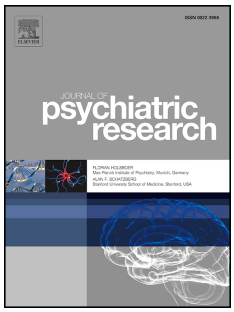
Title: Relations between personality changes and cerebrospinal fluid biomarkers of Alzheimer's disease pathology.
Authors: Tautvydaitė D, Antonietti JP, Henry H, von Gunten A, Popp J
Journal: Journal of psychiatric research
Year: 2017 Feb 4
Volume: 90
Pages: 12-20
DOI: 10.1016/j.jpsychires.2016.12.024

Accepted Manuscript



Relations between personality changes and cerebrospinal fluid biomarkers of Alzheimer's disease pathology

D. Tautvydaitė, J.P. Antonietti, H. Henry, A. von Gunten, J. Popp

PII: S0022-3956(16)30199-6

DOI: 10.1016/j.jpsychires.2016.12.024

Reference: PIAT 3053

To appear in: *Journal of Psychiatric Research*

Received Date: 8 August 2016

Revised Date: 15 December 2016

Accepted Date: 16 December 2016

Please cite this article as: Tautvydaitė D, Antonietti JP, Henry H, von Gunten A, Popp J, Relations between personality changes and cerebrospinal fluid biomarkers of Alzheimer's disease pathology, *Journal of Psychiatric Research* (2017), doi: 10.1016/j.jpsychires.2016.12.024.

Relations between personality changes and cerebrospinal fluid biomarkers of Alzheimer's disease pathology

D Tautvydaitė [a], JP Antonietti [b], H Henry [c], A von Gunten [a], and J Popp [a]

[a] *Department of Psychiatry, Service of Old Age Psychiatry, Lausanne University Hospital (CHUV), Lausanne, Switzerland;* [b] *Institute of Psychology, University of Lausanne, Lausanne, Switzerland;* [c] *Service of Biomedicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland*

Corresponding author:

Dr. Julius Popp, MD

Email: julius.popp@chuv.ch

Tel. +41 (0)21 314 5151

Fax. 021 314 11 15

Address:

Dr. Julius Popp, MD

Service universitaire de psychiatrie de l'âge avancé (SUPAA)

Département de psychiatrie

Route du Mont - 1008 Prilly

Switzerland

Abstract

Specific changes in personality profiles may represent early non-cognitive symptoms of Alzheimer's disease (AD). Evaluating the subject's personality changes may add significant clinical information, as well as help to better understand the interaction between personality change, cognitive decline, and cerebral pathology. With this study we aimed to describe the relationship between personality changes and cerebrospinal fluid (CSF) markers of AD pathology at early clinical stages of the disease. One hundred and ten subjects, of whom 66 cognitively impaired patients (57 with mild cognitive impairment (MCI), and 9 with mild dementia) and 44 healthy controls, had neuropsychological examination as well as lumbar puncture to determine concentrations of CSF biomarkers of AD pathology (amyloid beta$_{1-42}$ (Aβ_{1-42}), phosphorylated tau (ptau-181), and total-tau (tau)). The Revised NEO Personality Inventory (NEO-PI-R) was administered twice, once to evaluate subjects' current personality and once to assess personality traits retrospectively 5 years before evaluation. Subjects with an AD CSF biomarker profile showed significant increase in neuroticism and decrease in conscientiousness over time as compared to non-AD CSF biomarker group. In regression analysis controlling for global cognition as measured by the MMSE score, increasing neuroticism and decreasing extraversion, openness to experience and conscientiousness were associated with lower Aβ_{1-42} concentrations but not with tau and ptau-181 concentrations. Our findings suggest that early and specific changes in personality are associated with cerebral AD pathology. Concentrations of CSF biomarkers, additionally to severity of the cognitive impairment, significantly contribute in predicting specific personality changes.

Keywords: Personality changes; cerebrospinal fluid biomarkers; Revised NEO Personality Inventory (NEO-PI-R); Alzheimer's disease (AD); mild cognitive impairment (MCI)

1. Introduction

With the rising number of elderly people suffering from Alzheimer's disease (AD), it is of high clinical importance to investigate and address its early clinical changes. Patients with mild cognitive impairment (MCI) are characterized by a noticeable decline in cognitive abilities, which is relatively greater than normal age-related change observed in healthy population, and have increased risk of developing AD dementia during the following year (Petersen et al., 1999; Winblad et al., 2004).

Neuropathological changes, in particular the cerebral accumulation of amyloid pathology, tau hyper-phosphorylation, and neuronal injury precede the first symptoms of dementia by years (Jack Jr et al., 2013; Jansen et al., 2015) and are paralleled by decreasing concentrations of amyloid beta 1-42 ($A\beta_{1-42}$), and increasing of tau phosphorylated at threonine 181 (ptau-181) and total tau (tau) in the cerebrospinal fluid (CSF), respectively, at the pre-symptomatic and the MCI stages). The presence of both amyloid and tau pathology is required to consider an individual as having AD pathology and the ratios of CSF tau/$A\beta_{1-42}$ and ptau/$A\beta_{1-42}$ (or $A\beta_{1-42}$/tau and $A\beta_{1-42}$/ptau) have been shown to outperform single markers in identifying subjects with dementia due to AD and predicting cognitive decline in subjects with MCI (Duits et al., 2014).

Cognitive decline and progress to dementia is accompanied by personality changes that occur alongside and sometimes manifest before the cognitive symptoms (Balsis et al., 2005; von Gunten et al., 2009). Personality traits represent individual tendencies to think, feel and behave in certain ways that affect the individual's interactions with external world (Krueger et al., 2000). The five-factor model (Goldberg, 1990) (Costa Jr and McCrae, 1990) is a widely used model describing human personality along the dimensions of neuroticism, extraversion, openness to experiences, agreeableness, and conscientiousness. Studies report that these personality traits remain stable across the life span (Costa Jr and McCrae, 1992; Costa et al., 2000), but can be modified in relation to brain changes resulting from neurological diseases

(Duberstein et al., 2011; Terracciano et al., 2005; Wang et al., 2009). A systematic review on personality changes in AD dementia found increase in neuroticism, and decrease in extraversion, openness, agreeableness and conscientiousness (Robins Wahlin and Byrne, 2011). Recently, changes in conscientiousness and neuroticism were found in clinically diagnosed AD dementia (Pocnet et al., 2013). Similar results were reported in subjects with MCI compared to controls: MCI subjects showed decreased conscientiousness and extraversion and increased neuroticism (Donati et al., 2013). However, patients with MCI represent a heterogeneous group regarding the aetiology of cognitive impairment and only a part of them may have cerebral AD pathology and develop AD dementia over time. None of the previous studies included clinical follow-up or biomarkers of disease pathology to confirm the diagnosis of AD, and to address the question whether the observed personality changes are due to cognitive impairment of different aetiologies or may be more specifically related to AD pathology. Information about changes in personality is accessible through questionnaires completed by patients relatives, and do not involve any invasive techniques. Evaluating the subject's personality changes may add significant clinical information (Balsis et al., 2005), as well as help to better understand the interaction between personality change, cognitive decline, and cerebral pathology. With this study we aim to explore the relations between changes in personality and CSF biomarkers of AD pathology.

