

Original Article

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Late-life cynical hostility is associated with white matter alterations and the risk of Alzheimer's disease

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Abstract

Background. Cynical hostility (CH), a specific dimension of hostility that consists of a mistrust of others, has been suggested as a high-risk trait for dementia. However, the influence of CH on the incidence of Alzheimer's disease (AD) remains poorly understood. This study investigated whether late-life CH is associated with AD risk and structural neuroimaging markers of AD.

Methods. In community-dwelling older adults from the French ESPRIT cohort ($n = 1388$), incident dementia rate according to CH level was monitored during an 8-year follow-up and analyzed using Cox proportional hazards regression models. Brain magnetic resonance imaging volumes were measured at baseline ($n = 508$). Using automated segmentation procedures (Freesurfer 6.0), the authors assessed brain grey and white volumes on all magnetic resonance imaging scans. They also measured white matter hyperintensities volumes using semi-automated procedures. Mean volumes according to the level of CH were compared using ANOVA.

Results. Eighty-four participants developed dementia (32 with AD). After controlling for potential confounders, high CH was predictive of AD (HR 2.74; 95% CI 1.10–6.85; $p = 0.030$) and all dementia types are taken together (HR 2.30; 95% CI 1.10–4.80; $p = 0.027$). High CH was associated with white matter alterations, particularly smaller anterior corpus callosum volume ($p < 0.01$) after False Discovery Rate correction, but not with grey matter volumes.

Conclusions. High CH in late life is associated with cerebral white matter alterations, designated as early markers of dementia, and higher AD risk. Identifying lifestyle and biological determinants related to CH could provide clues on AD pathophysiology and avenues for prevention strategies.

Introduction

Alzheimer's disease (AD) is the most frequent cause of dementia. Due to population aging, the increasing global prevalence of AD will pose huge challenges to public health and elderly care systems in all countries across the world (GBD 2015 Neurological Disorders Collaborator Group, 2017). Given the current lack of any curative treatment, identifying new modifiable risk factors and their associated biological changes could provide new insights on AD pathophysiology and pave the way for prevention strategies. Previous studies have identified dementia risk factors, such as health and lifestyle factors (for instance, diabetes mellitus, smoking, hypertension, and physical activity) and also psychological risk factors [for instance, depression (Vos *et al.*, 2017), chronic psychological distress (Sutin, Stephan, & Terracciano, 2018)]. Many of these psychological risk factors are associated with personality traits themselves involved in AD. These traits include mainly neuroticism and negative thoughts (Marchant *et al.*, 2020; Terracciano *et al.*, 2014) whereas openness and agreeableness are associated with a slightly reduced risk of AD (Terracciano *et al.*, 2014). Personality traits influence lifestyle patterns such as health behavior, dietary habits, cognitive activity, and social relationships (Roberts, Kuncel, Shiner, Caspi, & Goldberg, 2007; Stephan, Boiché, Canada, & Terracciano, 2014; Weston, Edmonds, & Hill, 2020), and these factors in turn are related to the risk of developing dementia in later life (Scarmeas & Stern, 2003; Stern, 2012). Risk traits are relatively stable (Just & Alloy, 1997) but like other traits, they can also be modified through intervention (Gu, Strauss, Bond, & Cavanagh, 2015; Watkins *et al.*, 2011). Therefore, personality characteristics may represent important determinants of dementia risk.

