyloid Imaging.—Amyloid PET imaging was acquired using either florbetapir (^{18}F-AV-45) or [^{11}C] PiB. Full details of the scanning procedure have been described elsewhere (Su et al., 2013). Imaging data were converted to standardized uptake value ratios (SUVRs) using the cerebellar cortex as the reference region. A regional spread function approach was used for partial volume correction and amyloid deposition was quantified as an average across the following regions: left and right lateral orbitofrontal, medial orbitofrontal, rostral middle frontal, superior frontal, superior temporal, middle temporal, and precuneus.

Hippocampal Volume.—MRI scans were obtained on a Sonata 1.5T, Vision 1.5T, or Trio 3.0T scanner (Siemens Corporation). Structural MRI processing steps have been described in detail previously (Buckner et al., 2004; Xiong et al, 2011) and included motion correction, averaging across scans, atlas transformation, and inhomogeneity correction. Regional volumes were obtained via the Freesurfer image analysis suite (Version 4.1.0, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts). Hippocampal volume was selected as the region of interest (ROI) in this analysis and corrected for total brain volume.

CSF AB42 and CSF tau.—Following Fagan et al. (2007), after participants fasted overnight, 20- to 30-mL samples of CSF were collected via a lumbar puncture, then aliquoted (500 μl) in polypropylene tubes, and stored at −84°C. Samples were analyzed after a single thaw using ELISA (INNOTEST, Fujirebio [formerly Innogenetics], Ghent, Belgium).

Statistics

NEO scores and biomarker values were converted to *z* scores standardized to the first NEO assessment (and closest associated biomarker) for the entire sample of CDR 0s and CDR 0.5s. Age, also z-scored, was treated as a covariate in all of the following analyses[2]. Logistic regression analyses were performed to determine whether: (1) neuroticism and conscientiousness discriminate CDR 0 and CDR 0.5 groups; (2) biomarkers discriminate CDR 0 and CDR 0.5 groups; (3) baseline neuroticism and conscientiousness predict conversion from CDR 0 to CDR 0.5 or greater; (4) baseline biomarkers predict conversion from CDR 0 to CDR 0.5 or greater. There were 47 individuals in this sample who converted from CDR 0 to CDR 0.5 or greater during this study period. To maximize our sample size, we only included two times of testing for the longitudinal analyses, which averaged 6.95 years apart.

Linear regression analyses were performed to determine whether biomarkers mediated any observed relationship: (1) between neuroticism/conscientiousness and CDR status; (2) between neuroticism/conscientiousness and dementia conversion. Mediation analyses were conducted using the lavaan package (Yves, 2012) in the R statistical environment. In each model, personality was specified as the independent variable and CDR status or conversion as the outcome. Individual biomarkers were entered into the model as proposed mediators. The indirect effect (i.e., the extent to which a biomarker mediates the relationship between personality and CDR) was calculated as the product of the beta weights predicting the biomarker from personality (the “a” path) and predicting CDR status from the biomarker (the “b” path). Standard errors of these estimates were generated using the delta method (Oehlert, 1992). A significance value of $p < .01$ was adopted across all analyses due to multiple comparisons.

Results

Discriminating healthy aging (CDR 0) from the very earliest stage of AD (CDR 0.5)

As predicted, based on self-report, the CDR 0.5 group had lower conscientiousness scores ($p < .001$) and marginally higher neuroticism ($p = .021$) than the CDR 0 group (Table 2). Also, as shown in Table 2, these differences were even larger in the informant report data, with both conscientiousness and neuroticism producing highly reliable effects (both p’s < .0001). Of course, one might be concerned that the higher neuroticism ratings in the informant report may be due to some participants having very mild depression (as reflected by GDS scores) in the CDR 0.5 group. However, the higher neuroticism ratings in the CDR 0.5 group remained after controlling for GDS scores, $p = .01$.

Amyloid imaging, hippocampal volume, CSF Aβ42 and CSF tau discriminated the CDR 0 vs CDR 0.5 groups (Table 2) indicating clear sensitivity of these biomarkers. Interestingly, the partial correlations (controlling for age) between each of the biomarkers and neuroticism and conscientiousness were unsystematic and quite small, with the exception of hippocampal volume which was negatively related to neuroticism (−.17, $p < .001$ for

[2]In order to insure gender was not influencing our results, we also conducted all analyses with gender as an additional covariate. None of the results changed.

informant report and −.10, $p < .05$, for self report) and positively related to conscientiousness (.19, $p < .001$ for informant report and .10, $p < .05$, for self report). The only remaining correlations which approached significance were between CSF tau and neuroticism (.10, $p < .10$ for informant ratings, and .11, $p < .05$ for self ratings).

