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Conscientiousness is Negatively Associated with Grey Matter Volume in Young *APOE* ε4-Carriers

Lukas Kunz[a,b,c,*], Martin Reuter[d,e], Nikolai Axmacher[a,b,c] and Christian Montag[f,g,*]
[a] *German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany*
[b] *Department of Epileptology, University of Bonn, Bonn, Germany*
[c] *Department of Neuropsychology, Institute of Cognitive Neuroscience, Ruhr-University Bochum, Bochum, Germany*
[d] *Department of Psychology, University of Bonn, Bonn, Germany*
[e] *Center for Economics and Neuroscience, University of Bonn, Bonn, Germany*
[f] *Institute for Psychology and Education, Ulm University, Ulm, Germany*
[g] *Key Laboratory for NeuroInformation/Center for Information in BioMedicine, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, China*

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Abstract. The etiology of late onset Alzheimer's disease (LOAD) depends on multiple factors, among which the *APOE* ε4 allele is the most adverse genetic determinant and conscientiousness represents an influential personality trait. A potential association of both factors with brain structure in young adulthood may constitute a constellation that sets the course toward or against the subtle disease progression of LOAD that starts decades before clinical manifestation. Hence, in the present study, we examined the modulating effects of *APOE* ε4 on the relation between personality dimensions, including conscientiousness, and total grey matter volume (GMV) in young healthy adults using an *a priori* genotyping design. 105 participants completed an inventory assessing the Five Factor Model of Personality (NEO-FFI) and a structural MRI scan. Total GMV was estimated using both Freesurfer as well as VBM8. Across all participants, total GMV was positively associated with extraversion and negatively related to age. In *APOE* ε4-carriers—but not in *APOE* ε4-non-carriers—conscientiousness was negatively associated with total GMV. In line with the hypothesis of antagonistic pleiotropy of the *APOE* ε4 allele, this result suggests that young *APOE* ε4-carriers with increased total GMV may particularly benefit from cognitive advantages and thus have a lower need to engage in conscientious behavior. In this subset of young *APOE* ε4-carriers, the reduction in conscientiousness could then bring along adverse health behavior in the long run, potentiating the risk for LOAD. Hence, young *APOE* ε4-carriers with increased total GMV may be at a particularly high risk for LOAD.

Keywords: Alzheimer's disease, apolipoprotein E, big five, Freesurfer, NEO-FFI, personality, voxel-based morphometry

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and represents a devastating condition of the human brain. Patients suffer from cognitive dysfunction, behavioral disturbances, and difficulties with performing activities of daily living [1]. Besides pain for the afflicted patients and caring families, AD elicits strong financial burden on society [2]. AD can be subdivided into an early onset and a late onset

*Correspondence to: Prof. Dr. Christian Montag, Heisenberg Professor, Institute of Psychology and Education, Zentrum für Biomedizinische Forschung, Ulm University, Helmholtzstr. 8/1, D-89081 Ulm, Germany. Tel.: +49 731 50 26550; E-mail: christian.montag@uni-ulm.de and Lukas Kunz, Department of Neuropsychology, Institute of Cognitive Neuroscience, Ruhr-University Bochum, Universitätsstraße 150, 44801 Bochum, Germany. E-mail: lukas.kunz@uni-bonn.de.

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variant, the latter accounting for the majority of AD cases. Whereas early onset AD is mainly caused by mutations in three distinct genes [3], the development of late onset AD (LOAD) is influenced by multiple risk factors including age and genetic determinants, but also personality dimensions [4, 5].

Regarding genetic risk factors, the *APOE* gene is the most prominent determinant for LOAD [6]. Three main allelic variants of the human *APOE* gene exist (frequencies are shown in round brackets according to [7]): ε2 (6.4%), ε3 (78.3%), and ε4 (14.5%). In humans, all six potential genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4) can be found [8, 9]. The most common genotype is *APOE* ε3/ε3, followed by *APOE* ε3/ε4 and *APOE* ε2/ε3, whereas the allele combinations *APOE* ε2/ε2, *APOE* ε2/ε4, and *APOE* ε4/ε4 are rare [10]. Individuals carrying the *APOE* ε4 allele are at increased risk for LOAD compared with those carrying the more common *APOE* ε3 allele, whereas the *APOE* ε2 allele decreases risk [11]. One *APOE* ε4 allele increases the risk by a factor of 4, and two *APOE* ε4 alleles increase the risk by a factor of more than 10 [12]. However, the genotype information taken alone is not a reliable diagnostic source for detecting LOAD in patient groups [13]. The resulting gene product of *APOE* ε4, apolipoprotein E4, amplifies the deposition of Aβ and increases tangle formation [14], the two histopathological hallmarks in the development of AD [15, 16]. Already in young adults, the *APOE* ε4 allele leads to adverse effects on the human brain: for example, neuropathological studies showed increased initial neurofibrillary changes [17], structural magnetic resonance imaging (MRI) revealed reduced entorhinal cortical thickness [18], and functional MRI detected impaired grid-cell-like representations that are important for spatial navigation [19]. These findings jointly support the view that the pathological cascade of LOAD starts decades before the clinical manifestation [20, 21].