2. Material and Method

2.1 Sample

One hundred and ten community dwelling participants were included in this study, of whom 44 were cognitively healthy volunteers and 66 had mild cognitive impairment (MCI, N=57) or mild dementia (N=9). The participants with cognitive impairment were recruited among patients attending the Memory clinics of the Department of psychiatry and the Department of clinical neurosciences at the Lausanne University Hospital. The patients had no major psychiatric or neurological disorders, nor substance abuse

or severe or unstable physical illness that explained cognitive impairment. Healthy subjects were recruited in the community through journal announcements and word of mouth. All participants had a comprehensive medical, psychiatric, neuropsychological and psychosocial evaluation, as well as brain MRI or CT scans and venous and lumbar puncture. The MRI and CT scans were used in order to exclude patients with cerebral pathologies possibly interfering with cognitive performance, including relevant vascular damages.

2.2 Procedure

The study was approved by the Ethics Committee of the Faculty of Biology and Medicine of the University of Lausanne. The aims of the research project were clearly explained to all participants and the informed written consent to participate in the study was administered and signed by all. Clinical data from a part of the participants (N=41) was also considered in two previous publications (Pocnet et al., 2013) (Donati et al., 2013).

Diagnosis of MCI or mild dementia was based on neuropsychological and clinical evaluation and was made at a consensus conference of psychiatrists, neuropsychologists, and/or neurologists prior to inclusion into the study. MCI was diagnosed according to widely used consensus recommendations (Winblad et al., 2004). The participants in this group had memory impairment (<–1.5 standard deviation (SD) below the means adjusted for gender, age and education in the verbal memory task of Buschke Double Memory Test (Buschke et al., 1997)) and/or impairment in another cognitive domain, and a Clinical Dementia Rating Scale (CDR) (Morris, 1993) score of 0.5. The diagnosis of probable AD dementia was based on the clinical diagnostic criteria for probable dementia due to AD according to recommendations from the National Institute on Aging and Alzheimer's Association (McKhann et al., 2011) and DSM-IV criteria for dementia of the Alzheimer type (American-Psychiatric-Association, 1994). Participants in this group had a CDR score of 1. The control subjects had no history or evidence of cognitive impairment, and their CDR score was 0.

The CDR is a semi-structured, clinician-rated interview with the patient and an appropriate informant, widely used to assess the progression of dementia. It is based on the ratings of the patient's cognitive and functional impairment in 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Morris, 1993). Scores in each of area range from 0 to 3, representing "none" to "severe" impairment. CDR has a very high interrater reliability (Rockwood et al., 2000) and thus appears to be a reliable and valid measurement for assessing cognitive performance stages in dementia.

2.3 CSF biomarkers and APOE genotyping

Venous and lumbar punctures were performed between 8:30 and 9:30 am after overnight fasting at the recruiting Memory centres. CSF was collected by lumbar puncture, using a standardized technique with a 22G "atraumatical" spinal needle while the patient was sitting or lying (Popp et al., 2007). Ten to twelve ml of CSF were obtained using polypropylene tubes. Routine cell count and protein quantification were performed. Remaining CSF was frozen in aliquots and stored at -80 °C until assay. We measured $A\beta_{1-42}$, tau, and ptau-181 concentrations with ELISA kits, using commercially available assays (Fujirebio, Gent, Belgium). A pathological CSF AD biomarker profile was defined as a ptau-181/$A\beta_{1-42}$ ratio >0.078, based on previous analysis of center data and published recommendations (Duits et al., 2014; Molinuevo et al., 2014). The centre cut-off was determined in a previous unpublished study using data from 120 subjects (48 healthy volunteers with normal cognition and 72 memory clinic patients with MCI or mild dementia of AD type) as the value that optimized the Youden index of the Received Operating Characteristic (ROC) curve of prediction for CDR categories (CDR = 0 vs. CDR > 0). The cut-off was further shown to be a highly significant predictor of cognitive decline after controlling for multiple possible confounders (unpublished data).

Carrying the APOEε4 allele is the strongest known genetic risk factor for sporadic AD. It may influence the relationships between AD pathology, personality and clinical manifestations (Dar-Nimrod et al., 2012), and accelerate the generation of amyloid pathology at very early disease stages (Jansen et al., 2015; Popp et al., 2010). Accordingly, the APOE genotype was determined and considered to evaluate possible interactions and effects on the addressed relationships. Leukocyte genomic DNA was isolated from EDTA blood with the Qiagen blood isolation kit (Qiagen, Hilden, Germany) and the APOE genotype was determined on the LightCycler (Roche Diagnostics, Basel, Switzerland).

2.4 Neuropsychological and functional assessment

Neuropsychological tests were used to assess cognitive performance in the domains of memory (spontaneous and cued-recall 48-item task (Van der Linden and Adam, 2004), executive function (a verbal fluency task (categorical and literal fluency in 2 min), a flexibility task - the Trail Making Test A and B (Reitan, 1958), and an inhibition task - the Stroop test (Bayard et al., 2009), and visuospatial functions (CERAD copy image test). The MMSE (Folstein et al., 1975) was used to assess participants' cognitive level. Depression and anxiety were assessed using the Hospital Anxiety and Depression scale (HAD) (Zigmond and Snaith, 1983). Cognitive complaints questionnaire (Questionnaire de Plainte Cognitive, QPC, (Thomas-Antérion et al., 2004; Thomas-anterion et al., 2004)) was employed to evaluate participants' memory failures and cognitive complaints.

Psychosocial and functional assessment included the ADL (Katz, 1997) and instrumental ADL (Lawton and Brody, 1970), the NPIQ (Cummings et al., 1994), and the IQCODE (Jorm and Jacomb, 1989) questionnaires, completed by the family members of the participants. All tests and scales are validated and widely used in the field.

2.5 Personality assessment

Patients' proxies were asked to complete the NEO Personality Inventory Revised (NEO-PIR, Form R (Costa and MacCrae, 1992)), which is based on the FFM (Costa Jr and McCrae, 1990). This dimensional personality model derived from factor analyses performed on a large number of self- and peer reports on personality-relevant adjectives and questionnaire items (Costa Jr and McCrae, 1990), that revealed five dimensions describing personality, i.e. neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Each of these dimensions is composed of six subcomponents or facets (see Table A in Annexes for description of the domain and facet scales). The NEO-PI-R is a questionnaire composed of 240 items and used for peer ratings which has well-established reliability and validity data in older populations (McCrae and Costa, 1987). In our study, each informant completed the NEO-PI-R twice, once to describe the patient as he/she was 5 years prior to the inclusion, and once to describe the participant at the time of the study.