Do biomarkers mediate the relationship between neuroticism and conscientiousness and dementia (CDR) status?

Table 3 displays both the direct effect between neuroticism/conscientiousness and CDR and the indirect effect which represents the extent to which a specific biomarker mediates a given personality-CDR relationship. First, consider the self-report data. As shown, there is relatively little evidence of biomarker mediation for neuroticism and conscientiousness, with the exception of two mediational effects that may be expected a priori (Jackson et al., 2011; Wilson et al., 2003; 2007). Specifically, there was a marginally reliable mediation of hippocampal volume on the relationship between both neuroticism ($p = .028$) and conscientiousness ($p = .047$) and CDR status. Turning to the informant report relationships, a similar but much stronger pattern is observed. Specifically, hippocampal volume significantly mediated the relationship between both neuroticism ($p < .001$) and conscientiousness ($p = .0002$) and CDR status, indicating that hippocampal volume accounts for some of the shared variance between personality and CDR status.

Predicting conversion from healthy aging (CDR 0) to early stage AD (CDR 0.5 or greater)

As shown in Table 4, baseline conscientiousness strongly predicted conversion in both self and informant report. Cognitively normal participants (CDR 0) lower in conscientiousness at baseline were more likely to convert to CDR 0.5 or greater than individuals high in conscientiousness at baseline.

The results also demonstrated clear sensitivity of the biomarkers in predicting conversion. Specifically, amyloid imaging estimates, hippocampal volume, CSF Aβ42 and CSF tau at baseline predicted conversion, see Table 4. It is noteworthy that the beta weights and corresponding odds ratios are much larger for hippocampal volume than the other biomarkers. Importantly, with the exception of hippocampal volume, conscientiousness was comparable to the remaining biomarkers in predicting conversion based on both self and informant reports. To further examine this issue, we included hippocampal volume and informant report of conscientiousness in a stepwise regression model and found that conscientiousness predicted conversion above and beyond hippocampal volume ($Chisq(1) = 7.31$, $p = .007$).

In addition to the above analyses, we also created a cognitive composite measure from the neuropsychological measures in Table 1 (z-scored to a reference sample of biomarker negative, healthy older adults (Hassenstab et al. 2016)) to assess if another powerful behavioral marker (cognition) predicted conversion. The results were quite clear. Although this cognitive composite strongly discriminated CDR 0 participants from CDR 0.5s, ($beta = −1.29$, $odds\ ratio = 3.61$, $p < .0001$), it did not predict conversion ($beta = −.183$, $odds\ ratio = 1.20$, $p > .05$) in these data, which further points to the unique predictive power of conscientiousness as an important behavioral marker for conversion. Finally, there were no

significant baseline differences between converters and nonconverters in education (15.7 vs 15.9, p =.99; GDS scores (1.2 vs .98, p = .39; or APOE+ status (47% vs 33%, p = .09).

Do biomarkers mediate the relationship between conscientiousness and conversion to early stage AD?

Remarkably, as shown in Table 5, none of the available biomarkers mediated the relationship between conscientiousness and conversion for either self or informant report, again supporting the unique predictive power of conscientiousness.

Discussion

The three primary issues addressed in the present study were (1) the relative extent to which neuroticism and conscientiousness discriminate healthy aging (CDR 0) from the earliest detectable stage of AD (CDR 0.5), (2) whether baseline neuroticism and/or conscientiousness predict conversion to early stage AD, and, (3) the role of well-established AD biomarkers in mediating the relationship between neuroticism and conscientiousness and CDR status and/or conversion to dementia. We now turn to a discussion of how the present work informed each of these issues.