Regarding personality, the two traits conscientiousness and neuroticism seem to be of particular relevance for LOAD. Besides extraversion, openness to experience, and agreeableness, they constitute the primary personality dimensions of the five-factor model of personality [22]. Whereas conscientiousness is characterized by higher accurateness, self-organization, and motivational stability as well as preference of long term goals over more immediate incentives, neuroticism comprises increased anxiety, worry, and loneliness as well as higher self-consciousness [23]. Individuals with low scores in conscientiousness or high scores in neuroticism are at three-fold increased risk for AD [5, 24, 25]. Similarly, higher scores in conscientiousness and lower scores in neuroticism (assessed 15 years before autopsy) seem to prevent the occurrence of clinical symptoms in older adults with apparent AD neuropathology, thus representing resilience factors [26]. Different factors may mediate the influence of conscientiousness on the development of AD: Conscientiousness is related to more beneficial health behavior [27–30], reduced levels of systemic inflammation [31, 32], higher longevity [33–35], and better job performance [36–38]. As LOAD promoting personality dimensions may aggravate adverse genetic preconditions, it is worth examining the interaction effects of genetic information and personality traits on cognitive decline. For example, elderly carriers of the *APOE* ε4 allele show a stronger decline in cognitive functions when they are either neurotic or extraverted [39] and chronic anxiety leads to a greater decline in problem solving skills in homozygous *APOE* ε4-carriers as compared to heterozygous *APOE* ε4-carriers and *APOE* ε4-non-carriers [40]. Vice versa, AD protective personality dimensions such as conscientiousness might attenuate adverse genetic preconditions, although this is speculative at the current stage.

In the present study, we address a related open question: how are the combined effects of *APOE* polymorphisms and personality dimensions related to brain structure? Particularly in young adulthood, specific constellations may emerge that set the course toward or against the disease initiation and progression of LOAD. We assessed brain structure as total GMV (normalized by intracranial volume), which was previously shown to correlate negatively with neuroticism [41] and to correlate slightly positively with conscientiousness [42], both findings being assessed irrespectively of *APOE* genotype. Rather, whether the relations between personality and brain structure depend on *APOE* genotype is currently unknown. Hence, in the present study we investigated how *APOE* ε4 modulates the relationship between personality dimensions and total GMV in 105 young healthy adults, which may identify a subgroup of young individuals at a particularly high risk for LOAD.

MATERIALS AND METHODS

Participants

The participants of this study are a subsample of a previous study [43] and an extension of a different functional MRI study [19]. They were recruited in different lectures of the University of Bonn, Bonn, Germany. All participants (N = 531) filled in a self-report measure of the Five Factor Model of Personality (NEO-FFI) [22] and provided buccal swaps for genotyping the *APOE* polymorphism. In order to heighten statistical power, we conducted an *a priori* genotyping design [44]. Please see [45] and [19] for successful applications of this design. Hence, all participants were genotyped first and subsequently 105 male and female participants (age range, 18–30 years) were randomly selected based on their *APOE* status to undergo a structural (N = 105) as well as a functional (n = 94) MRI scan. Exclusion criteria for participation were a history of or current psychiatric or neurological disorder. The functional MRI scan was used to assess neural correlates of spatial navigation in both genetic subgroups. The results from this experiment show reduced entorhinal grid-cell-like representations in *APOE* ε3/ε4-carriers as compared to *APOE* ε3/ε3-carriers and are published elsewhere [19]. Participants as well as experimenters were blinded to genotypes. *APOE* ε4-carriers (*APOE* ε3/ε4; $n = 54$) and *APOE* ε4-non-carriers (*APOE* ε3/ε3; $n = 51$) did not differ in demographic characteristics (Table 1) and reported no history of neurological or psychiatric disease. None of the participants reported alcohol or drug addiction as well as intake of amphetamine, cocaine, MDMA, or hallucinogens. Sample sizes are based on previous *APOE*-MRI-studies (e.g., [46–48]). Since homozygous *APOE* ε4/ε4-carriers are very rare (about 2% in the US population; [10]), we decided *a priori* to not invite homozygous *APOE* ε4/ε4-carriers to our study. The local Ethics Committee of the Medical Faculty of the University of Bonn approved the study and all participants signed a written informed consent form.

