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Neuroticism is associated with tau pathology in cognitively unimpaired individuals with autosomal dominant Alzheimer's disease

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Abstract

BACKGROUND: Greater neuroticism has been associated with higher risk for Alzheimer's disease (AD) dementia. However, the directionality of this association is unclear. We examined whether personality traits differ between cognitively-unimpaired carriers of autosomal-dominant AD and non-carriers, and are associated with *in-vivo* AD pathology.

METHODS: A total of 33 cognitively-unimpaired *Presenilin-1* E280A mutation carriers and 41 non-carriers (ages 27-46) completed neuropsychological testing and the NEO Five-Factor Personality Inventory. A subsample (n = 46; 20 carriers) also underwent tau and amyloid PET imaging.

RESULTS: Carriers reported higher neuroticism relative to non-carriers, although this difference was not significant after controlling for sex. Neuroticism was positively correlated with entorhinal tau levels only in carriers, but not with amyloid levels.

DISCUSSION: The finding of higher neuroticism in carriers and the association of this trait with tau pathology in preclinical stages of Alzheimer's disease highlights the importance of including

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personality measures in the evaluation of individuals at increased risk for cognitive impairment and dementia. Further research is needed to characterize the mechanisms of these relationships.

Keywords

Alzheimer's disease; presenilin-1; preclinical; neuroticism; biomarkers; personality

1. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia [1] and its early diagnosis is currently a major focus of research [2]. Neuroimaging markers of AD, such as increased levels of tau and amyloid in brain, as measured by positron emission tomography (PET), are known to become abnormal years before the onset of clinical symptoms [3, 4]. Studying carriers of autosomal-dominant AD (ADAD) mutations allows us to characterize these biomarkers and how they relate to changes in cognition in the preclinical stage of the disease, without the confounding of age-related comorbidities and other complications [5]. The world's largest cohort with ADAD resides in Antioquia, Colombia, and includes more than 1,200 carriers of the E280A mutation in the Presenilin-1 (*PSEN1*) gene [4, 6, 7]. Carriers from the Colombian ADAD kindred typically develop mild cognitive impairment (MCI) at the median age of 44, and dementia at the median age of 49 [7].

Research on personality traits in AD has been very limited, despite knowing that personality may influence decision-making and learning strategies, and impact behavior. Recent studies have shown that personality traits, such as neuroticism, are related to a higher risk of developing AD dementia [8]. Other studies have shown that neuroticism increases in the transition from preclinical to MCI in individuals at increased risk for late-onset AD [9–11]. Most research on personality traits and AD, however, has been conducted with older adults with an increased risk of sporadic AD based on AD biomarker abnormalities [12]. To our knowledge, the most recent studies that have examined personality in cohorts of individuals with ADAD, come from the Dominantly Inherited Alzheimer's Network (DIAN) [13], who, in a first study, found that there were no differences in personality traits between presymptomatic carriers and non-carriers [14]. However, in a later study they reported differences when personality traits were compared between non-carriers and a group of carriers that included presymptomatic and symptomatic subjects [15]. Additionally, DIAN studies that have explored the relationship between personality and AD pathology, in cognitively healthy older adults at risk of developing sporadic Alzheimer's disease, reported associations between high neuroticism levels with increased amyloid deposition in the brain; and correlations between tau pathology and traits such as openness, extraversion, and neuroticism. Furthermore, in the same study, higher amyloid deposition was related with lower scores in the personality facet of the intellect, in presymptomatic carriers of ADAD mutations [13]. Likewise, a recent study from the same group also reported a relationship between neuroticism, and total tau and phosphorylated tau in cerebrospinal fluid (CSF), in presymptomatic and symptomatic ADAD carriers [15]. However, it is unclear whether the associations between personality traits and markers of brain tau pathology can be observed using PET imaging in cognitively unimpaired carriers.

Understanding how neuroticism and AD are related is of great clinical importance given that personality traits influence behaviors, decision-making, and lifestyle; factors that are known to impact the progression of the disease [16]. The early characterization of neuroticism in individuals at increased risk of developing AD could help with early implementation of strategies aimed at modifying maladaptive behaviors influenced by personality, or even ways of responding to situations that may result in depression, anxiety, irritability, or vulnerability in the context of the disease.

We sought to extend the examination of the relationships between personality traits and markers of brain pathology in preclinical ADAD by studying both amyloid and tau pathology in cognitively unimpaired carriers of a single AD-mutation (*PSEN1* E280A) from the Colombian kindred. We hypothesized that mutation carriers would report higher rates of neuroticism relative to age-matched non-carriers, and that neuroticism would be associated with higher levels of pathology, as measured by PET imaging.

2. METHODS

2.1 Participants

Participants were recruited from the Colombia-Boston (COLBOS) Longitudinal Biomarker Study, which follows Colombian families with autosomal dominant Alzheimer's disease. These families are part of the prevention registry of the University of Antioquia, which currently includes more than 6,000 living members of the *PSEN1* E280A kindred [5]. The participants selected for the present study, both carriers and noncarriers, had a parent with dementia due to the *PSEN1* mutation. Only participants living in the metropolitan area of the Aburra Valley within 105 miles of the University of Antioquia, Medellin, Antioquia, Colombia, were invited to participate in the study. Potential participants were screened in advance for the presence of neurological and psychiatric disorders, drug use, and eligibility to undergo magnetic resonance imaging. Participants provided written informed consent before enrollment into study procedures. Participants were studied under guidelines approved by local institutional review boards. Ethics approval was obtained from the University of Antioquia Ethics Committee for procedures undertaken in Colombia and the Massachusetts General Hospital Institutional Review Board for procedures undertaken in the United States. All data were acquired by investigators who were masked to the participants' genetic status.

All participants included in this study were cognitively unimpaired (N= 74; 33 carriers and 41 non-carriers). They had to show no cognitive impairment on a standard cognitive battery, including a clinical diagnostic rating scale (CDR) [17] score of 0, Folstein Mini-Mental State Examination [18] score of 26 or greater, and a Functional Assessment Staging (FAST) [19] score <2.