Discriminating Healthy Controls from the Earliest Detectable Stage of AD

Consistent with previous work (Duberstein et al., 2011; Duchek et al., 2007; Terracciano et al., 2014), we found in cross-sectional analyses that both neuroticism and conscientiousness reliably discriminated cognitively normal older adults (CDR 0) from individuals in the earliest stages of AD (CDR 0.5). Specifically, both higher neuroticism and lower conscientiousness were associated with very mild AD based on both self and informant reports (although the effect in neuroticism in the self-report data was only marginal, p = .02). It is possible that the stronger CDR discrimination in the informant report may in part reflect the informant's more negative perceptions of the individual on these personality dimensions due to the diagnosis of early stage AD. However, Duchek et al. (2007) directly examined this issue, and the predictive power of neuroticism and conscientiousness to discriminate these groups did not change when informants did or did not know the diagnostic status of the very mild AD individuals. Hence, the present results are more consistent with the possibility that informant reports may be particularly good at identifying personality, compared to the individual's self-report. Of course, this would be expected especially in the very mildly demented individuals, since these individuals may lose some ability to report on their own personality due to meta-cognitive changes. Indeed, the value of informant reports has been established in more general cognitive domains. For example, Carr et al (2000) reported that informant reports of memory problems are more predictive of cognitive performance and subsequent dementia onset than self-reports. Moreover, there also is evidence that even healthy individuals are less likely to be able to report on their own personality (relying on long-standing self-perceptions), compared to close informants (e.g., Balsis, Cooper, & Oltmanns, 2015).

All biomarkers in the present study strongly discriminated dementia status (CDR 0 vs CDR 0.5). Importantly, however, most standard AD biomarkers did not mediate the relationship

between neuroticism and conscientiousness and CDR status, with one exception. Hippocampal volume mediated the relationship between both neuroticism and conscientiousness and CDR status based on informant report. Reduced volume in various brain regions, including prefrontal and medial temporal areas, has been associated with higher neuroticism and lower conscientiousness in older adults (e.g., Jackson et al., 2011). As indicated earlier, the well-established links between reduced hippocampal volume and chronic stress, memory decline, and AD onset lend support to the notion that high neuroticism may render an individual more susceptible to the buildup of AD pathology and thus at increased risk for the onset of AD symptomatology (Terracciano et al., 2013; Wilson et al., 2003; 2007). Moreover, individuals high in conscientiousness also are more likely to engage in health related activities (Rhodes & Smith, 2006), and indeed there is evidence that hippocampal volume is related to health activities, such as exercise (e.g., Erickson et al., 2009; 2011).

Personality and Dementia Conversion

Of course, the cross-sectional analyses do not address the important question of whether the group differences in neuroticism and conscientiousness reflect changes in personality in the earliest stage of the disease or whether these specific personality traits at baseline predispose individuals to develop AD. The longitudinal conversion to dementia analyses shed light on this question. Again, our results are straightforward. In our sample of cognitively normal older adults (CDR 0), baseline conscientiousness predicted later conversion to dementia. Based on both self and informant reports, lower conscientiousness at baseline was associated with greater risk of conversion to AD. Our results are consistent with Terracciano et al. (2017) who found no evidence for preclinical change in personality before onset of the disease, thus indicating that lower conscientiousness is a risk factor for, rather than consequence of dementia. Interestingly, and contrary to some reports in the literature (e.g., Terracciano et al, 2014; 2017; Wilson et al., 2003), neuroticism did not reliably predict conversion to dementia in our sample, although the betas were in the predicted direction. It is possible that variations in the measurement of neuroticism (e.g., Terracciano et al., 2017 used the Midlife Development Inventory) or using extreme values (e.g., Wilson et al., 2003 compared individuals with scores from the NEO in the top 10% vs the lower 10%) increase the sensitivity of neuroticism to predict conversion in these past studies. Moreover, it is apparent in our sample that GDS scores were quite low. Studies that have investigated the specific facet scores of neuroticism have found that depression, anxiety, and vulnerability to stress are significant predictors of AD onset (Terracciano et al., 2014; Wilson et al., 2011) and indeed the predictive power of neuroticism is reduced when controlling for depressive symptoms (Wilson et al., 2005). Thus, the trait of neuroticism may be tapping overlapping aspects of depression, which were quite low in our sample.

Although all of the current biomarkers predicted conversion to dementia, none of the biomarkers reliably mediated the relationship between conscientiousness and conversion to dementia. Remarkably, both self and informant report of conscientiousness were comparable predictors of conversion compared with the standard biomarkers, with the exception of hippocampal volume (see Table 4). Moreover, multiple regression analyses indicated that conscientiousness predicted conversion above and beyond hippocampal volume and a highly

sensitive cognitive measure for discrimination did not reliably predict conversion in this sample. These results again suggest that conscientiousness at baseline may serve as a strong and independent behavioral predictor of dementia onset.