To date, few studies have focused on personality traits and looked at premorbid personality traits as possible predictors of cognitive decline and dementia (Cipriani, Borin, Del Debbio, & Di Fiorino, 2015; Tautvydaitė et al., 2017), some personality traits have yet to be explored. Cynical hostility (CH), as defined by Cook & Medley (1954), refers to a specific dimension of hostility that consists in the mistrust of others, a psychological attitude towards others characterized by the belief that they are mainly motivated by selfish concerns (Gurol et al., 2006). CH has been prospectively associated with higher cardiovascular morbidity and related mortality, as well as all-cause mortality (Tindle et al., 2009). Although many cardiovascular risk factors have been associated with dementia, only one study investigated whether people with higher levels of CH in late-life were more susceptible to dementia (Neuvonen et al., 2014). Despite the scarce literature, it has been hypothesized that psychological factors, such as CH, could influence the risk of a disease like dementia through different biological mechanisms, for instance dysregulated β -adrenergic receptor function (Hughes, Sherwood, Blumenthal, Suarez, & Hinderliter, 2003), elevated pro-inflammatory activity mediated by cytokine production (Janicki-Deverts, Cohen, & Doyle, 2010), and telomere shortening (Brydon et al., 2012). However, no study has assessed the link between CH and AD-related early brain alterations, or brain alterations in general. While previous neuroimaging studies have provided insight into neural correlates of personality traits, the current knowledge of relationships between brain structures, especially white matter, and personality traits remains limited. Knowledge of white matter changes underlying a personality trait such as CH holds significant implications for understanding the neurobiological factors related to behavioral tendencies and cognitive skills likely to promote the emergence of AD (Privado, Román, Saénz-Urturi, Burgaleta, & Colom, 2017; Xu & Potenza, 2012).

Only one study demonstrated significant correlations between CH and regional gray matter density in the right anterior mid-cingulate cortex, bilateral dorsolateral prefrontal cortex, left dorsomedial prefrontal cortex and premotor cortex (Nakagawa et al., 2017). To our knowledge, no study has investigated white matter integrity in CH, or whether brain alterations in people with CH could be related to early neuroimaging biomarkers of dementia.

Among the core neuroimaging markers of AD, hippocampal atrophy is the best described and validated (Jack et al., 2011). Classically, the medial temporal lobe, which contains hippocampus, entorhinal cortex, and amygdala, is affected very early during AD development (Braskie & Thompson, 2014). Cortical atrophy then extends to the remainder of the cortex along a temporal-parietal-frontal trajectory that correlates with the disease severity and the appearance of clinical symptoms (Apostolova et al., 2008; Lerch et al., 2005). This progression is consistent with the spatial distribution of the neurodegenerative changes known to occur in AD from post-mortem studies (Braak & Braak, 1991; Vemuri et al., 2008). Evidence also supports white matter degradation in the early disease stages in the cingulum, fornix, and prominently in the corpus callosum (CC) (Radanovic et al., 2013; Teipel et al., 2010).

The first objective of this study was to investigate the association between late-life CH and incident AD in a community sample of older adults from Southern France during an 8-year follow-up. The second objective was to examine the association between early structural MRI brain markers of AD and CH level.

Methods

Study population

Subjects were selected among the population recruited for the ESPRIT project (Montpellier, France) between 1999 and 2001 (Ritchie et al., 2004). The ESPRIT study ($N = 1863$) is part of a wider, multi-site cohort study (three-City Study; 3C) of community-dwelling people aged 65 and older selected from the electoral rolls of Bordeaux, Dijon and Montpellier, France. The main aim of the ESPRIT study was to construct a comprehensive database that incorporates clinical, biological, genetic, and environmental risk factors of neurological and psychiatric diseases, including neuroimaging data. Random sampling was carried out separately for each of the 15 electoral registers of the Montpellier District between the dates of March 1999 and February 2001, in order to obtain 1/15 of the total population for the purposes of the ESPRIT study. Non-participants were replaced by other participants drawn from the same electoral register through an additional random sampling procedure so that each electoral division was equally represented. Non-participants were slightly older than participants and more likely to live alone (Ritchie et al., 2004). Standardized interviews, neuropsychological tests, neurological and psychiatric examinations were carried out at baseline (phase 1) and at year 2 (phase 2), 4 (phase 3), 7 (phase 4), and 10 (phase 5) of the follow-up. At baseline (phase 1), 760 randomly selected participants younger than 80 years of age underwent an MRI brain scan. The study protocol was approved by the Bicêtre University Hospital Ethical Committee (France), and written informed consent was obtained from each participant after receiving a complete description of the study. The present study included only subjects from the ESPRIT cohort who completed the Buss and Durkee Hostility Inventory (BDHI) for CH assessment (Buss & Durkee, 1957) at phase 2 ($N = 1388$). Brain MRI data were available for $N = 508$ of the selected individuals (Fig. 1). All patients with dementia at phase 1 and 2 were excluded.