Additionally, participants needed to have basic literacy skills, with normal visual capacity or corrected to normal vision. All participants underwent a clinical assessment that included neuropsychological [20–22] and personality tests, and staging measures, such as Global Deterioration Scale [23]. Furthermore, depression and anxiety were assessed using the Geriatric Depression Scale (GDS) [24], and the Geriatric Anxiety Inventory (GAI) [25].

A subset of participants (N= 46; 20 carriers and 26 non-carriers) traveled from Medellín, Colombia to Boston, MA, to undergo PET imaging (tau and amyloid) examinations.

2.2 Personality Assessment

Participants completed the revised personality inventory NEO (NEO-FFI) in Spanish [26]. This personality test can be administered by a clinician or self-administered by the participant and includes 60 items that measure the five traits that constitute personality. In this study, the NEO-FFI was self-administered. Research staff were available to answer any questions. They also provided assistance to participants with low literacy skills, when needed. The traits evaluated in the NEO-FFI include: Neuroticism (N), Extraversion (E), Openness, (O), Agreeableness (A) and Conscientiousness (C). Participants respond using a Likert-type scale of 5 options: “Totally disagree,” “Disagree,” “Neutral,” “Agree,” and “Totally agree”. Personality tests were completed within 3 months of the PET imaging.

2.3 Brain Imaging

Participants underwent tau and amyloid PET imaging at Massachusetts General Hospital, Boston, MA. As previously reported [4], the radiotracer used in amyloid PET was the Carbon 11-labeled Pittsburgh Compound-B (11C PiB), which is a radioactive chemical substance that joins the beta-amyloid protein. The images were acquired with an 8.5 to 15 mCi bolus injection followed immediately by a 60-minute dynamic acquisition in 69 frames (12x15 seconds, 57x60 seconds). The radiotracer used in tau PET was the Flortaucipir (F18), which selectively joins the aggregates of brain tau. The images were acquired 80-100 minutes after a 9.0 to 11.0 mCi bolus injection in 4 x 5-minute frames. Scores higher than 1.3 was considered as abnormal accumulation of the Tau protein.

11C PiB PET data were expressed as the distribution volume ratio (DVR) with cerebellar grey as reference tissue; regional time-activity curves were used to compute regional DVRs for each region if interest (ROI) using the Logan graphical method applied to data from 40 to 60 minutes after injection [27]. 11C PiB retention was assessed using a large cortical ROI aggregate that included frontal, lateral temporal and retrosplenial cortices as described previously [28]. Scores higher than 1.2 were considered as an abnormal accumulation of brain amyloid in the DVR.

(F18) FTP specific binding was expressed in FS ROIs as the standardized uptake value ratio (SUVR) to cerebellum, similar to a previous report [29], using the FS cerebellar grey ROI as reference. The spatially transformed SUVR PET data was smoothed with an 8mm Gaussian kernel to account for individual anatomic differences [30]. SUVR values were represented graphically on vertices at the pial surface. Regional FTP-SUVR’s analyses were conducted in the entorhinal cortex and the inferior temporal cortex since these regions were found to be associated with early FTP-SUVR increases over age in the PSEN1 E280A kindred [4]. Consistent with previous studies with this same cohort, PET data were corrected for partial volume effects using the geometric transfer matrix method [31].

2.4 Statistical Analyses

Demographic, cognitive and clinical characteristics of the groups included age, education, sex (p-value calculated with Chi-Squared), MMSE, GDS and GAI were analyzed using measures of central tendency, dispersion, and frequency.

For comparisons of mean scores of the NEO-FFI traits and the biomarker values (tau and amyloid) of the carriers and non-carriers, the Mann Whitney U test for nonparametric samples was used. The effect size of the possible differences in personality traits between the groups was calculated trough the formula $r = z/\sqrt{N}$ (effect size for non-parametric samples) [32]. Additionally, follow up analyses of variance (ANCOVA) were conducted to examine these group differences controlling for age and sex.

Bivariate correlations between personality traits and biomarkers were established through Spearman Rho correlations. To ensure that high neuroticism scores were not a result of depression or anxiety, bivariate correlations were controlled for GAI and GDS, using partial correlations. All statistical analyses were carried out on IBM SPSS version 24.0 [33].
An exploratory whole-brain analysis was carried out, examining the relationship between tau burden and neuroticism in *PSEN1* mutation carriers. We reported results that were significant at p<0.05 with and without cluster-wise false discovery rate (FDR) correction for multiple comparisons (minimum cluster extent = 100mm^2). Vertex-wise correlations were carried out in R (version 3.4.1); clustering and FDR correction were carried out in FreeSurfer (version 6.0). Likewise, some additional analyzes were carried out to explore whether there was any difference in the spatial distribution of tau and amyloid burden between mutation carriers with higher and lower neuroticism. Carriers were divided into high- and low-neuroticism based on a median split of the neuroticism variable.

3. RESULTS

3.1 Demographic, Cognitive and Clinical characteristics of the Sample

Table 1 shows the demographic, cognitive, and clinical characteristics of the total sample of carriers and non-carriers of *PSEN1* E280A. There were not significant differences in age, education, clinical staging, or performance on the MMSE between cognitively unimpaired carriers and non-carriers. Sex differences were found for the total sample ($\chi 2 = 4.35$; $p < 0.05$; Table 1). There were significantly more females in the carrier group compared to non-carriers.

Table 2 displays the demographic, cognitive, and clinical characteristics of the subsample of 20 carriers and 26 non-carriers of *PSEN1* E280A who underwent PET imaging. No significant differences in age, education, sex, clinical or cognitive measures were observed between cognitively unimpaired carriers and non-carriers in this subsample.

3.2 Personality Traits

The results of the personality traits showed that carriers had higher scores in Neuroticism ($U = 471.5$, $p = .02$) compared to non-carriers, with a relatively small effect size (0.26). When adjusting the analyses for age, this difference remained significant [F (1, 71) =

5.31, p = .024]. In contrast, when controlling the analyses for sex, results showed a trend towards higher neuroticism scores in carriers compared to non-carries [F (1, 70) = 3.71, p = .058]. Post hoc analyses were conducted to compare the levels of neuroticism between men and women across mutation carriers and non-carriers, and within carriers and non-carriers, separately. There were no sex differences in levels of neuroticism (see Table 4).