As previously discussed, various explanations have been offered for the role of conscientiousness as a protective factor for AD onset (e.g., Boggs & Roberts, 2013; Duberstein et al., 2011; Terracciano et al., 2013; Wilson, 2007). Specifically, the self-discipline facet (i.e., high self-discipline) has been shown to be strongly related to reduced dementia risk (Terracciano et al., 2014). As noted, a conscientious behavioral lifestyle protects against various health conditions that increase risk for disease onset (e.g., cardiovascular disease, diabetes, obesity) and promote certain behaviors that may reduce risk for AD (e.g., exercise, cognitive engagement). We believe that it is most likely that conscientiousness may serve as an important proxy for various protective lifestyle and health behaviors and thus is an important and relatively simple behavioral marker to assess in predicting risk for AD.

Importantly, we found that all of the biomarkers predicted dementia status and conversion to dementia in our sample of cognitively normal older adults. Thus, we were in an excellent position to test the extent to which these biomarkers mediated the influence of conscientiousness and neuroticism. Interestingly, only hippocampal volume reliably mediated the relationship between neuroticism and conscientiousness and dementia status. It is possible that changes in hippocampal volume represent neurodegenerative processes that occur after the buildup of amyloid and tau burden (Jack et al., 2013). Thus, the earlier biomarkers of amyloid imaging, CSF Aβ42 and CSF tau may not be as sensitive to the personality-dementia status/conversion relationship.

Although there is evidence in the longitudinal literature indicating neuroticism and conscientiousness as behavioral risk factors for AD onset (e.g., Duberstein et al., 2011; Terracciano et al, 2014; Wilson et al., 2003; 2007), there has been relatively little work addressing the mediating influences of biomarkers on this relationship. Tautvydaite et al (2017) reported that informant retrospective ratings of neuroticism and conscientiousness *modulated* the relationship between CSF biomarkers and cognitive performance. Specifically, high conscientiousness and, somewhat surprisingly, *high* neuroticism accompanied by abnormal levels of CSF biomarkers predicted better cognitive performance, as defined by the CDR sum of the box scores. Thus, it may seem surprising that hippocampal volume was the only biomarker that mediated the personality-dementia relationships in the present study. However, there are several differences between the present study and the Tautvydaite et al study. For example, in the latter study the sample size was relatively small and included both 44 cognitively normal adults and 66 individuals with either MCI or mild dementia. Moreover, the NEO was based upon retrospective informant reports of the participants' premorbid personality and cognitive performance was based upon the CDR sum of the box scores (Morris, 1993). Thus, there were no longitudinal data per se in the latter study. Our study included a much larger sample and only CDR 0 individuals were included in our longitudinal analyses of conversion. Importantly, we obtained the informant reports of personality at the current time of testing (i.e., prior to behavioral changes and the onset of clinical symptoms), rather than relying upon informants'

retrospective estimates of personality, as is often the case in the dementia literature (e.g., Tautvydaite et al., 2017). Thus, the informant reports of personality in this study provide unique support for the argument that personality is a risk factor for dementia onset.

It also should be noted that the current sample only included cognitively normal individuals (CDR 0) or individuals in the very earliest stage of the disease (CDR 0.5). It is possible that the biomarkers have a stronger influence on the personality-dementia relationship in the later stages of the disease. As previously mentioned, at autopsy Terracciano et al (2013) found that individuals low in neuroticism and high in conscientiousness were more likely to remain asymptomatic in the presence of AD neuropathology. Of course, eventual autopsy data on our sample will be particularly useful to replicate this pattern.

The present study also has some limitations. As mentioned, the present study only included two times of testing for the longitudinal analyses (average 6.95 years apart)[3] to examine the relationships among personality, biomarkers, and dementia conversion. To further elucidate these relationships future studies should examine more extensive longitudinal data of personality and biomarkers, as well as more subtle behavioral measures of cognitive decline. Although several biomarkers were available for the present sample, it is possible that other biomarkers may be related to personality traits. For example, Schultz et al. (2019) recently reported a relationship between neuroticism and regional tau deposition using positron emission tomography in a smaller cross-sectional sample (N = 128) of cognitively normal older adults. Similarly, Gatchel et al (2017) reported an association between depressive symptoms and tau deposition in a cognitively normal sample and Terracciano et al (2013) reported an association between neuroticism and more advanced staging of neurofibrillary tangles in an autopsy study. Finally, as noted above, we have emphasized the earliest stages of AD, i.e., cognitively normal vs very mildly demented individuals. Future work should consider the relationship, especially between informants and biomarkers, in individuals who are in the very mild and mild stage of dementia.