Assessment of cynical hostility

The BDHI (Buss & Durkee, 1957) is a measure of general aggression and hostility, composed of 75 items with true-false answers. It has eight subscales, seven of which are designed to measure different components of hostility: assault, verbal aggression, indirect hostility, irritability, negativism, resentment, and suspicion. Using the suspicion component, factor analyses allowed extracting three questions related to CH (questions 14, 46, and 54) that showed good internal reliability ($\alpha = 0.7$): 'I tend to be on my guard with people who are somewhat more friendly than I expected'; 'My motto is "never trust strangers"', and 'I commonly wonder what hidden reason another person may have for doing something nice for me'. The sum of these three questions' scores gives a total score between 0 and 3. Based on this score, participants were divided into three groups: none (score = 0), moderate (score = 1), and high levels (score = 2–3) of CH.

Diagnosis of dementia

At each phase, the diagnosis of dementia was based on a three-step procedure. First, trained psychologists administered a battery of neuropsychological tests that assessed different cognitive domains including verbal fluency (Isaacs Set Test) (Isaacs & Kennie, 1973), immediate visual memory (Benton Visual Retention Test) (Benton, 1965), attention and visuomotor

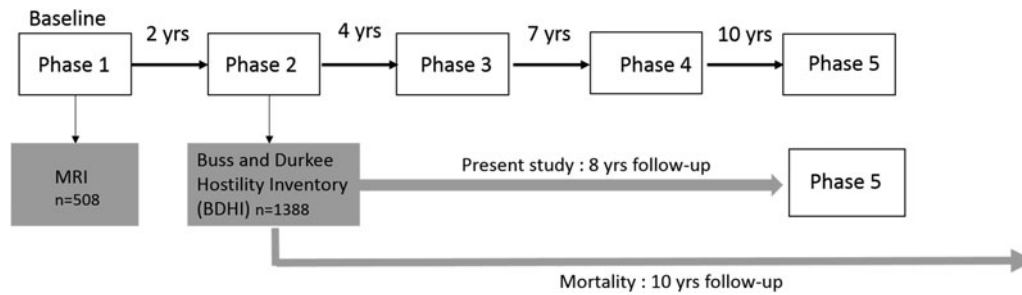


Fig. 1. Flow-chart with the different study phases. Neuropsychological evaluations and diagnosis of dementia are conducted at each phase.

processing speed and executive function (Trail Making Test) (Reitan, 1958), verbal episodic memory (Free and Cued Selective Reminding Test) (Grober, Buschke, Crystal, Bang, & Dresner, 1988). The Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was used as an index of global cognitive performance. Second, all participants were examined by a neurologist. Third, an independent committee of neurologists reviewed all potential prevalent and incident cases of dementia to obtain a consensus on the diagnosis and etiology, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR). Cases of dementia, including AD, were classified according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association Criteria (McKhann et al., 1984), and cases of mixed/vascular dementia according to the National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria (Román et al., 1993). Mixed dementia was defined as a diagnosis of AD with either cerebrovascular lesions on brain imaging, or a documented history of stroke and presence of prominent executive function deficits in addition to an AD-type cognitive profile. During the 8-year follow-up (Fig. 1), the following cases of dementia were identified: AD ($N = 52$), mixed ($N = 12$), Lewy body ($N = 8$), vascular ($N = 7$), Parkinson ($N = 2$), frontotemporal ($N = 1$), and others ($N = 2$). In the context of this work, 'AD' refers to dementia due to Alzheimer's disease.