Other personality traits did not differ between groups (Extraversion [$U = 575.5$, $p = .27$], Openness [$U = 620.5$, $p = .54$] Agreeableness [$U = 656.5$, $p = .83$], and Conscientiousness [$U = 641.0$, $p = .70$]) (see Table 3, Figure 1 and Supplementary Figure 1).

3.3 PET markers of AD pathology

The assessment of biomarkers carried out through PET shows, as predicted, that the group of cognitively unimpaired carriers had higher levels of cortical PiB DVR compared with the group of non-carriers ($U = 17$, $p < .001$). Relative to non-carriers, higher levels of tau PET binding were also observed in the entorhinal cortex ($U = 98$, $p < .001$) and inferior temporal cortex ($U = 157$, $p = .022$) (see Table 5).

3.4 Correlations between neuroticism with age

No correlation between the neuroticism or the other personality treats and the age were found (see Table 6, Figure 1 and Supplementary Figure 1).

3.5 Correlations between neuroticism and PET markers of AD pathology

In the 46 participants who underwent PET imaging, a positive correlation was found between neuroticism and entorhinal tau levels in *PSEN1* E280A carriers ($r = .47$, $p = .04$); this correlation survived after controlling for depressive and anxiety symptoms, and was not observed in non-carriers. No additional correlations were found between personality traits and levels of tau in the inferior temporal lobe or mean cortical amyloid (see Figure 1 and Supplementary Figure 1).

We performed an exploratory analysis of the associations between neuroticism and tau burden in the whole cortex in *PSEN1* mutation carriers. Vertex-wise correlations between tau burden and neuroticism showed a pattern consistent with findings from regions selected a priori, in inferior and medial temporal regions (i.e., entorhinal cortex), and parietal regions (i.e., precuneus), predominantly in the right hemisphere (see Figure 2). However, these results were not significant after FDR correction for multiple comparisons.

Additional exploratory analysis, using the median for neuroticism in the whole sample (18.5) as the threshold for high and low, showed that carriers with high neuroticism appear to have higher amyloid (lateral frontal, medial parietal and occipital regions) and tau (entorhinal cortex in both hemispheres, precuneus in right hemisphere) compared to those with low neuroticism. However, group comparisons (t-tests) were not significant (High-neuroticism carriers N=12, Low-neuroticism carriers N=10) (see Figures 3 and 4).

4. DISCUSSION

In this study of personality traits and PET markers of AD pathology in a sample of cognitively unimpaired ADAD mutation carriers and non-carrier family members, we found that *PSEN1* E280A carriers reported higher neuroticism relative to age-matched non-carriers, although that difference did not remain significant after controlling for sex. Additionally, neuroticism was correlated with entorhinal tau levels only in mutation carriers. No other associations between personality traits and AD brain pathology were found.

To our knowledge, this is the first study to examine neuroticism levels in cognitively unimpaired mutation carriers, several years before the estimated age at MCI onset for this kindred [22, 34]. It is important to note that when adjusting the analyses for sex, this difference did not remain significant, and only showed a trend towards significance. Since our carrier sample included more women than men, and it has been suggested that women have greater neuroticism than men [35], to analyze the impact of sex on this personality trait in our study, we compared neuroticism levels between men and women in the total sample and in each group (carriers and non-carriers), and found no significant differences between groups. Furthermore, when comparing carrier men with non-carrier men, and carrier women with non-carrier women, the mean levels of neuroticism of the carrier subjects were always higher, which suggests that neuroticism could be higher in carriers regardless of sex. Therefore, the lack of significance after controlling the analyses for sex, could be due to the limited power of our sample.

Contrary to our results, past research from the Dominantly Inherited Alzheimer Network (DIAN) found no differences in personality traits when comparing presymptomatic mutation carriers (CDR = 0, age = 34.6) with non-carriers (age = 40.4) [14]. A possible explanation for this discrepancy would be the heterogeneity or homogeneity of the samples. The DIAN study included different types of mutations, including subjects belonging to different families, living in different countries, social and cultural contexts, while our study included subjects with a single mutation, belonging to the same extended family, with similar socioeconomic background and geographical area. On the other hand, the use of different instruments to assess personality could have led to different results. Although both instruments used in these studies are based on the same model of the big five personality traits, the DIAN study used the International Personality Item Pool (IPIP), which includes 120 questions, while our study used the NEO-FFI, which includes 60 items. In addition to the different number of items, the cutoffs used for neuroticism are also different for each test, which can contribute to the variability. Another study from DIAN found that presymptomatic carriers rated themselves similarly to non-carriers on all personality domains, but informants rated presymptomatic carriers lower on conscientiousness and higher on neuroticism than non-carriers [36]. A more recent research conducted by the same group with a larger sample reported that carriers exhibited higher levels of neuroticism compared to non-carriers. However, unlike our study, the group of carriers consisted of subjects in different stages of the disease, ranging from presymptomatic to symptomatic (CDR = 0 and > 0.5) [15]. Most studies that have reported differences in personality traits have either included older adults at risk for sporadic AD or symptomatic individuals [8, 37]. Taken together, these results suggest that levels of neuroticism may be elevated in mutation

carriers compared to non-carriers, even in preclinical stages of the disease. However, additional analyses, with larger samples, are required to verify whether neuroticism and other personality traits may differ between carriers and non-carriers in early stages.

To the best of our knowledge, this is the first investigation to examine the relationship between tau pathology (measured by PET imaging) and personality traits in young ADAD mutation carriers in the preclinical stage. In our study, we focused on tau in the entorhinal and inferior temporal cortices because these are two regions in which tau aggregates early in our cohort of *PSEN1* E280A mutation carriers [4]. In addition, we conducted an exploratory vertex-wise analyses exploring the correlations between tau burden in the whole cortex and neuroticism.