Conclusions

The present results extend the existing literature indicating that neuroticism and conscientiousness serve as behavioral/lifestyle indicators of dementia risk (e.g., Duberstein et al., 2011; Duchek et al., 2007; Terracciano et al, 2014; 2017; Wilson et al.,2003; 2007). It is particularly noteworthy that conscientiousness at baseline for CDR 0s is as strong a predictor of later conversion as standard biomarkers, with the only exception being hippocampal volume. Given the cost and demands of obtaining CSF and imaging biomarkers, the present results indicate that there is considerable clinical potential in the additional 5 minutes necessary to obtain estimates of conscientiousness and neuroticism.

[3]In order to verify that differential lengths of follow-up were not influencing our results, we conducted a Cox Proportional Hazards analysis on survival time (i.e., the time from the first NEO assessment to the first clinical dementia rating greater than 0). Self and informant reports were entered in separate models after controlling for age at baseline. The results are consistent with the main analysis and show that self-reported conscientiousness predicted survival time (HR = 0.93, 95% CI = 0.89:0.98, p = 0.002) whereas self-reported neuroticism was marginal (HR = 1.04, 95% CI = 0.99 : 1.08, p = 0.08). Similarly, informant reported conscientiousness predicted survival time (HR = 0.94, 95% CI = 0.90:0.97, p = < .001) but neuroticism did not (HR = 1.01, 95% CI = 0.97 : 1.06, p = 0.54).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Table 1

Participant Demographic Characteristics, NEO Raw Scores and Biomarkers a function of CDR and Self-vs Informant Report

CDR 0 - Self Report (N=436)				**CDR 0 - Informant Report (N=406)**			
	Mean	**S.D.**	**Range**		**Mean**	**S.D.**	**Range**
Neuroticism	15.0	7.5	0–40	Neuroticism	13.6	8.0	0–41
Conscientiousness	34.9	6.6	11–48	Conscientiousness	37.6	7.8	11–48
Age	65.9	9.2	42–93				
Education	15.8	2.6	6–24				
MMSE	29.1	1.3					
GDS	1.0	1.4	0–8				
Animal fluency	21.6	5.5	9–37				
fcSRT	31.1	5.8	15–46				
Trailmaking A	31.1	10.6	10–77				
Trailmaking B	76.9	32.2	19–180				
Amyloid Imaging	10.0	25.8	−10.1 – 139.1				
Hippocampal Volume	3,891.1	493.1	1825–5293				
CSF Aβ42	1,438.2	674.1	307.4 – 4,203				
CSF Tau	217.4	92.4	80.0—668.0				
CDR 0.5 - Self Report (N=74)				**CDR 0.5 - Informant Report (N=73)**			
	Mean	**S.D.**	**Range**		**Mean**	**S.D.**	**Range**
Neuroticism	16.6	7.6	1–36	Neuroticism	19.3	8.4	2–35
Conscientiousness	31.8	6.6	13–46	Conscientiousness	31.2	8.5	9–48
Age	72.8	6.4	51–87				
Education	15.8	2.7	8–21				
MMSE	27.2	2.3					
GDS	2.2	2.4	0–11				
Animal fluency	17.0	5.1	2–27				
fcSRT	21.9	7.7	1–42				
Trailmaking A	41.4	15.5	17–104				
Trailmaking B	109.8	42.5	40–180				
Amyloid Imaging	58.8	43.6	−8.8 – 142				

Hippocampal Volume	3,300.5	549.6	2291–4987
CSF Aβ42	870.2	456.5	289–2,162
CSF Tau	296.1	145.1	80.0–952.0

Note: GDS refers to the Geriatric Depression Scale (short form – scored 0–15, score of ≥ 5 suggests depression). Animal fluency is scored as the # of animals named in 1 minute. fcSRT represents the Free and Cued Selective Reminding Test, free recall score. Trailmaking A and B are scored as # of seconds (180 max).