2.6 Statistical analyses

The data was analysed using SPSS, version 20, and R (R Development Core Team, 2009). To characterize and compare the cognitively impaired (CI, including patients with MCI and mild dementia) and control groups we applied descriptive statistics (Cohen, 2013), Mann-Whitney test (Field, 2013) and chi-square test for non-normally distributed data and Student's t-test for independent samples. Comparison of personality changes between subjects who have non pathological CSF biomarker levels (non-AD CSF group) and those who have pathological CSF biomarker levels (AD CSF group) was performed using Welch's t-test (Welch, 1938) and also Mann-Whitney test. The change in personality was computed by subtracting the retrospective from the current scores. To screen for relations between personality changes and cerebral pathology we counted correlations for the change in each NEO-PI-R domain and each biomarker. Further, series of linear regressions were conducted for the CI and control groups combined to determine whether CSF biomarker concentrations predict changes in personality. We included MMSE score

and CSF biomarker level in our model as predictors and change in each personality domain separately as dependent variable. In order to control for influential observations in our data we further performed the robust regression on the same variables. To assign the measures of accuracy we applied ordinary non-parametric bootstrapping. We then performed series of regressions where we included the change in each personality domain as dependent variable and age, gender, MMSE score, and concentrations of CSF biomarkers as predictors.

3. Results

Descriptive statistics of the sample are shown in Table 1. The CI and control groups differed significantly in age and APOEε4 status. There were significantly more females than males in the control group, although gender distribution in the CI group was equal. The mean MMSE score was relatively high in the subjects with CI (26.0 points) suggesting a very mild impairment in global cognitive performance in this group. The HAD depression and anxiety scores were similar in both groups. Furthermore, participants in CI group scored significantly higher than controls on QPC and IQ-code questionnaires.

3.1 Personality change and CSF biomarker concentrations among CI and control groups

The concentration of CSF biomarkers was significantly different in two groups (see Table 1). The concentrations of tau, ptau-181, and the tau/$A\beta_{1-42}$ and ptau-181/$A\beta_{1-42}$ ratios were significantly higher in the CI group than in healthy controls, while $A\beta_{1-42}$ level was lower in the CI group compared to controls.

The personality changes in the CI group were markedly different from those in the control group. The mean personality change score was increased in neuroticism, decreased in extraversion, agreeableness, and conscientiousness for the CI group compared to the healthy controls (table 2). Effect sizes were larger for neuroticism and conscientiousness than for the other traits. Concerning retrospective personality scores, openness to experience was significantly lower in CI group compared to controls. Current per-

sonality scores between the two groups differed in domains of extraversion, openness to experience and conscientiousness (see table 2).

3.2 Personality changes and CSF biomarkers

Subjects with an AD biomarker profile had lower anxiety and MMSE score, but did not differ in depression score (see table 3). Mann-Whitney test performed on changes in personality domains score revealed significant increase in neuroticism and decrease in conscientiousness in the AD CSF group compared to non-AD CSF group (see table 3, figure 1).

We further performed a correlation analysis which revealed robust relationships between changes in personality domains and cerebral pathology as measured by the CSF biomarkers (see table 5).

Multiple linear regression models, including MMSE score, $A\beta_{1-42}$ concentrations, tau concentrations as predictors and change in each personality dimension separately as dependent variables, revealed that increase in domain of neuroticism was predicted by lower MMSE score (β = -0.822, $p < .05$) and lower $A\beta_{1-42}$ concentrations (β = -0.011, $p < .05$). The decrease in extraversion was only predicted by lower $A\beta_{1-42}$ concentrations (β = 0.01, $p < .01$), and not by MMSE score (β = 0.577, p = 0.09). Both lower MMSE score and lower levels of $A\beta_{1-42}$ contributed significantly to decrease in conscientiousness (β = 2.375, $p < .001$; β = 0.012, $p < .05$ respectively). Decrease in agreeableness was predicted by lower MMSE score (β = 0.047, $p < .05$), and not by $A\beta_{1-42}$ concentrations (β = -0.0002, p = 0.9). The concentrations of tau did not reach significant level in predicting changes in any of the personality domains. Those results were confirmed by robust linear regression model (see table 4a) and by bootstrapping procedure.

Similar results were obtained when including ptau concentrations instead of tau concentrations as predictor (see table 4b for model estimates). Additionally to the results described previously, in the model with ptau levels, the decrease in openness to experience was associated to lower $A\beta_{1-42}$ levels (β = 0.004, $p < .05$), although this association was not confirmed by robust regression. The ptau levels did not con-

tribute in explaining any of personality domains. Robust linear regression and bootstrapping procedure confirmed those results.

In the regression analysis including age, gender, MMSE score, $A\beta_{1-42}$, tau, or ptau) concentrations the $A\beta_{1-42}$ concentrations were positively associated with changes in neuroticism ($F=5.481$, $p<0.001$; $\beta=-0.234$, $p=0.024$) , extraversion ($F=5.195$, $p=0.001$; $\beta=0.307$, $p=0.003$),openness to experience ($F=2.935$, $p=0.024$; $\beta=0.238$, $p=0.027$), and conscientiousness ($F=12.386$, $p<0.001$; $\beta=0.206$, $p=0.028$). The tau and ptau levels did not contribute in predicting personality changes.

4. Discussion

In this study we found that biomarkers of AD pathology are associated with specific changes in personality domains. Subjects with pathological CSF biomarker levels show increase in neuroticism and decrease in conscientiousness as compared to subjects with normal CSF biomarker levels. Furthermore, lower $A\beta_{1-42}$ concentrations independently contribute in predicting increasing levels of neuroticism, and decreasing levels of extraversion and conscientiousness when controlling for global cognitive performance.

When comparing CI and control groups we found that in CI subjects neuroticism increased, while extraversion, conscientiousness and agreeableness decreased over the 5 years period prior to the cognitive assessment. These findings are in line with studies that investigated the association between changes in personality and cognitive impairment and dementia in the elderly. Personality changes towards higher neuroticism and lower extraversion, conscientiousness and openness to experience have been observed in memory-impaired subjects (Siegler et al. (1991). Patients with clinically diagnosed AD dementia have been shown to undergo significant personality changes as reported by the patients' caregivers, the most consistently reported being decreases in conscientiousness and extroversion, and increase in neuroticism (Chatterjee et al., 1992; Pocnet et al., 2013). Likewise, changes in the same personality domains were observed in subjects with MCI (Donati et al., 2013). Together, these findings suggest a predictable

direction of personality changes in subjects with MCI and dementia. Results coming from our study confirm this pattern of changes.

The evolution of personality over the life span has been explored by several longitudinal studies and personality was shown to keep a certain stability in adulthood and throughout normal ageing (Haan et al., 1986; McCrae and Costa, 1987) except for slight possible changes including a decrease in extraversion and an increase in agreeableness (Field and Millsap, 1991). In dementia, changes in agreeableness may follow the opposite direction when compared to normal ageing while changes in extraversion follow the same direction (Robins Wahlin and Byrne, 2011). Our study not only shows that there is a distinctive pattern of personality changes in subjects with cognitive impairment, but it also reveals that this pattern is specific and is associated with concentrations of CSF markers reflecting AD pathology. Intriguingly, we observed associations of personality changes with $A\beta_{1-42}$, but we did not find any association with the tau and ptau-181 levels. While the tau/$A\beta_{1-42}$ and ptau-181/$A\beta_{1-42}$ ratios may be considered as markers of concomitant cerebral AD pathology (amyloid pathology and tau-related neurodegeneration), their associations with personality changes seem to be largely due to associations with the $A\beta_{1-42}$ concentrations. The lack of associations with tau and ptau181 levels in the multivariate models does not exclude relationships with personality changes. In particular, our observation of correlations between both tau and ptau-181 levels and changes in neuroticism diserves investigation in future studies. Regarding the robust associations of personality changes with $A\beta_{1-42}$, we can only speculate about their underlying mechanisms. One possible explanation is that personality changes may start very early in the clinical course of AD, along with very subtle cognitive changes that have been recently described to be associated with amyloid pathology (Petersen et al., 2016), while changes in tau and ptau-181 concentrations are still ongoing and, hence, at an intermediate level (Jack Jr et al., 2013). Interestingly, a recent study found associations between cerebral amyloid pathology as measured by Pittsburgh compound B (PiB)-PET imaging and cognitive complaints in cognitively unimpaired subjects with high neuroticism (Snitz et al.,