Our finding of a positive association between neuroticism and entorhinal tau in cognitively unimpaired carriers, after controlling for depressive and anxiety symptoms, suggests that this personality trait is associated with AD pathology in a region known to be vulnerable to early tau accumulation in AD [38–40]. A similar study, carried out in cognitively normal older adults and using PET imaging, also found associations between high levels of neuroticism and high levels of tau accumulation in the amygdala, entorhinal cortex, and inferior temporal cortex [41]. Similarly, the PREVENT-AD study showed that older adults at risk for sporadic AD with lower neuroticism and neuropsychiatric symptoms, and higher levels of openness and extraversion, were related to less tau deposition in brain structures such as the entorhinal cortex and the medial and lateral temporal lobes [13]. There is additional evidence of the relationship between neuroticism and tau pathology from CSF studies performed in cognitively unimpaired subjects with ADAD. Consistent with our results, some studies have shown that self-reported higher neuroticism levels are related to higher levels of total tau and phosphorylated tau in CSF in ADAD mutation carriers, compared to non-carriers [15, 42]. Taken together, these findings suggest that high levels of neuroticism are associated with AD pathology in ADAD mutation carriers and in adults at risk of developing AD. Although the scope of our study has limitations and does not assert causality, it could be hypothesized that the associations between neuroticism and tau pathology could be due to the tau accumulation progression, which is believed to begin in the entorhinal cortex and progresses towards other structures in the limbic system, which is also involved in emotional processing and relates to neuroticism [43]. Changes in the structure and function of medial temporal lobe regions have also been linked to early changes in emotional functioning [44], including anxiety and depression, which are common in individuals with high levels of neuroticism and in risk of cognitive impaired [45].

Through a whole-brain exploratory analysis, we found vertex-wise correlations between tau burden and neuroticism in mutation carriers in a pattern consistent with our findings of regional tau accumulation (i.e., entorhinal cortex and inferior temporal lobe), as well as other neocortical regions know to be important for AD (e.g., precuneus). Nevertheless, these correlations were exploratory and did not survive after FDR correction for multiple comparisons, which could be due to the small size sample or the limited range of tau values in cognitively unimpaired *PSEN1* mutation carriers. Additional exploratory analysis seems to suggest that carriers with high neuroticism have more amyloid and tau compared

to carriers with low neuroticism; however, the differences are not significant, likely due to small group sizes.

In the current study, we did not find an association between any of the personality traits and amyloid pathology. In the previously mentioned DIAN study [13], the researchers also examined these associations in a sample of young adults with ADAD mutations. In line with our results, their findings evidenced that there was no relationship between PET amyloid burden and most personality traits, including neuroticism, in cognitively unimpaired carriers. In contrast, the main factors related to amyloid deposition were fewer years of education, lower scores on the intellect facet, and a higher burden of neuropsychiatric symptoms. Additionally, another DIAN study reported similar results such that no correlations between personality and amyloid pathology were found in a sample that included presymptomatic and symptomatic carriers [15]. Similar studies carried out on cognitively unimpaired older adults at risk of sporadic AD have shown an opposite pattern, with results demonstrating a positive relationship between amyloid burden and neuroticism [13]. Importantly, it has been postulated that amyloid can moderate the effect of the relationship between tau and personality traits [41].

The lack of a significant association between amyloid burden and personality traits in our study might be due to the fact that only a few mutation carriers showed significant amyloid burden, at levels toward the lower end of the amyloid range. This may have impacted our ability to detect any relationships between amyloid and personality traits. Therefore, it is important to study these same variables in a larger sample of ADAD that includes broader ranges of amyloid burden to further clarify these relationships.

Finally, we did not find relationships between neuroticism or other traits with age in carriers and non-carriers. Considering that all subjects in the study are in preclinical stages of the disease, these findings are in line with the assumption that levels of neuroticism are relatively stable before the onset of dementia [37]. Further studies should examine the longitudinal changes of neuroticism as these mutation carriers progress from preclinical stages to mild cognitive impairment and dementia.

5. LIMITATIONS AND FUTURE DIRECTIONS

The limitations of our study must be noted. First, the ability to characterize the statistical relationships between variables could be affected by our relatively small sample size, in comparation with other studies related to personality and AD. Second, the homogeneity of our single-mutation ADAD cohort raises questions about the generalizability of our findings to other ADAD mutation and the sporadic AD population. Third, given the cross-sectional nature of this study and the restricted clinical stage of our participants (i.e., cognitively unimpaired), it was not possible to analyze how neuroticism may change at different stages of the disease, such as from preclinical to MCI or dementia. However, these participants are part of a longitudinal biomarker study, and information about their personality traits will be collected over time and will be included in future analyses. The current study only included self-reported data. Future studies should consider including informant report ratings as well, since they can provide complementary and relevant information about one’s behavioral

and emotional functioning. On the other hand, despite the fact that when analyzing the differences in the levels of neuroticism between men and women, these differences were not significant, the lack of an equivalent proportion in sex within the group of carriers could be considered a limitation. Follow up studies should further explore the effect of sex on neuroticism in ADAD and sporadic Alzheimer's disease. Furthermore, since the subjects in the carrier group were young, few showed significant amyloid and tau loads, potentially impacting our ability to detect additional relationships between biomarkers and personality traits in cerebral regions such as the frontal lobe, subcortical structures, or other important areas related with personality. Lastly, some studies have suggested that neuropsychiatric symptoms in AD are likely associated with subcortical neurofibrillary tangle accumulation [46]. Thus, it is important to acknowledge that as tau-PET binding is less sensitive to subcortical structures, our approach may have limited our ability to detect associations between the earliest accumulation of tau and personality traits.

Despite these limitations, our study expands the literature on the relationship between neuroticism and AD in the preclinical stage by examining a group of cognitively unimpaired carriers who are destined to develop the AD clinical syndrome with virtually 100% certainty. Likewise, this study highlights the clinical utility provided by the identification of personality traits, especially since these traits further influence behaviors, decision-making, and lifestyle, which are all known to affect the risk and progression of the disease.