Table 1
Sociodemographic features, total grey matter volume, and personality dimensions within genetic subgroups

Feature	*APOE* ε3/ε3	*APOE* ε3/ε4	*p*
Number	51	54	
Sex (male/female)	26/25	24/30	0.503
Age (days)	8615 ± 150	8368 ± 149	0.246
Education (years)	16.39 ± 0.32	16.02 ± 0.32	0.411
Freesurfer total GMV (%)[a]	57.8 ± 0.2	57.9 ± 0.3	0.729
VBM8 total GMV (%)[a]	56.7 ± 0.2	56.8 ± 0.3	0.823
Neuroticism	2.66 ± 0.09	2.54 ± 0.08	0.299
Extraversion	3.40 ± 0.06	3.59 ± 0.06	0.032[b]
Openness to Experience	3.69 ± 0.07	3.54 ± 0.07	0.142
Agreeableness	3.68 ± 0.07	3.67 ± 0.06	0.965
Conscientiousness	3.64 ± 0.09	3.57 ± 0.07	0.540

Values represent the number of participants or mean ± standard error of the mean. *p*-values (not corrected for multiple comparisons) refer to *t*-tests (parametric data) and χ^2-tests (categorical data). [a]Values are expressed as percentage of whole-brain volume, see Materials and Methods. [b]This effect was not present in a larger population (see [43]) and would not hold for multiple testing.

Self-report measure

The questionnaire NEO-FFI [22] measures the so-called Five Factor Model of Personality. These dimensions originally have been derived by factor analysis, using a lexical approach. The dimensions are called neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Each dimension is measured with twelve items being scored on by a five point Likert scale ranging from “strongly disagree” to “strongly agree”. In the present study we computed scale means for each dimension (with a range from 1 to 5).

APOE genotyping

Automated purification of genomic DNA was conducted by means of the MagNA Pure® LC system using a commercial extraction kit (MagNA Pure LC DNA isolation kit; Roche Diagnostics, Mannheim, Germany). Analysis of the *APOE* polymorphism was conducted with real time polymerase chain reaction (PCR) on a Light Cycler System by Roche. Primers and hybridization probes were provided by TIBMOLBIOL, Berlin, Germany.

MRI

Scanning was performed at the German Center for Neurodegenerative Diseases (DZNE), Bonn, using a *Skyra* 3T MRI Scanner (Siemens, Erlangen, Germany) with a 20-channel head receive coil. Participants underwent a T1 weighted structural scan, for which a whole-head magnetization-prepared rapid gradient-echo imaging sequence (MP-RAGE) with the following parameters was used: 1 mm isotropic resolution; inversion time (TI) = 1100 ms; repetition time (TR) = 2500 ms; echo time (TE) = 4.37 ms; flip angle = 7°; total acquisition time (TA) = 5:08 min.

Analysis of total grey matter volume using Freesurfer

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, which is documented and freely available for download online (v5.3.0, http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications [49–51]. Briefly, this processing includes removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures, intensity normalization, tessellation of the grey matter/white matter boundary, automated topology correction, and surface deformation. Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths. Extracted subject-specific values of raw total GMV were divided by the subject-specific values of total intracranial volume (so-called "BrainSegVolNotVent" Freesurfer output variable) resulting in normalized total GMV.

Analysis of total grey matter volume using VBM8 in SPM8

To corroborate our findings, we also extracted total GMV using VBM8 (http://dbm.neuro.uni-jena.de/vbm8) in SPM8 (http://www.fil.ion.ucl.ac.uk/spm) running under Matlab (2014a, The MathWorks Inc., MA, USA). First, T1 images were normalized to a template space (SPM MNI template) using the high-dimensional DARTEL normalization method and were segmented into grey matter, white matter, and cerebrospinal fluid afterwards. All images were checked and sample homogeneity was examined using covariance to ensure processing quality. Then, extracted subject-specific values of raw total GMV were divided by the subject-specific sums of grey matter and white matter leading to normalized total GMV.