2015) while another study in subjects with MCI reported an association between amyloid pathology and anxiety (Bensamoun et al., 2015). In our study, anxiety score did not differ between CI and control groups but was lower in the AD CSF group as compared to the non-AD CSF participants. This last finding might have emerged from the fact that the group with a non-AD CSF profile included both CI and control subjects. Depression and anxiety symptoms may in part explain cognitive impairment in this group, and their relative contribution may be higher as compared to the group of participants with an AD CSF profile.There may be different explanations for the observed personality changes in patients developing cognitive impairment and dementia. Some researchers emphasize the role of premorbid personality in modulating the risk of cognitive impairment in later life. For example, a study showed an association between higher levels of premorbid conscientiousness and reduction in MCI and AD incidence, as well as with reduced cognitive decline (Wilson et al., 2007). In a longitudinal study in subjects confirmed post-mortem to have AD neuropathology, greater scores on conscientiousness and lower scores on neuroticism were associated with a reduced risk or delay to develop clinical dementia (Terracciano et al., 2013). Thus, lower conscientiousness may represent an increased vulnerability, while lower neuroticism suggests an increased resilience of developing clinical dementia, even among people with AD neuropathology. Premorbid personality may thus be acting as a determinant factor so that the original personality changes as AD advances (Welleford et al., 1995). Furthermore, lower consciousness and higher neuroticism is also associated with greater vulnerability to metabolic syndrome (Sutin et al., 2010a), inflammatory risk profile (Sutin et al., 2010b), smaller volume of medio-temporal and prefrontal regions and greater decline in volume with advancing age (Jackson et al., 2011), and with severity of white matter lesions in MCI patients (Duron et al., 2014). While premorbid personality characteristics may influence the risk of developing cerebral pathology and related cognitive impairment, changes in personality may represent the adaptive reaction to the individual's experience of cognitive and functional impairment or may be more directly related to developing cerebral pathology, or both. Our findings show for the first

time that specific changes in personality domains, more precisely, increasing neuroticism and decreasing extraversion and conscientiousness are predicted not only by severity of cognitive impairment, but also by cerebral amyoid pathology as measured by the CSF $A\beta_{1-42}$.

Concerning the APOEε4 factor, one previous study showed that the carriers of APOEε4 with high scores on neuroticism and extraversion had poorer cognitive functioning and higher incidence of AD compared to APOEε4 carriers with lower neuroticism and extraversion scores (Dar-Nimrod et al. (2012). Terracciano et al. (2014) found that including APOE ε4 allele as an additional covariate did not moderate the association between personality and increased AD incident. In our study, APOEε4 status, as expected, differed significantly across clinical and control groups, but was not associated with changes in personality domains.

The main strengths of our study are the usage of validated instruments, the comprehensive personality and clinical assessment and the inclusion of factors with established effects on the relationship between cerebral pathology and clinical manifestations. One limitation is that the personality traits were not assessed objectively, since the questionnaire to assess personality characteristics was filled by the subjects' proxies. In addition, evaluating subjects' premorbid personality retrospectively does not necessarily provide reliable descriptions, as it may be influenced by the impact of the cognitive decline on the personal relationship between caregiver and patient. Although personality description made by participants' relatives may be considered as subjective and not reliable, this approach corresponds to clinical practice when investigating cognitive decline in single patients. Some of the predictive biomarkers effect on personality change faded when taking into account age, gender, cognitive status, and APOEε4 status as covariate variables. The reason for this might be that the regression models controlled for many variables, and the sample size might not be large enough to detect the effects of biomarkers on the changes of some personality domains. While the comprehensive personality assessment by the NEO-PI-R may be

too time consuming to be used in clinical practice, short instruments focussing on specific personality changes, notably in domains of neuroticism, extraversion and conscientiousness, may be considered when examining elderly patients with cognitive decline.

5. Conclusions

Subjects with cognitive decline undergo early and specific personality changes as compared to healthy controls. There is an association between cerebral AD pathology, as measured by CSF biomarkers and specific changes in personality characteristics, in particular in neuroticism, extraversion and conscientiousness. Our findings suggest that in elderly subjects there is a specific pattern of personality changes related to cerebral amyloid and tau pathology. Likely to be more than a behavioural and emotional reaction to cognitive decline, personality changes may represent the manifestation of AD pathology at early clinical disease stages. Further studies with larger sample are needed in order to confirm these findings and their potential clinical implications, and to better understand the nature of personality changes in relation to brain pathology.

6. Declarations

6.1 List of abbreviations

$A\beta_{1-42}$	Amyloid-β_{1-42}
AD	Alzheimer's disease
ADL	Activities of daily living
APOEε4	ε4 allele of the Apolipoprotein E
CDR	Clinical Dementia Rating Scale
CI	Cognitive Impairment
CSF	Cerebrospinal fluid

DSM	Diagnostic and Statistical Manual of Mental Disorders
FFM	Five-Factor Model
HAD	Hospital Anxiety and Depression Scale
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
MMSE	Mini-Mental State Examination
ml	Millilitre
NEO-PI-R	Revised NEO Personality Inventory
NPI	Neuropsychiatric Inventory
ptau-181	Phosphorylated tau
SD	Standard deviation
tau	total-tau

6.2 Ethics approval and consent to participate

This study was approved by the local ethics committee (Commission cantonale Vaud d'éthique de la recherche sur l'être humain; reference number: 171/13) and informed consent was obtained from all study participants.

6.3 Consent for publication

Not applicable.

6.4 Competing interests

The authors declare no conflict of interest.

6.5 Funding

This study was supported by the Swiss National Research Foundation (grant number: FNS 3200B0-122263 to AG and FNS 320030-14117 to JP).

7. References

American-Psychiatric-Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Press, Washington, DC.

Balsis, S., Carpenter, B.D., Storandt, M., 2005. Personality change precedes clinical diagnosis of dementia of the Alzheimer type. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences 60(2), P98-P101.

Bayard, S., Erkes, J., Moroni, C., 2009. Test du Stroop Victoria-Adaptation francophone. CPCN-LR, Gignac.

Bensamoun, D., Guignard, R., Furst, A.J., Derreumaux, A., Manera, V., Darcourt, J., Benoit, M., Robert, P.H., David, R., 2015. Associations between Neuropsychiatric Symptoms and Cerebral Amyloid Deposition in Cognitively Impaired Elderly People. J. Alzheimers Dis. 49(2), 387-398.

Buschke, H., Sliwinski, M.J., Kuslansky, G., Lipton, R.B., 1997. Diagnosis of early dementia by the Double Memory Test: encoding specificity improves diagnostic sensitivity and specificity. Neurology 48(4), 989-997.