6. CONCLUSION

In summary, our study found that cognitively unimpaired mutation carriers reported higher neuroticism relative to age-matched non-carriers, although this difference did not remain significant after controlling for sex. Furthermore, the neuroticism trait was associated with entorhinal tau pathology, but not with amyloid burden, even after controlling for self-reported levels of anxiety and depression. These findings suggest that a neurotic personality profile is associated with tau pathology. Our results suggest that personality assessment could be a useful measure in the preclinical stage of AD and should be used together with traditional cognitive measures, in order to identify individual characteristics of patients and contribute to the development of coping-stress strategies that favor cognitive, behavioral and adaptive responses, which in turn could improve the patient's quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AD	Alzheimer's disease
ADAD	Autosomal-Dominant Alzheimer's Disease
PSEN1	Presenilin-1
MCI	Mild cognitive impairment
COLBOS	Colombia-Boston Study
CDR	Clinical Dementia Rating Scale
MMSE	Mini-Mental State Examination
FAST	Functional Assessment Staging test
GDS	Geriatric Depression Scale
GAI	Geriatric Anxiety Inventory
PiB	Pittsburg Compound B
FTP	Flortaucipir
DVR	Distribution volume ratio
ROI	Region of interest
SUVR	Standardized uptake value ratio
CSF	Cerebrospinal Fluid

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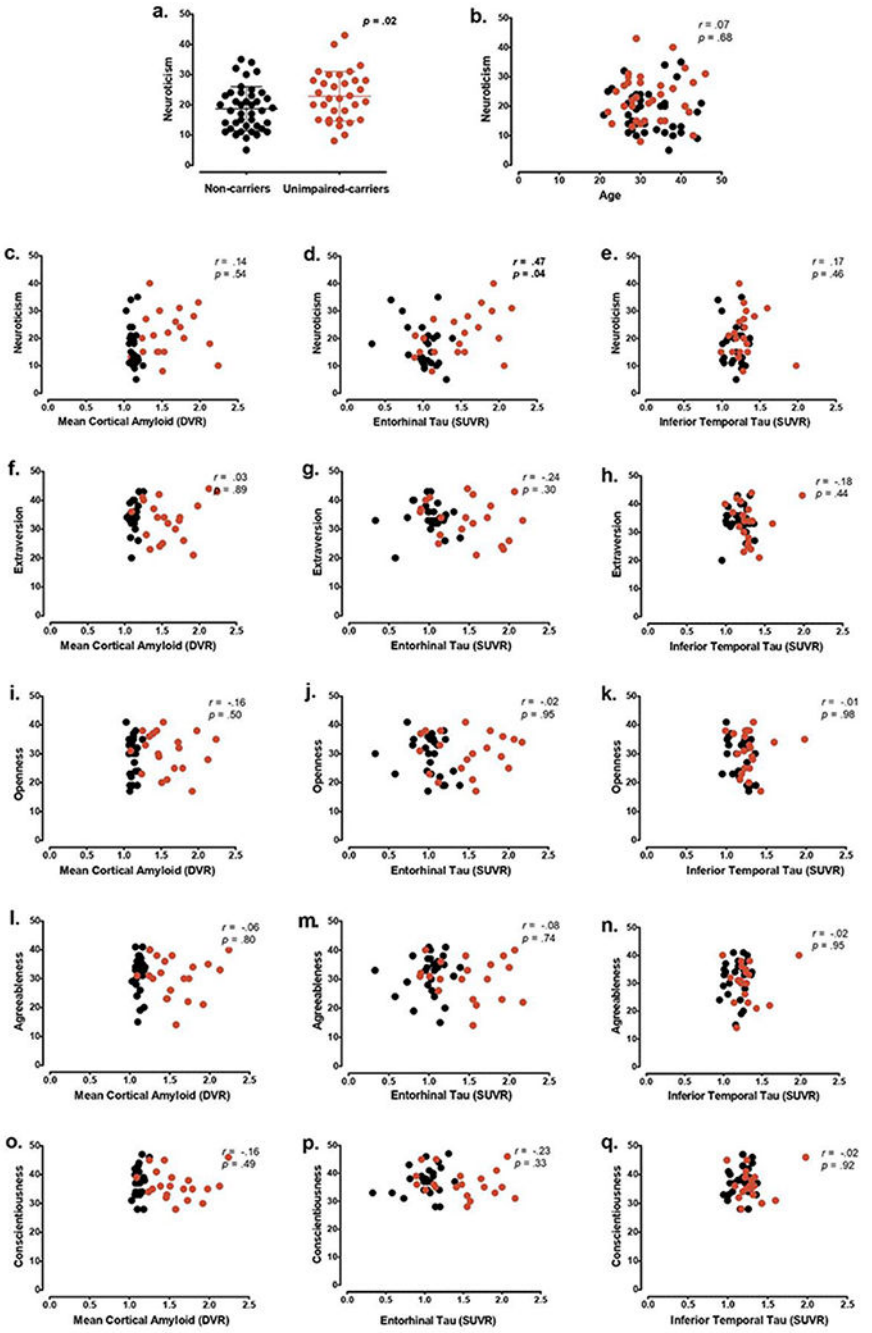

Figure 1. Neuroticism, age and brain pathology in carriers and non-carriers

Note. DVR: distribution volume ratio; SUVR: standardized uptake value ratio. Scatter plots show (a) differences in neuroticism levels between carries and non-carrier, and correlations between (b) neuroticism and age, (c, d & e) neuroticism and biomarkers, (f, g & h) extraversion and biomarkers, (i, j & k) openness and biomarkers, (l, m & n) agreeableness and biomarkers, (o, p & q) conscientiousness and biomarkers. Neuroticism levels are expressed in row scores. Black circles represent noncarriers, red circles represent cognitively unimpaired *PSEN1* mutation carriers. Statistical values included correspond to

the correlation coefficients in the mutation carriers. Selected Biomarkers: Mean Cortical Amyloid (DVR), Entorhinal Tau (SUVR) and Inferior Temporal Tau (SUVR).