Statistical analyses

All statistical analyses were performed in SPSS (version 23.0, IBM Corp., NY). First, we performed a multivariate analysis of covariance (MANCOVA) to examine direct effects of *APOE* genotype and sex on the personality dimensions (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness), with age as a covariate. Second, we conducted linear multiple regression analyses across all participants to analyze overall effects of personality on total GMV (independent variables: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness; dependent variable: total GMV). Third, we performed the same linear regression analyses within genetic subgroups to assess *APOE* dependent effects of personality on total GMV. As controls, the same linear regression models (across all participants as well as within genetic subgroups) were also computed including age and sex as additional predictor variables to exclude potential confounds (independent variables: neuroticism, extraversion, openness to experience, agreeableness, conscientiousness, age, and sex; dependent variable: total GMV). We then focused on the *APOE*-dependent relation between conscientiousness and total GMV by calculating *post-hoc* Pearson correlations within genetic subgroups. Differences between correlation coefficients were evaluated using the Fisher *r*-to-*z* transformation. For all analyses, an alpha of $p < 0.05$ was considered significant.

RESULTS

Participants

The genetic subgroups ($n = 51$ *APOE* ε3/ε3-carriers, $n = 54$ *APOE* ε3/ε4-carriers) were matched in age and sex and did not differ regarding total GMV (Table 1). Internal consistencies of the personality dimensions ranged from good to very good (neuroticism = 0.84, extraversion = 0.75, openness to experience = 0.73, agreeableness = 0.74, conscientiousness = 0.84). Validity and reliability of the NEO-FFI questionnaire have been demonstrated before (e.g., [22, 52–54]).

APOE polymorphism, sex, age, and personality

We performed a multivariate analysis of covariance (MANCOVA) with genotype and sex as independent variables, age as covariate and the personality dimensions as dependent variables to examine direct effects of genotype and sex on personality. This revealed that genotype was not associated with any of the personality dimensions ($F_{5,96} = 1.737$, $p = 0.133$, Wilk's $\Lambda = 0.917$; see also Table 1). Two personality dimensions varied as a function of sex ($F_{5,96} = 6.922$, $p < 0.001$, Wilk's $\Lambda = 0.735$) such that females showed higher values of agreeableness (*post-hoc* ANCOVA, $F_{1,100} = 12.535$, $p = 0.001$) as well as higher values of conscientiousness (*post-hoc* ANCOVA, $F_{1,100} = 5.177$, $p = 0.025$) in comparison to males. There was no interaction effect of genotype and sex ($F_{5,96} = 1.355$, $p = 0.248$, Wilk's $\Lambda = 0.934$)

and no effect of age ($F_{5,96} = 1.085$, $p = 0.374$, Wilk's $\Lambda = 0.947$) on any of the personality dimensions.

Personality and total GMV

Freesurfer and VBM8 led to highly similar estimates of total GMV (Pearson's $r = 0.941$, $p < 0.001$). Across all participants, we observed a strong positive association between extraversion and total GMV (Freesurfer, $p = 0.008$; VBM8, $p = 0.003$; Table 2) and a trend for a negative association between conscientiousness and total GMV (Freesurfer, $p = 0.054$; VBM8, $p = 0.114$). These findings were similar when including age and sex as additional predictors in a separate regression analysis (Table 3). Additionally, older age was highly associated with reduced total GMV (Freesurfer and VBM8, $p < 0.001$).

APOE polymorphism, personality, and total GMV

Next, we performed the linear regression analyses separately for both genetic subgroups, which revealed three findings (Tables 4 and 5).