Chatterjee, A., Strauss, M.E., Smyth, K.A., Whitehouse, P.J., 1992. Personality changes in Alzheimer's disease. Arch. Neurol. 49(5), 486-491.

Cohen, J., 2013. Statistical power analysis for the behavioral sciences. Academic press.

Costa Jr, P., McCrae, R., 1992. Psychological research in the Baltimore Longitudinal Study of Aging. Z. Gerontol. 26(3), 138-141.

Costa Jr, P.T., McCrae, R.R., 1990. Personality disorders and the five-factor model of personality. Journal of personality disorders 4(4), 362-371.

Costa, P.T., Herbst, J.H., McCrae, R.R., Siegler, I.C., 2000. Personality at midlife: Stability, intrinsic maturation, and response to life events. Assessment 7(4), 365-378.

Costa, P.T., MacCrae, R.R., 1992. Revised NEO personality inventory (NEO PI-R) and NEO five-factor inventory (NEO FFI): Professional manual. Psychological Assessment Resources.

Cummings, J.L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D.A., Gornbein, J., 1994. The Neuropsychiatric Inventory comprehensive assessment of psychopathology in dementia. Neurology 44(12), 2308-2308.

Dar-Nimrod, I., Chapman, B.P., Franks, P., Robbins, J., Porsteinsson, A., Mapstone, M., Duberstein, P.R., 2012. Personality Factors Moderate the Associations Between Apolipoprotein Genotype and Cognitive Function as Well as Late Onset Alzheimer Disease. The American Journal of Geriatric Psychiatry 20(12), 1026-1035.

Donati, A., Studer, J., Petrillo, S., Pocnet, C., Popp, J., Rossier, J., von Gunten, A., 2013. The evolution of personality in patients with mild cognitive impairment. Dement. Geriatr. Cogn. Disord. 36(5-6), 329-339.

Duberstein, P.R., Chapman, B.P., Tindle, H.A., Sink, K.M., Bamonti, P., Robbins, J., Jerant, A.F., Franks, P., 2011. Personality and risk for Alzheimer's disease in adults 72 years of age and older: a 6-year follow-up. Psychol. Aging 26(2), 351.

Duits, F.H., Teunissen, C.E., Bouwman, F.H., Visser, P.J., Mattsson, N., Zetterberg, H., Blennow, K., Hansson, O., Minthon, L., Andreasen, N., Marcusson, J., Wallin, A., Rikkert, M.O., Tsolaki, M., Parnetti, L., Herukka, S.K., Hampel, H., De Leon, M.J., Schroder, J., Aarsland, D., et al., 2014. The cerebrospinal fluid "Alzheimer profile": easily said, but what does it mean? Alzheimer's & dementia : the journal of the Alzheimer's Association 10(6), 713-723.e712.

Duron, E., Vidal, J.-S., Bounatiro, S., Ben Ahmed, S., Seux, M.-L., Rigaud, A.-S., Hanon, O., Viollet, C., Epelbaum, J., Martel, G., 2014. Relationships between personality traits, medial temporal lobe atrophy, and white matter lesion in subjects suffering from mild cognitive impairment. Front. Aging Neurosci. 6, 195.

Field, A., 2013. Discovering statistics using IBM SPSS statistics. Sage.
Field, D., Millsap, R.E., 1991. Personality in advanced old age: continuity or change? J. Gerontol. 46(6), P299-P308.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12(3), 189-198.
Galasko, D., Chang, L., Motter, R., Clark, C., Kaye, J., Knopman, D., Thomas, R., Kholodenko, D., Schenk, D., Lieberburg, I., 1998. High cerebrospinal fluid tau and low amyloid β42 levels in the clinical diagnosis of Alzheimer disease and relation to apolipoprotein E genotype. Arch. Neurol. 55(7), 937-945.
Goedert, M., Spillantini, M., Crowther, R., 1991. Tau proteins and neurofibrillary degeneration. Brain Pathol. 1(4), 279-286.
Goldberg, L.R., 1990. An alternative" description of personality": the big-five factor structure. J. Pers. Soc. Psychol. 59(6), 1216.
Haan, N., Millsap, R., Hartka, E., 1986. As time goes by: Change and stability in personality over fifty years. Psychol. Aging 1(3), 220.
Hardy, J., Allsop, D., 1991. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol. Sci. 12, 383-388.
Iqbal, K., Alonso, A.d.C., Chen, S., Chohan, M.O., El-Akkad, E., Gong, C.-X., Khatoon, S., Li, B., Liu, F., Rahman, A., 2005. Tau pathology in Alzheimer disease and other tauopathies. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1739(2), 198-210.
Jack Jr, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski, J.Q., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. The Lancet Neurology 12(2), 207-216.
Jack Jr, C.R., Knopman, D.S., Jagust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., Petersen, R.C., Trojanowski, J.Q., 2010. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. The Lancet Neurology 9(1), 119-128.
Jackson, J., Balota, D.A., Head, D., 2011. Exploring the relationship between personality and regional brain volume in healthy aging. Neurobiol. Aging 32(12), 2162-2171.
Jansen, W.J., Ossenkoppele, R., Knol, D.L., Tijms, B.M., Scheltens, P., Verhey, F.R., Visser, P.J., Aalten, P., Aarsland, D., Alcolea, D., Alexander, M., Almdahl, I.S., Arnold, S.E., Baldeiras, I., Barthel, H., van Berckel, B.N., Bibeau, K., Blennow, K., Brooks, D.J., van Buchem, M.A., et al., 2015. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA : the journal of the American Medical Association 313(19), 1924-1938.
Jorm, A., Jacomb, P., 1989. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol. Med. 19(04), 1015-1022.
Katz, I.R., 1997. Diagnosis and treatment of depression in patients with Alzheimer's disease and other dementias. The Journal of clinical psychiatry 59, 38-44.
Krueger, R.F., Caspi, A., Moffitt, T.E., 2000. Epidemiological Personology: The Unifying Role of Personality in Population‐Based Research on Problem Behaviors. J. Pers. 68(6), 967-998.
Lawton, M., Brody, E.m., 1970. Assessment Of Older People: Self-Maintaining And Instrumental Activities Of Daily Living. Nurs. Res. 19(3), 278.
Mayer, J.D., 2007. Asserting the definition of personality. The online newsletter for personality science 1, 1-4.
McCrae, R.R., Costa, P.T., 1987. Validation of the five-factor model of personality across instruments and observers. J. Pers. Soc. Psychol. 52(1), 81.

McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R., Jr., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 7(3), 263-269.

Mischel, W., Shoda, Y., & Smith, R. E, 2004. Introduction to personality: Toward an integration. John Wiley & Sons., New York

Molinuevo, J.L., Blennow, K., Dubois, B., Engelborghs, S., Lewczuk, P., Perret-Liaudet, A., Teunissen, C.E., Parnetti, L., 2014. The clinical use of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper from the Alzheimer's Biomarkers Standardization Initiative. Alzheimer's & dementia : the journal of the Alzheimer's Association 10(6), 808-817.

Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology.

Mudher, A., Lovestone, S., 2002. Alzheimer's disease – do tauists and baptists finally shake hands? Trends Neurosci. 25(1), 22-26.