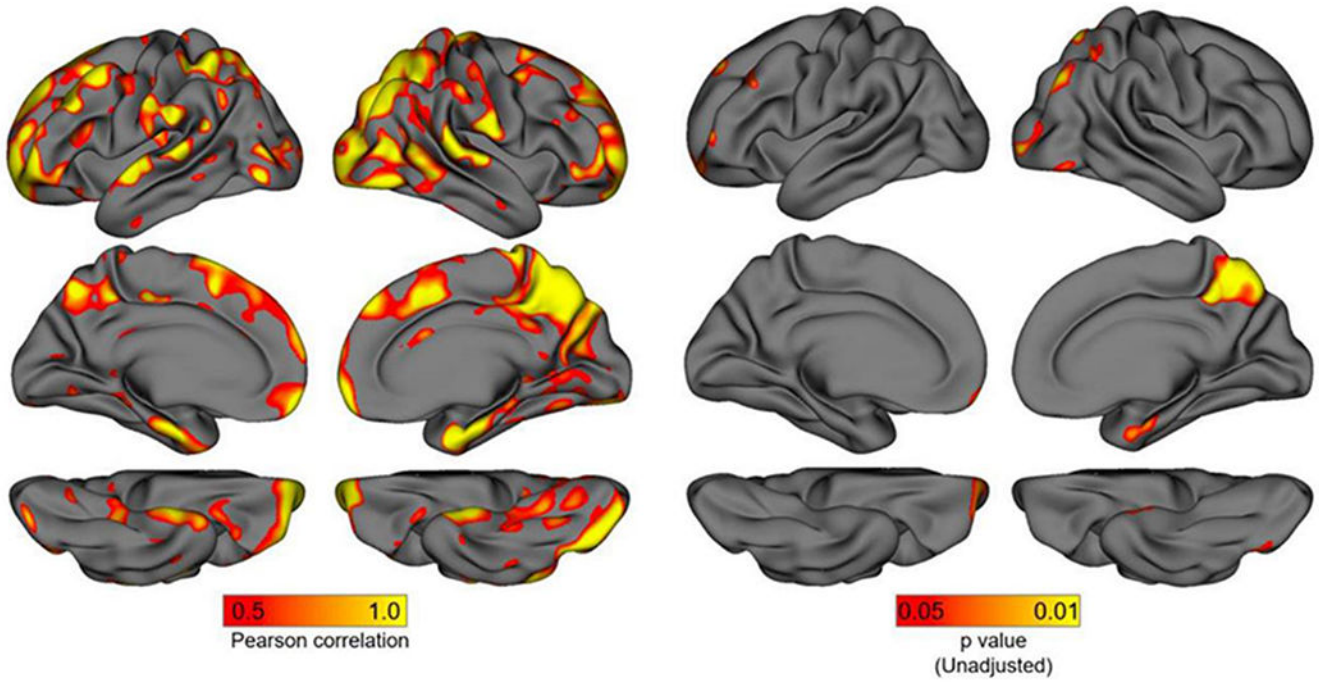

Figure 2. Associations between neuroticism and tau PET in mutation carriers

Images with clustering (minimum cluster extent = 100mm2). P values not adjusted for multiple comparisons. No correlations remain significant after FDR correction for multiple comparisons.

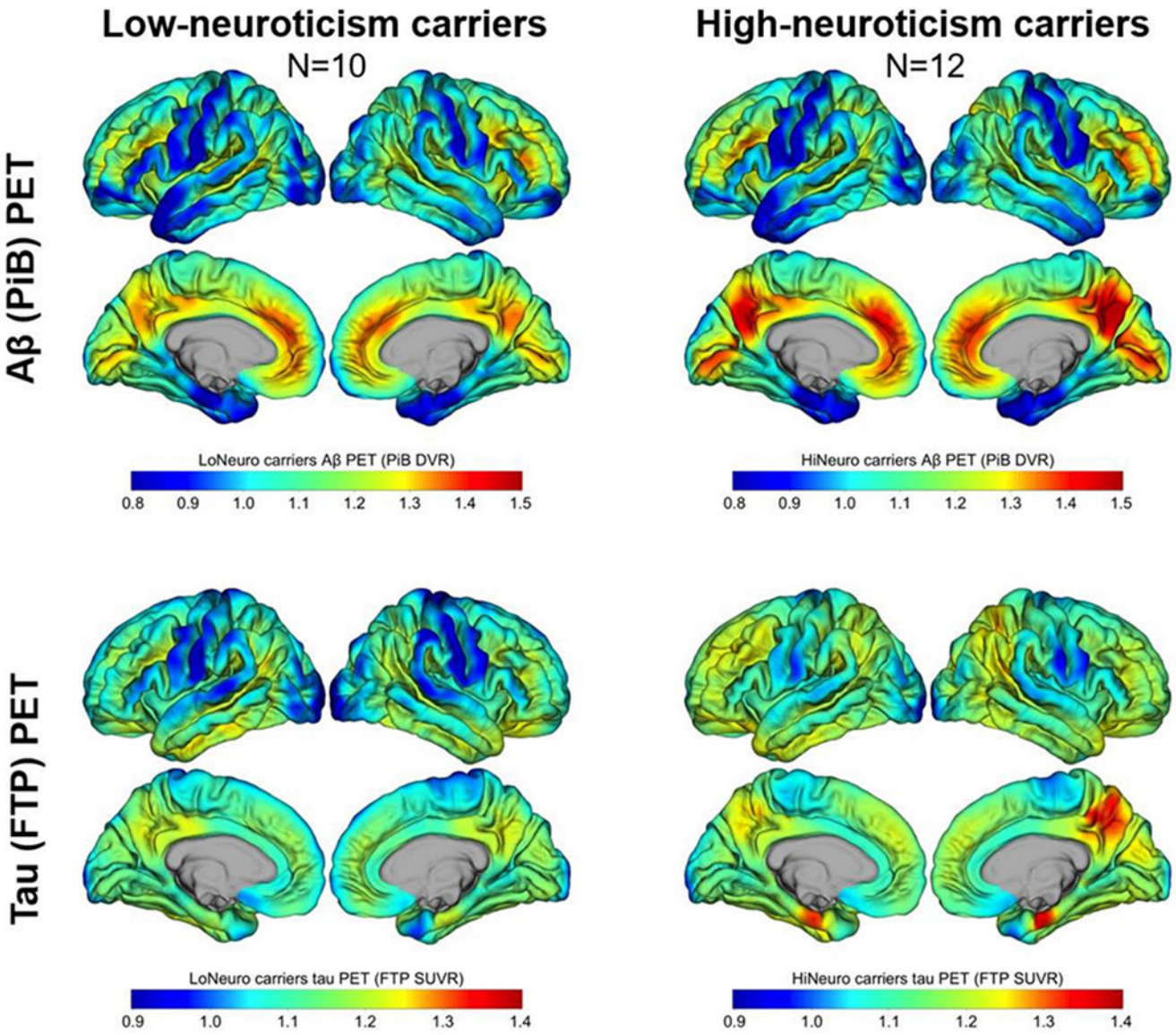

Figure 3. Plotted mean tau and amyloid PET for carriers with high- and low-neuroticism

Note. PiB: Pittsburg Compound B; DVR: Distribution Volume Ratio; FTP: Flortaucipir; SUVR: Standardized Uptake Value Ratio.