First, the positive association between extraversion and total GMV was similarly strong in both genetic subgroups (Table 4). Second, the trend for a negative association between conscientiousness and total GMV was driven by *APOE* ε4-carriers (*APOE* ε3/ε3, $\beta = 0.092$, $p = 0.594$; *APOE* ε3/ε4, $\beta = -0.410$, $p = 0.002$; Table 4). Qualitatively identical results were obtained when including age and sex as additional predictor variables in a separate linear regression analysis (Table 5). Furthermore, *post-hoc* Pearson correlations between conscientiousness and total GMV separately for both genetic subgroups corroborated the robustness of this finding: Again, increased values of conscientiousness were significantly related to lower total GMV in *APOE* ε4-carriers (Pearson's $r = -0.288$, $p = 0.035$), but not in *APOE* ε4-non-carriers (Pearson's $r = 0.194$, $p = 0.173$). In addition, the correlation coefficients were significantly different between both genetic subgroups (Fisher r-to-z transformation, $z = -2.45$, $p = 0.014$). Third, we observed a negative relation between neuroticism and total GMV preferentially in *APOE* ε4-carriers (*APOE* ε3/ε3, $\beta = 0.063$, $p = 0.728$; *APOE* ε3/ε4, $\beta = -0.296$, $p = 0.028$; Table 4). However, this relation was not robust against the inclusion of age and sex as additional predictor variables in a separate linear regression analysis (Table 5), was not clearly confirmed by *post-hoc* Pearson correlations (*APOE* ε3/ε3, Pearson's $r = -0.166$, $p = 0.245$; *APOE* ε3/ε4, Pearson's $r = -0.241$, $p = 0.080$), and the correlation coefficients were not significantly different between genetic subgroups (Fisher r-to-z transformation, $z = 0.39$, $p = 0.697$).

Note that the results in Table 3 (and 5) are a slightly modified version of those in Table 2 (and 4). Therefore, three independent models are tested in total. Both models that contain significant relations between personality and total GMV remain significant after Bonferroni correction for multiple comparisons (three tests; $p = 0.05/3 = 0.017$; see the table legends for the F-values, p-values, and R^2-values of the models).

APOE, conscientiousness, and regional GMV of the orbitofrontal cortex

Finally, since a previous study showed that regional GMV of the orbitofrontal cortex is positively associated with conscientiousness in healthy aging [42], we tested this specific hypothesis in our data. Indeed, in *APOE* ε4-non-carriers, we found that higher values of conscientiousness were related to increased regional GMV (obtained using Freesurfer and normalized

Table 2
Effects of personality on total grey matter volume across all participants (N = 105 participants)

Personality dimension	Freesurfer[a]		VBM8[b]	
	β	p	β	p
Neuroticism	–0.164	0.141	–0.128	0.251
Extraversion	0.280	0.008**	0.312	0.003**
Openness to experience	–0.115	0.221	–0.094	0.319
Agreeableness	0.051	0.601	0.034	0.724
Conscientiousness	–0.202	0.054(*)	–0.166	0.114

[a] $F_{5,99} = 3.733$, $p = 0.004$, adjusted $R^2 = 0.116$. [b] $F_{5,99} = 3.574$, $p = 0.005$, adjusted $R^2 = 0.110$. $^{(*)}p < 0.10$; $^{**}p < 0.01$.

Table 3
Effects of personality on total grey matter volume across all participants controlling for age and sex (N = 105 participants)

Personality dimension	Freesurfer[a]		VBM8[b]	
	β	p	β	p
Neuroticism	–0.174	0.122	–0.163	0.145
Extraversion	0.217	0.030*	0.243	0.015*
Openness to experience	–0.073	0.411	–0.046	0.602
Agreeableness	0.027	0.784	–0.012	0.906
Conscientiousness	–0.169	0.108	–0.153	0.143
Age	–0.333	<0.001***	–0.334	<0.001***
Sex (male/female)	0.076	0.452	0.139	0.167

[a] $F_{7,97} = 5.139$, $p < 0.001$, adjusted $R^2 = 0.218$. [b] $F_{7,97} = 5.344$, $p < 0.001$, adjusted $R^2 = 0.226$. $^{*}p < 0.05$; $^{***}p < 0.001$.

Table 4
APOE-dependent effects of personality on total grey matter volume (N = 105 participants)

Personality dimension	Freesurfer				VBM8			
	APOE ε3/ε3[a]		*APOE* ε3/ε4[b]		*APOE* ε3/ε3[c]		*APOE* ε3/ε4[d]	
	β	p	β	p	β	p	β	p
Neuroticism	0.063	0.728	–0.296	0.028*	0.097	0.593	–0.263	0.051(*)
Extraversion	0.379	0.034*	0.239	0.060(*)	0.397	0.025*	0.284	0.027*
Openness to experience	–0.078	0.591	–0.100	0.412	–0.076	0.595	–0.064	0.600
Agreeableness	–0.090	0.565	0.175	0.156	–0.125	0.419	0.180	0.148
Conscientiousness	0.092	0.594	–0.410	0.002**	0.129	0.450	–0.372	0.006**

[a]$F_{5,45} = 1.477$, $p = 0.216$, adjusted $R^2 = 0.045$. [b]$F_{5,48} = 4.427$, $p = 0.002$, adjusted $R^2 = 0.244$. [c]$F_{5,45} = 1.643$, $p = 0.168$, adjusted $R^2 = 0.060$. [d]$F_{5,48} = 4.213$, $p = 0.003$, adjusted $R^2 = 0.233$. $^{(*)}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$.