Olsson, B., Lautner, R., Andreasson, U., Öhrfelt, A., Portelius, E., Bjerke, M., Hölttä, M., Rosén, C., Olsson, C., Strobel, G., 2016. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. The Lancet Neurology 15(7), 673-684.

Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J. Intern. Med. 256(3), 183-194.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 56(3), 303-308.

Petersen, R.C., Wiste, H.J., Weigand, S.D., Rocca, W.A., Roberts, R.O., Mielke, M.M., Lowe, V.J., Knopman, D.S., Pankratz, V.S., Machulda, M.M., 2016. Association of elevated amyloid levels with cognition and biomarkers in cognitively normal people from the community. JAMA neurology 73(1).

Pocnet, C., Rossier, J., Antonietti, J.-P., von Gunten, A., 2013. Personality features and cognitive level in patients at an early stage of Alzheimer's disease. Pers. Individ. Dif. 54(2), 174-179.

Popp, J., Lewczuk, P., Frommann, I., Kolsch, H., Kornhuber, J., Maier, W., Jessen, F., 2010. Cerebrospinal fluid markers for Alzheimer's disease over the lifespan: effects of age and the APOEepsilon4 genotype. Journal of Alzheimer's disease : JAD 22(2), 459-468.

Popp, J., Riad, M., Freymann, K., Jessen, F., 2007. [Diagnostic lumbar puncture performed in the outpatient setting of a memory clinic. Frequency and risk factors of post-lumbar puncture headache]. Nervenarzt 78(5), 547-551.

R Development Core Team, 2009. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Reitan, R.M., 1958. Validity of the Trail Making Test as an indicator of organic brain damage. Percept. Mot. Skills 8(3), 271-276.

Robins Wahlin, T.B., Byrne, G.J., 2011. Personality changes in Alzheimer's disease: a systematic review. Int. J. Geriatr. Psychiatry 26(10), 1019-1029.

Rockwood, K., Strang, D., MacKnight, C., Downer, R., Morris, J.C., 2000. Interrater reliability of the Clinical Dementia Rating in a multicenter trial. J. Am. Geriatr. Soc. 48(5), 558-559.

Siegler, I.C., Welsh, K.A., Dawson, D.V., Fillenbaum, G.G., Earl, N.L., Kaplan, E.B., Clark, C.M., 1991. Ratings of personality change in patients being evaluated for memory disorders. Alzheimer Dis. Assoc. Disord. 5(4), 240-250.

Snitz, B.E., Weissfeld, L.A., Cohen, A.D., Lopez, O.L., Nebes, R.D., Aizenstein, H.J., McDade, E., Price, J.C., Mathis, C.A., Klunk, W.E., 2015. Subjective Cognitive Complaints, Personality and Brain Amyloid-beta in Cognitively Normal Older Adults. The American Journal of Geriatric Psychiatry.

461 Sunderland, T., Linker, G., Mirza, N., Putnam, K.T., Friedman, D.L., Kimmel, L.H., Bergeson, J., Manetti,
462 G.J., Zimmermann, M., Tang, B., 2003. Decreased β-amyloid1-42 and increased tau levels in
463 cerebrospinal fluid of patients with Alzheimer disease. JAMA 289(16), 2094-2103.
464 Sutin, A.R., Costa Jr, P.T., Uda, M., Ferrucci, L., Schlessinger, D., Terracciano, A., 2010a. Personality and
465 metabolic syndrome. Age 32(4), 513-519.
466 Sutin, A.R., Terracciano, A., Deiana, B., Naitza, S., Ferrucci, L., Uda, M., Schlessinger, D., Costa, P., 2010b.
467 High neuroticism and low conscientiousness are associated with interleukin-6. Psychol. Med.
468 40(09), 1485-1493.
469 Terracciano, A., Iacono, D., O'Brien, R.J., Troncoso, J.C., An, Y., Sutin, A.R., Ferrucci, L., Zonderman, A.B.,
470 Resnick, S.M., 2013. Personality and resilience to Alzheimer's disease neuropathology: a
471 prospective autopsy study. Neurobiol Aging 34(4), 1045-1050.
472 Terracciano, A., McCrae, R.R., Brant, L.J., Costa Jr, P.T., 2005. Hierarchical linear modeling analyses of the
473 NEO-PI-R scales in the Baltimore Longitudinal Study of Aging. Psychol. Aging 20(3), 493.
474 Terracciano, A., Sutin, A.R., An, Y., O'Brien, R.J., Ferrucci, L., Zonderman, A.B., Resnick, S.M., 2014.
475 Personality and risk of Alzheimer's disease: new data and meta-analysis. Alzheimer's & Dementia
476 10(2), 179-186.
477 Thomas-Antérion, C., Ribas, C., Honoré-Masson, S., Berne, G., Ruel, P., Laurent, B., 2004. Le
478 Questionnaire de Plainte Cognitive (QPC): outil de dépistage de la plainte des sujets présentant
479 une maladie d'Alzheimer ou un MCI. Rev. Neurol. (Paris) 160(4), 71.
480 Thomas-anterion, C., Ribas, C., Honore-masson, S., Million, J., Laurent, B., 2004. Evaluation de la plainte
481 cognitive de patients Alzheimer, de sujets MCI, anxiodépressifs et de témoins avec le QPC
482 (Questionnaire de Plainte Cognitive). NPG Neurologie - Psychiatrie - Gériatrie 4(20), 30-34.
483 Van der Linden, M., Adam, S., 2004. L'évaluation des troubles de la mémoire: Présentation de quatre
484 tests de mémoire épisodique (avec leur étalonnage). Solal, Marseille.
485 von Gunten, A., Pocnet, C., Rossier, J., 2009. The impact of personality characteristics on the clinical
486 expression in neurodegenerative disorders—A review. Brain Res. Bull. 80(4–5), 179-191.
487 Wang, H.-X., Karp, A., Herlitz, A., Crowe, M., Kåreholt, I., Winblad, B., Fratiglioni, L., 2009. Personality and
488 lifestyle in relation to dementia incidence. Neurology 72(3), 253-259.
489 Welch, B.L., 1938. The significance of the difference between two means when the population variances
490 are unequal. Biometrika 29(3/4), 350-362.
491 Welleford, E.A., Harkins, S.W., Taylor, J.R., 1995. Personality change in dementia of the Alzheimer's type:
492 relations to caregiver personality and burden. Exp. Aging Res. 21(3), 295-314.
493 Wilson, R.S., Schneider, J.A., Arnold, S.E., Bienias, J.L., Bennett, D.A., 2007. Conscientiousness and the
494 incidence of Alzheimer disease and mild cognitive impairment. Arch. Gen. Psychiatry 64(10),
495 1204-1212.
496 Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.O., Nordberg, A., Bäckman, L.,
497 Albert, M., Almkvist, O., 2004. Mild cognitive impairment–beyond controversies, towards a
498 consensus: report of the International Working Group on Mild Cognitive Impairment. J. Intern.
499 Med. 256(3), 240-246.
500 Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67(6),
501 361-370.

502

503

8. Figures titles and legends

Figure 1 Differences in anxiety, MMSE, change in neuroticism, and change in conscientiousness scores between non-pathological and pathological CSF biomarker level groups.

ChangeN, change in neuroticism; ChangeC, change in conscientiousness; MMSE, Mini Mental State Examination; NP CSF, non-pathological CSF biomarkers level group; P CSF, pathological CSF biomarkers level group.