Carriers divided into high- low-neuroticism based on a median (neuroticism) for whole sample = 18.5 (PIB DVR and FTP SUVR).

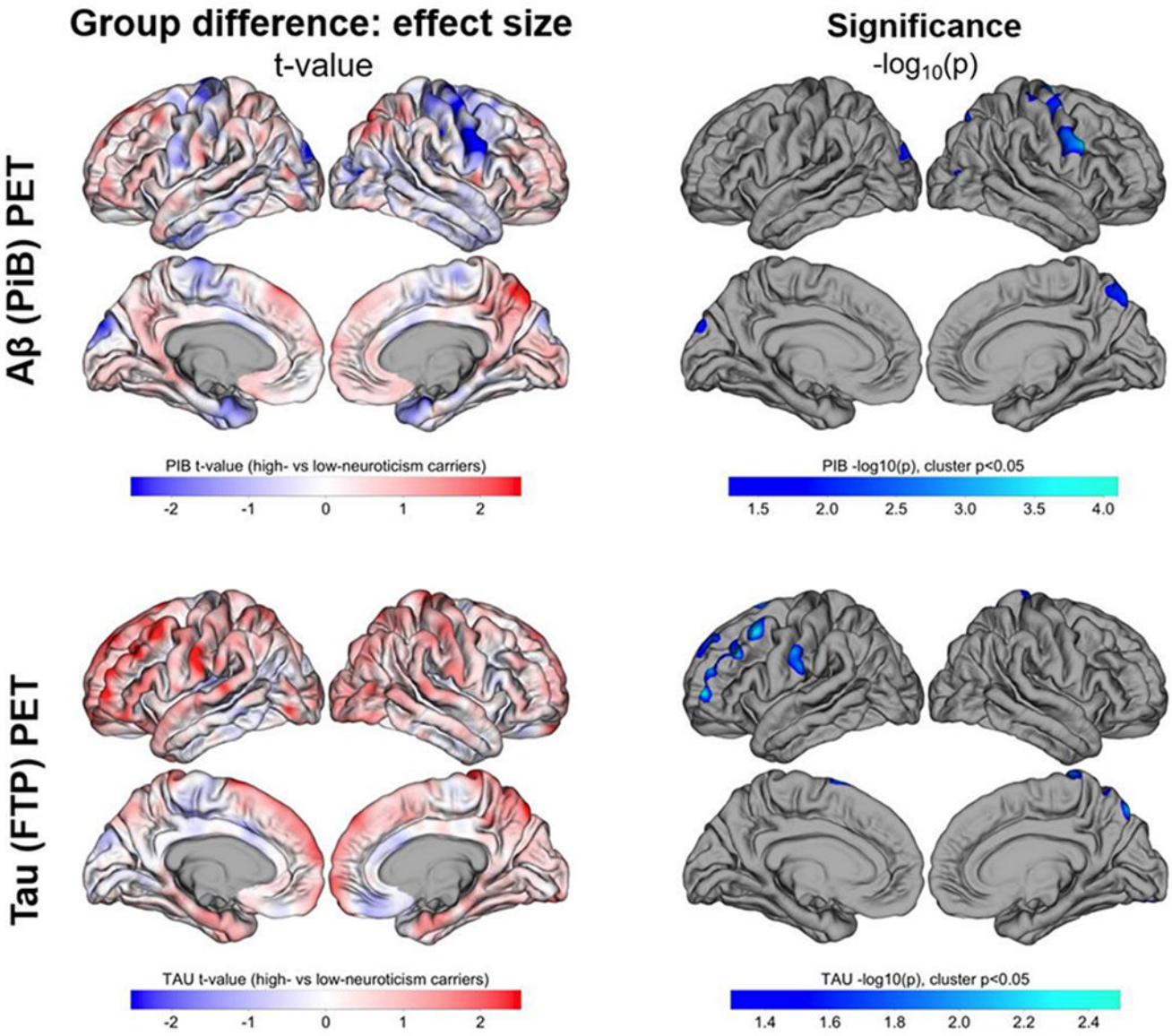

Figure 4. Group comparisons of tau and amyloid PET for carriers with high- versus low-neuroticism

Note. PiB: Pittsburg Compound B; FTP: Flortaucipir

Group comparisons high- low-neuroticism and PIB (t-tests) and FTP. $p<0.05$

Table 1.

Demographic characteristics for all participants

Characteristic	**Non-Carriers (*n* = 41)**		**Carriers (*n* = 33)**		**p-value**
Sex (χ^2 = 4.35)	Females	20	Females	24	.04
	Males	21	Males	9	
	Mean	**SD**	**Mean**	**SD**	
Age	32.56	6.2	32.18	6.37	0.73
Education	10.49	4.05	10.03	3.75	0.58
MMSE/30	29.12	0.9	28.91	0.98	0.34
GDS	1.34	1.7	1.39	2.49	0.33
FAST	1.12	0.33	1.18	0.39	0.48
Global Deterioration Scale	1.10	0.30	1.18	0.39	0.30

Note. MMSE = Mini-Mental State Examination; FAST= Functional Assessment Staging; GDS = Geriatric Depression Scale; SD = Standard Deviation; χ^2 = Chi-Squared.

Additional p-values are defined by a Mann-Whitney U test of independent samples for healthy mutation carriers vs. non-carriers.

Table 2.