Table 5
APOE-dependent effects of personality on total grey matter volume controlling for age and sex (N = 105 participants)

Personality dimension	Freesurfer				VBM8			
	APOE ε3/ε3[a]		*APOE* ε3/ε4[b]		*APOE* ε3/ε3[c]		*APOE* ε3/ε4[d]	
	β	p	β	p	β	p	β	p
Neuroticism	–0.009	0.961	–0.264	0.077(*)	0.007	0.966	–0.258	0.084(*)
Extraversion	0.307	0.076(*)	0.215	0.087(*)	0.341	0.044*	0.248	0.049*
Openness to experience	–0.029	0.833	–0.057	0.635	–0.009	0.946	–0.025	0.834
Agreeableness	–0.138	0.390	0.161	0.217	–0.205	0.191	0.144	0.270
Conscientiousness	0.058	0.733	–0.354	0.010*	0.067	0.684	–0.330	0.016*
Age	–0.349	0.012*	–0.278	0.026*	–0.341	0.012*	–0.290	0.020*
Sex (male/female)	0.179	0.257	0.012	0.933	0.253	0.102	0.071	0.627

[a]$F_{7,43-} = 2.580$, $p = 0.026$, adjusted $R^2 = 0.181$. [b]$F_{7,46} = 4.151$, $p = 0.001$, adjusted $R^2 = 0.294$. [c]$F_{7,43} = 3.061$, $p = 0.011$, adjusted $R^2 = 0.224$. [d]$F_{7,46} = 4.155$, $p = 0.001$, adjusted $R^2 = 0.294$. $^{(*)}p < 0.10$; $^{*}p < 0.05$.

to total intracranial volume) of the orbitofrontal cortex (Pearson's $r = 0.323$, $p = 0.021$). By contrast, in *APOE* ε4-carriers, this effect was not present (Pearson's $r = –0.167$, $p = 0.228$). Correlation coefficients were significantly different between genetic subgroups (Fisher *r*-to-*z* transformation, $z = 2.5$, $p = 0.012$).

DISCUSSION

In the present study, we examined the association between brain structure and two important determinants of LOAD, namely the *APOE* polymorphism and personality traits, particularly conscientiousness, in young healthy adults. Brain structure was assessed as total GMV using both Freesurfer and VBM8 ruling out that our findings were due to algorithmic details of a specific software. We showed that total GMV is negatively associated with conscientiousness in *APOE* ε4-carriers, but not in *APOE* ε4-non-carriers. This result suggests the existence of specific relationships between brain structure, conscientiousness, and genetic risk for LOAD in young adults that may augment early disease processes underlying the pathological cascade of LOAD [21].

The finding of an inverse relationship between total GMV and conscientiousness in *APOE* ε4-carriers may be surprising at first sight, since greater total GMV is generally thought to be beneficial: In older adults, total GMV correlates with short term memory [55] and resilience of memory functions to aging [56]. In young adults, increased total GMV is related to better average cognitive and spatial performance [57] as well as higher intelligence [58, 59] and higher Spearman's *g*, which is a proxy for general intelligence [60]. However, against the backdrop of the hypothesis of antagonistic pleiotropy, which states that the *APOE* ε4 allele exerts transient beneficial effects in youth despite its adverse effects at an older age [61–64], one may speculate that a subgroup of young *APOE* ε4-carriers showing increased total GMV particularly benefits from specific cognitive advantages (see, for example, the findings of [65–69]) and thus has a lower need to engage in especially conscientious behavior. In this subgroup of young *APOE* ε4-carriers, reduced conscientiousness could then bring along adverse health behavior [27], increased systemic inflammation [32], and worsened job performance in the long run [37], amplifying the risk for LOAD [25]. Please note, however, that this speculation partially exceeds the hypothesis of antagonistic pleiotropy, since the cognitive advantages are not assigned to *APOE* ε4-carriers in general, but to a specific subgroup of *APOE* ε4-carriers (exhibiting increased total GMV), which might be more compatible with the diverse results of *APOE* ε4 on cognitive functioning in previous studies [64]. Accordingly, our results point at the importance of considering the interplay between *APOE* and other risk factors for LOAD in future *APOE* studies. Furthermore, the development of total GMV in *APOE* ε4-carriers over time is currently unknown. One may speculate for example that young *APOE* ε4-carriers with increased total GMV show a stronger loss of total GMV during aging.