Table 1 **Demographics and descriptive statistics**

		Controls n = 44	**CI n = 66**	**Statistical test**	**P**
Gender	Males Females	N=14 (31.8%) N=30 (68.2%)	N=30 (45.5%) N=36 (54.5%)	chi	0.155
Age	Mean SD	66 6.57	74 6.54	t	<0.001
Education level	≤ 9 years 10-12 years > 12 years	N=3 (6.8%) N=22 (50.0%) N=19 (43.2%)	N=11 (16.7%) N=34 (51.5%) N=21 (31.8%)	chi	0.113
MMSE	Mean SD	28.5 1.42	26.0 3.36	t	<0.001
HAD Depression score	Mean SD	3.79 3.56	4.18 3.06	t	0.55
HAD Anxiety score	Mean SD	6.79 4.24	6.45 3.2	t	0.65
QPC score	Mean SD	1.56 1.5	2.54 1.89	t	<0.01
IQCODE score	Mean SD	3.067 0.42	3.467 0.54	t	<0.001
APOEε4 carriers	no yes	36 (81.8%) 8 (18.2%)	36 (54.5%) 29 (43.9%)	chi	<0.01
$A\beta_{1-42}$ pg/ml	Median IQR	1053 289.6	668.75 357.8	U	<0.001
tau pg/ml	Median IQR	209.3 115.4	394.35 361.3	U	<0.001
ptau-181 pg/ml	Median IQR	46.5 25.2	62.3 44.5	U	<0.001
tau/$A\beta_{1-42}$ pg/ml	Median IQR	0.219 0.115	0.554 0.765	U	<0.001
ptau-181/$A\beta_{1-42}$ pg/ml	Median IQR	0.047 0.02	0.101 0.097	U	<0.001

CI, Cognitive impairment; MMSE, Mini Mental State Examination; HAD, Hospital Anxiety and Depression Scale; APOEε4, epsilon 4 allele of the Apolipoprotein E; QPC, cognitive complaints questionnaire; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; IQR, Interquartile range; U, Mann-Whitney U statistics.

Table 2 **Personality changes between groups**

	Controls (N=44)	**CI (N=66)**		
Personality domains	**Mean (SD)**	**Mean (SD)**	**U**	**P**
RetroN	83.52 (22.94)	79.27 (21.26)	1303	0.363
RetroE	105.32 (15.99)	100.68 (22.68)	1290	0.324
RetroO	107.59 (17.27)	94.45 (17.22)	801	< 0.001
RetroA	128.82 (16.46)	127.76 (19.15)	1420	0.845
RetroC	128.16 (20.40)	123.89 (19.70)	1295	0.338
CurrentN	83.95 (22.78)	88.38 (23.47)	1326	0.442
CurrentE	103.02 (18.35)	92.85 (24.59)	1058	< 0.05
CurrentO	106.75 (18.82)	92.76 (18.09)	810	< 0.001
CurrentA	128.70 (15.55)	125.68 (19.79)	1282	0.299
CurrentC	127.66 (19.97)	109.98 (22.90)	859	< 0.001
ChangeN	0.43 (10.01)	9.11 (13.00)	710	< 0.001
ChangeE	-2.30 (7.26)	-7.83 (11.86)	888	< 0.001
ChangeO	-0.84 (5.69)	-1.70 (4.26)	1279	0.396
ChangeA	-0.11 (2.31)	-2.08 (6.44)	1059	< 0.05
ChangeC	-0.50 (4.50)	-13.91 (19.63)	647	< 0.001

ChangeN, change in Neuroticism; ChangeE, change in Extraversion; ChangeO, change in openness to experience; ChangeA, change in agreeableness; ChangeC, change in conscientiousness; SD, Standart Deviation; Controls, Healthy Controls; CI, cognitive impairment; U, Mann-Whitney U statistics.

Table 3 **Non-pathological and pathological CSF biomarkers levels groups comparison**

	Non-AD CSF (N=66)	**AD CSF (N = 44)**	**p**
Depression score	4.21	3.64	0.369
Anxiety score	7.16	5.69	< 0.05
MMSE score	27.9	25.8	< 0.01
Personality changes			
Neuroticism	2.9	8.8	< 0.05
Extraversion	-3.6	-6.8	0.081
Openness	-0.6	-1.9	0.158
Agreeableness	-0.9	-1.6	0.536
Conscientiousness	-4.6	-12.7	< 0.05

MMSE, Mini Mental State Examination; non-AD CSF, non-pathological CSF biomarkers level group; AD CSF, pathological CSF biomarkers level group.

Table 4a **Model estimates in linear and robust regressions**

		Linear regression				Robust regression		
		β	**t**	**Adj. R^2**	**F**	**β**	**t**	**F**
Change N	MMSE	-0.822*	-1.986			-0.793***	-3.831	
	$A\beta_{1-42}$	-0.011*	-2.303	0.12	6.36***	-0.005*	-2.073	12.17***
	tau	0.001	0.487			0.002	1.081	
Change E	MMSE	0.577	1.676			0.735***	3.611	
	$A\beta_{1-42}$	0.011*	2.599	0.14	7.24***	0.008***	3.502	12.99***
	tau	-0.003	-0.857			0.001	0.468	
Change O	MMSE	0.157	0.946			0.117	1.562	
	$A\beta_{1-42}$	0.003	1.812	0.05	3.14*	0.001	1.744	3.02
	tau	0.001	-0.592			0.000	-0.215	
Change A	MMSE	0.047*	2.622			0.287***	4.301	
	$A\beta_{1-42}$	-0.000	-0.12	0.04	2.76*	0.000	1.022	8.15***
	tau	-0.000	-0.064			0.000	0.058	
Change C	MMSE	2.375***	4.807			2.016***	5.720	
	$A\beta_{1-42}$	0.012*	2.145	0.30	16.58***	0.009*	2.268	19.51***
	tau	-0.002	-0.632			-0.003	-1.063	

ChangeN, change in Neuroticism; ChangeE, Change in Extraversion; ChangeO, change in Openness to Experience; ChangeA, change in Agreeableness; ChangeC, change in Conscientiousness; MMSE, Mini Mental State Examination.

β,unstandartised regression coefficient.

* p < .05 ; ** p < .01 ; *** p < .001 .

Table 4b **Model estimates in linear and robust regressions**

		Linear regression				Robust regression		
		β	**t**	**Adj. R^2**	**F**	**β**	**t**	**F**
Change N	MMSE	-0.909*	-2.129			-0.889***	-4.574	
	$A\beta_{1-42}$	-0.013**	-2.684	0.13	6.42***	-0.006**	-2.766	14.69***
	ptau	-0.009	-0.297			-0.011	-0.764	
Change E	MMSE	0.634	1.776			0.783***	3.761	
	$A\beta_{1-42}$	0.012**	3.012	0.14	6.90***	0.009***	3.686	13.48***
	ptau	-0.000	-0.024			0.012	0.753	
Change O	MMSE	0.167	0.968			0.137	1.696	
	$A\beta_{1-42}$	0.004*	2.054	0.05	2.97*	0.002	1.874	2.99*
	ptau	-0.002	-0.182			0.001	0.243	
Change A	MMSE	0.497**	2.658			0.302***	4.553	
	$A\beta_{1-42}$	-0.000	-0.036	0.05	2.75*	0.001	1.073	8.44***
	ptau	0.005	0.386			0.003	0.587	
Change C	MMSE	2.556***	5.012			2.208***	6.071	
	$A\beta_{1-42}$	0.015**	2.629	0.30	16.42***	0.011**	2.716	19.33***
	ptau	0.031	0.805			0.047	1.725	

ChangeN, change in Neuroticism; ChangeE, Change in Extraversion; ChangeO, change in Openness to Experience; ChangeA, change in Agreeableness; ChangeC, change in Conscientiousness; MMSE, Mini Mental State Examination.