Demographic and cognitive characteristics for subset of subjects with PET Imaging

Characteristic	**Non-Carriers (*n* = 26)**		**Carriers (*n* = 20)**		**p-value**
Gender (χ^2 = 0.86)	Females	12	Females	12	.35
	Males	14	Males	8	
	Mean	**SD**	**Mean**	**SD**	
Age	35.69	5.32	35.7	5.58	0.97
Education	10.42	4.37	10.05	3.98	0.75
MMSE/30	28.84	0.93	28.45	0.89	0.11
GDS	1.12	1.63	1.65	2.98	0.94
FAST	1.08	0.27	1.2	0.41	0.22
Global Deterioration Scale	1.12	0.33	1.25	0.44	0.24
CERAD Word List Learning	20.65	3.11	18.4	3.98	0.08
CERAD Word List Delayed Recall	7.42	1.17	6.55	2.14	0.27
CERAD Word List Recognition	9.65	0.63	9.55	0.76	0.73
Semantic Fluency (Animals)	19.35	3.66	20.95	5.13	0.24

Note. MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale; SD = Standard Deviation; χ^2 = Chi-Squared.

Additional p-values are defined by a Mann-Whitney U test of independent samples for healthy mutation carriers vs. non-carriers.

Table 3.

Personality traits in mutation carriers and noncarriers

Trait	Non-Carriers (*n* = 42)		Carriers (*n* = 33)		p-value
	Mean	SD	Mean	SD	
Neuroticism	18.66	7.29	22.85	8.16	.02 [.058 *]
Extraversion	34.20	5.55	32.55	6.12	.27
Openness	29.54	5.93	30.49	6.18	.54
Agreeableness	32.10	6.18	31.82	6.46	.83
Conscientiousness	36.56	4.61	36.12	4.37	.70

Note. SD, Standard Deviation.

Big Five personality traits assessed with the NEO-FII inventory. p-value defined by a Mann-Whitney U test of independent samples for healthy carriers of presenilin 1 mutation versus non-carriers.

* p-value calculated for ANCOVA test, after adjusting for sex.

Table 4.

Comparison in levels of neuroticism between men and women

	Neuroticism Levels		
	Mean	**Difference**	**p-value**
Women	21.77	3.07	.15
Men	18.70		
Carrier Women	23.38	1.93	.54
Carrier Men	21.44		
Non-Carrier Women	19.85	2.33	.31
Non-Carrier Men	17.52		

p-values are defined by a Mann-Whitney U test of independent samples.

Table 5.

Cortical amyloid and regional tau binding in mutation carriers and noncarriers.

Region	Non-Carriers (*n* = 26)		Carriers (*n* = 20)		p-value
	Mean	SD	Mean	SD	
Cortical Amyloid (DVR)	1.12	0.05	1.59	0.31	< .001
Entorhinal Tau (SUVR)	1.01	0.22	1.49	0.41	< .001
Inferior Temporal Tau (SUVR)	1.18	0.12	1.30	0.20	.022

Note. SUVR, standardized uptake value ratio; DVR, Volume Distribution Ratio; SD, Standard Deviation. Partial Volume Correction (PVC) was applied to the PET data.

p-value defined by a Mann-Whitney U test of independent samples for healthy carriers of presenilin 1 mutation versus non-carriers.

Table 6.

Correlations between personality, age and brain pathology levels.

		AGE		TAU Entorhinal		TAU Inferior temporal		PIB DVR	
		NC	**C**	**NC**	**C**	**NC**	**C**	**NC**	**C**
Neuroticism	*r*	−0.23	0.07	−0.20	.47*	−0.13	0.17	−0.33	0.15
	IC95%	[−0.56, 0.18]	[−0.38, 0.5]	[−0.55, 0.20]	**[0.03, 0.75]**	[−0.5, 0.27]	[−0.29, 0.57]	[−0.64, 0.06]	[−0.32, 0.55]
	Sig.	0.16	0.68	0.33	0.04	0.54	0.46	0.10	0.54
Extraversion	*r*	−0.08	0.01	−0.24	−0.24	−0.08	−0.18	0.29	0.03
	IC95%	[−0.46, 0.31]	[−0.43, 0.45]	[−0.57, 0.17]	[−0.62, 0.22]	[−0.45, 0.32]	[−0.58, 0.28]	[−0.11, 0.61]	[−0.42, 0.47]
	Sig.	0.61	0.96	0.25	0.30	0.70	0.44	0.16	0.89
Openness	*r*	−0.07	0.05	−0.19	−0.02	−0.31	−0.01	0.01	−0.16
	IC95%	[−0.45, 0.32]	[−0.40, 0.48]	[−0.54, 0.21]	[−0.46, 0.43]	[−0.62, 0.09]	[−0.45, 0.44]	[−0.38, 0.39]	[−0.56, 0.30]
	Sig.	0.65	0.78	0.35	0.95	0.13	0.98	0.98	0.50
Agreeableness	*r*	0.00	−0.14	0.10	−0.08	0.16	−0.02	0.14	−0.06
	IC95%	[−0.39, 0.39]	[−0.55, 0.32]	[−0.30, 0.47]	[−0.50, 0.38]	[−0.25, 0.51]	[−0.46, 0.43]	[−0.26, 0.50]	[−0.49, 0.39]
	Sig.	0.99	0.43	0.63	0.74	0.45	0.95	0.51	0.80
Conscientiousness	*r*	−0.12	−0.08	0.17	−0.23	0.19	−0.02	0.22	−0.16
	IC95%	[−0.48, 0.28]	[−0.50, 0.38]	[−0.23, 0.52]	[−0.61, 0.24]	[−0.21, 0.54]	[−0.46, 0.42]	[−0.19, 0.56]	[−0.57, 0.3]
	Sig.	0.47	0.66	0.41	0.33	0.36	0.92	0.29	0.49

Note. Sig, Significance. SUVR, standardized uptake value ratio. DVR, Volume Distribution Ratio. NC, No Carriers. C, Carriers.

The correlations were calculated through r, Rho Spearman and 95% confidence intervals are shown in brackets. Partial Volume Correction (PVC) was applied to the PET data.

* $p < 0.05$