Table 2

Beta Weights and Odds Ratios (95% CI) for CDR Discrimination based on NEO Self and Informant Reports and Biomarkers

	Self-Report		Informant Report	
	Beta	**Odds Ratio**	**Beta**	**Odds Ratio**
Neuroticism	.308 (.047, .570)	1.36(1.04, 1,77)	**.905 (.608,1.20)** ****	**2.47 (1.85,3.36)** ****
Conscientiousness	**−.449 (−.708, −.189)** ***	**1.56 (1.20, 2.03)** ***	**−.834 (−1.12, −.557)** ****	**2.30 (1.76,3.07)** ****
Amyloid imaging	**.889 (.603,1.18)** ****	**2.43 (1.84,3.28)** ****		
Hippocampal Volume	**−1.06 (−1.43, −.726)** ****	**2.90 (2.09, 4.12)** ****		
CSF Aβ42	**−1.26 (−1.69, −.839)** ****	**3.53 (2.37,5.52)** ****		
CSF tau	**.457 (.220, .695)** ***	**1.58 (1.25, 2.01)** ***		

** $p < .01$

*** $p < .001$

**** $p < .0001$

Table 3

Beta Weights for the Personality-CDR Relationship as Mediated by Biomarkers as a Function of Self and Informant Reports

Self-Report								
	Amyloid		**Hippocampal Vol**		**CSF Aβ42**		**CSF tau**	
	Direct	**Indirect**	**Direct**	**Indirect**	**Direct**	**Indirect**	**Direct**	**Indirect**
Neuroticism	.143	−.004	.138	**.040** *	**.173** *	.005	**.152** *	**.026** *
Conscientiousness	**−.280** **	−.020	**−.221** **	**−.039** *	**−.237** **	−.023	**−.249** **	−.011
Informant Report								
	Amyloid		**Hippocampal Vol**		**CSF Aβ42**		**CSF tau**	
	Direct	**Indirect**	**Direct**	**Indirect**	**Direct**	**Indirect**	**Direct**	**Indirect**
Neuroticism	**.466** ***	.020	**.419** ***	**.078** ***	**.480** ***	.017	**.475** ***	.021
Conscientiousness	**−.368** ***	−.033	**−.397** ***	**− .083** ***	**−.435** **	−.045	**−.465** ***	−.015

Note: The direct effect represents the direct relationship between neuroticism/conscientiousness and CDR. The indirect effect represents the relationship between neuroticism/conscientiousness and CDR, mediated by each biomarker.

* $p < .05$

** $p < .01$

*** $p < .001$

Table 4

Beta Weights and Odds Ratios (95% CI) for Conversion to Dementia based on NEO Self and Informant Reports and Biomarkers

	Self-Report		Informant Report	
	Beta	**Odds Ratio**	**Beta**	**Odds Ratio**
Neuroticism	.225 (−.108, .558)	1.25 (.894,1.74)	.052 (−.345, .450)	1.05 (.701, 1.56)
Conscientiousness	**−.455 (−.782, −.127)** **	**1.58(1.14,2.19)** **	**−.525 (−.885,−.164)** **	**1.69 (1.18, 2.43)** **
Amyloid imaging	**.582 (.271, .893)** ***	**1.78 (1.31, 2.45)** ***		
Hippocampal Volume	**−1.069 (−1.547, −.592)** ****	**2.92 (1.83, 4.78)** ****		
CSF Aβ42	**−.668 (−1.07, −.269)** **	**1.95 (1.34, 2.98)** **		
CSF tau	**.439 (.129, .750)** **	**1.55 (1.13, 2.12)** **		

** $p < .01$

*** $p < .001$

**** $p < .0001$

Table 5

Beta Weights for the Personality-Conversion Relationship as Mediated by Biomarkers as a Function of Self and Informant Reports

Self-Report								
	Amyloid		**Hippocampal Vol**		**CSF Aβ42**		**CSF tau**	
	Direct	**Indirect**	**Direct**	**Indirect**	**Direct**	**Indirect**	**Direct**	**Indirect**
Neuroticism	.110	−.010	.099	.027	.132	−.007	.113	.012
Conscientiousness	**−.246****	.012	**−.236****	−.015	**−.256****	.018	**−.261****	.010
Informant Report								
	Amyloid		**Hippocampal Vol**		**CSF Aβ42**		**CSF tau**	
	Direct	**Indirect**	**Direct**	**Indirect**	**Direct**	**Indirect**	**Direct**	**Indirect**
Neuroticism	.001	−.023	−.015	.032	.043	−.026	.008	.009
Conscientiousness	**−.250****	.024	**−.253***	−.012	**−.285****	.020	**−.277****	.011

Note: The direct effect represents the direct relationship between neuroticism/conscientiousness and conversion. The indirect effect represents the relationship between neuroticism/conscientiousness and conversion, mediated by each biomarker.

* $p < .05$

** $p < .01$