β,unstandartised regression coefficient.

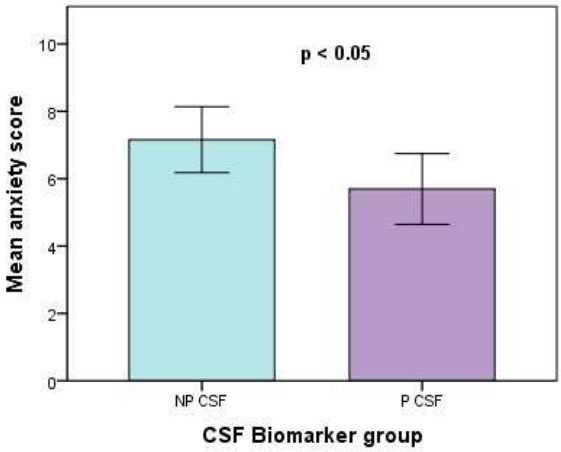
* p < .05 ; ** p < .01 ; *** p < .001 .

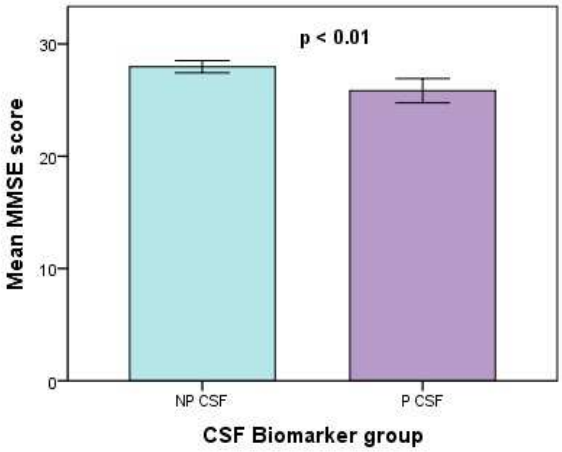
Table 5 **Spearman's correlations between CSF biomarkers and personality changes, retrospective, and current personality assessments (N=110)**

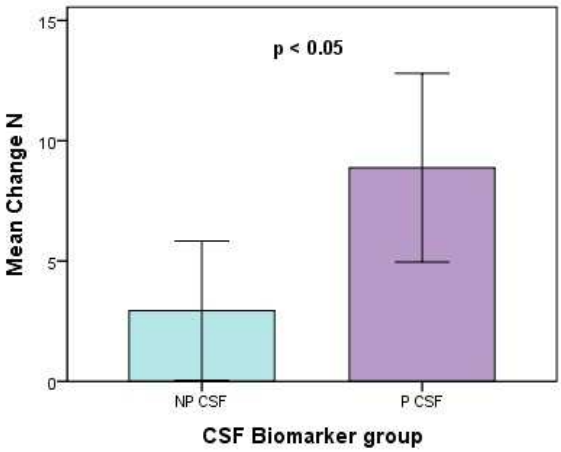
Personality domains	**$A\beta_{1-42}$**	**tau**	***p*tau-181**	**tau/$A\beta_{1-42}$**	**ptau-181/ $A\beta_{1-42}$**
RetroN	0.17	0.00	0.00	-0.04	-0.10
RetroE	-0.01	-0.17	-0.13	-0.16	-0.15
RetroO	0.15	-0.38 **	-0.38 **	-0.36 **	-0.38 **
RetroA	-0.02	-0.07	0.00	-0.06	-0.01
RetroC	-0.10	-0.03	-0.04	0.03	0.04
CurrentN	-0.03	0.14	0.07	0.13	0.07
CurrentE	0.16	-0.23 *	-0.16	-0.27 **	-0.24 *
CurrentO	0.21 *	-0.38 **	-0.38 **	-0.39 **	-0.41 **
CurrentA	0.04	-0.11	-0.05	-0.12	-0.08
CurrentC	0.18	-0.18	-0.16	-0.21 *	-0.21 *
ChangeN	-0.36 ***	0.39 ***	0.32 **	0.46 ***	0.41 ***
ChangeE	0.38 ***	-0.10	-0.05	-0.21 *	-0.21 *
ChangeO	0.17	-0.13	-0.13	-0.17	-0.20 *
ChangeA	0.20 *	-0.20 *	-0.18	-0.22 *	-0.21 *
ChangeC	0.34 ***	-0.22 *	-0.18	-0.32 **	-0.31 **

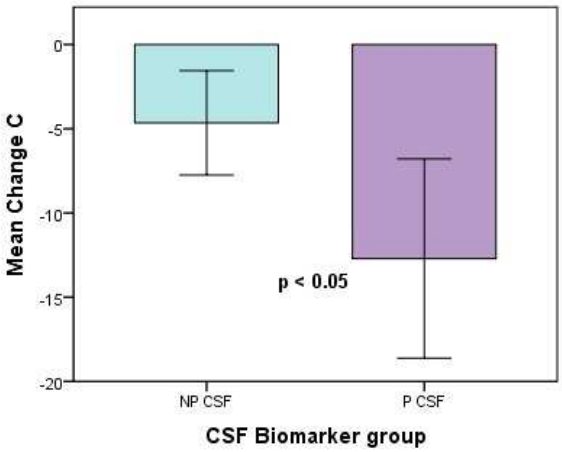
Retro, retrospective personality assessment; Current, current personality assessment; Change, personality change;

N, Neuroticism; E, Extraversion, O, Openness to Experience, A, Agreeableness; C, Conscientiousness.


Mean anxiety score
p < 0.05
10
8
6
4
2
0
NP CSF
P CSF
CSF Biomarker group


Mean MMSE score
p < 0.01
30
20
10
0
NP CSF
P CSF
CSF Biomarker group


Mean Change N
p < 0.05
15
10
5
0
NP CSF
P CSF
CSF Biomarker group


Mean Change C
0
-5
-10
-15
-20
p < 0.05
NP CSF
P CSF
CSF Biomarker group

9. Annexes

Instructions to proxy ratters (translated from French)

Read carefully these instructions before beginning. Below indicate the profession, age, gender, and education level of the person that you are about to evaluate. This questionnaire contains 240 statements. Read carefully each of them. For each statement choose the answer that describes your proxy the best 5 years before the beginning of the first symptoms, then choose the answer that describes your proxy the best at this moment.

There are no “good” or “bad” answers and you do not need to have a special expertise to fill this questionnaire. The goal of this questionnaire will be reached if you describe the person and you express your opinion as accurately as possible. Please answer every question. If you happen to make a mistake or if you change your opinion, do not erase your answer. Note an “X” on the wrong answer and surround the correct answer.