Consistent with a previous study [42], *APOE* ε4-non-carriers showed a numerically positive, although not statistically significant, relation between conscientiousness and total GMV as well as a significant positive correlation between conscientiousness and regional GMV of the orbitofrontal cortex, which closely resembles prior findings [42, 70]. This result seems plausible as the orbitofrontal cortex is considered to be important for encoding economic value [71], monitoring reward value and evaluation of punishers [72] as well as goal-directed decision making, specifically in representing task state [73]: A larger regional volume of the orbitofrontal cortex might enhance the ability to decompose the complexity of the world into well-defined states and to better assign specific values to these states. This may result in more accurate behavior, better self-organization, and preference of more rewarding long term goals over less rewarding short term goals, underlying the personality trait conscientiousness.

Regarding neuroticism, previous studies revealed that individuals with higher values of this personality trait show reduced total GMV [41, 74]. In our study, this effect reached significance only in *APOE* ε4-carriers. Being less neurotic could thus attenuate the negative effects of reduced conscientiousness in *APOE* ε4-carriers with increased total GMV. However, this relation was not robust against the inclusion of age and sex as control variables and was not confirmed in *post-hoc* correlation analyses.

Across all participants, higher values of extraversion were highly correlated with increased total GMV. This finding extends prior studies, which revealed that extraversion is positively related to amygdala and orbitofrontal volume [75–77]. There was no association with *APOE* status, however. In addition, the remaining personality traits openness to experience and agreeableness were not found to be associated with total GMV.

In our sample, *APOE* ε4 was not directly associated with any of the personality dimensions in line with previous findings [39, 43, 78]. *APOE* ε4 was also not directly related to total GMV, again consistent with previous results (e.g., [47, 79]). Subtle differences might only be captured by region-specific analyses focusing on areas subjected to very early LOAD related neuropathology such as the entorhinal cortex [18] and the subiculum [79].

Furthermore, our study showed that older age is strongly correlated with reduced total GMV, even though our participants were young and within a narrow age range (18–30 years), supporting numerous previous studies (e.g., [80, 81]). This association did not depend on *APOE* genotype, which may be due to the participants' young age. Only in older adults, *APOE* ε4 may induce a stronger loss of GMV across time [82], which was also shown in individuals with mild cognitive impairment [83].

A limitation of the present study is that we cannot explain the negative association between conscientiousness and total GMV in *APOE* ε4-carriers in greater depth. In future studies it could therefore be examined, whether this relation is for example mediated by intelligence, since fluid intelligence has been suggested to correlate inversely with conscientiousness [84–86] and intelligence is positively related to GMV [58, 59]. Furthermore, as we assessed the data only at one time point we are not being able to set up a causative model. Follow-up studies should therefore examine whether young *APOE* ε4-carriers with increased total GMV indeed show a stronger loss of GMV over time as speculated above. Additionally, it might be worth examining a third group consisting of homozygous *APOE* ε4/ε4-carriers, which was not possible in the present study since we decided *a priori* to not invite *APOE* ε4/ε4-carriers to our study due to the fact that they are very rare. In particular, finding a potential linear relationship between total GMV and conscientiousness in dependence of the number of *APOE* ε4-alleles would underscore the relevance of our results.

Taken together, in the present study we used a multimodal approach including genetics, personality information, and brain imaging to reveal associations between the *APOE* polymorphism, conscientiousness, and total GMV that could potentially augment early disease processes underlying the subtle initiation of LOAD starting decades before clinical manifestation. Given that lower values of conscientiousness are related to increased risk for LOAD [5, 24, 25] and that conscientiousness is a rather stable personality dimension [87, 88], our data suggest that young *APOE* ε4-carriers with increased total GMV are at a particularly high risk for LOAD. In general, multimodal approaches may constitute a promising research avenue to better understand the early pathophysiology of LOAD.

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