Socio-demographic and clinical parameters

The baseline interview contained items on socio-demographic characteristics, such as age, sex, marital status, education level (no formal education or primary school, lower secondary education, higher secondary education, and university degree), height, weight, smoking status (non-smoker, ex-smoker, and current smoker), and current alcohol consumption (>12 g/day). The body mass index (BMI) was calculated as follows: weight (kg)/height (m)². Each participant completed self-reported questionnaires on medical disorders, lifestyle, and subjectively evaluated health. History of cardiovascular disease included stroke, myocardial infarction, angina pectoris, arteritis, and coronary surgery.

The current level of depressive symptoms was evaluated with the Center for Epidemiologic Studies-Depression Scale (CESD) (Radloff, 1977); a >16 cut-off indicated a high level of symptoms. A standardized psychiatric examination was administered using the Mini International Neuropsychiatric Interview (MINI; French version 5.00) (Sheehan et al., 1998), based on the DSM IV and whose procedures have been well described elsewhere

(Ritchie et al., 2004). Mood and anxiety disorders, psychotic syndrome, and suicidal risk were assessed.

Blood pressure was measured twice during the interview using an OMRON M4 digital electronic tensiometer. Subjects were considered hypertensive when the mean of the two measurements was $\geq 160/95$ mm Hg, or if they were taking antihypertensive drugs. Blood was collected only at baseline after overnight fasting, for standard measurements of serum C-reactive protein, lipids, and glucose levels. Hypercholesterolemia was defined as total cholesterol ≥ 6.2 mmol/L and/or cholesterol-lowering therapy, and diabetes as treated diabetes or fasting blood glucose ≥ 7 mmol/L. All drugs used in the previous month were recorded from medical prescriptions and drug packages. Apolipoprotein E (APOE) genotyping (presence or absence of the allele $\epsilon 4$) was performed by Lille Génopôle, as previously described (Dufouil et al., 2005). An ultrasound examination of the carotid arteries was performed, as previously described (Plichart et al., 2011).

MRI data analysis

A Sigma 1.5T GE Imaging System (General Electric Medical Systems, Milwaukee, Wisconsin) was used to acquire T1-weighted sequences for volumetric estimations (repetition time = 12 ms, echo time = 2.8 ms, inversion time = 600, matrix size = 256×256 , pixel spacing = 0.9375×0.9375 mm², number of excitations = 1, slice thickness = 1.0 mm). Slices were then converted to isotropic (0.9375 mm³) and re-sliced to 1.00 mm³. T2-weighted 2D axial MR images were also obtained by using the spoiled gradient-echo sequence (RT = 97 ms, ET = 4 ms) that consisted of a set of 124 adjacent transverse sections parallel to the anterior commissure–posterior commissure line with a section thickness of 1.5 mm (no gap).

Automated measurements for grey matter region of interests (ROIs) and CC volumes

Regional reconstruction and segmentation were performed with the FreeSurfer version 6.0 image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). The first stage included the reconstruction of the cortical surface (Dale, Fischl, & Sereno, 1999). Normalized intensity images were created, corrected for variations in intensity due to magnetic field inhomogeneity. Voxels beyond the cerebral cortex, namely the skull, were then removed before beginning the segmentation. Segmentation was based on the geometric structure where grey and white matter interface, and subsequently the left and right hemispheres were separated as well as the cortical from subcortical structures. The resulting cortical volume was covered by a triangular tessellation and deformed to more accurately represent the grey and white matter interface

and the pial surface. Once the cortex was reconstructed, this volume was registered to a spherical atlas (Fischl, Sereno, & Dale, 1999a, 1999b) and parcellated into regions based on the sulcal and gyral structures (Desikan et al., 2006; Fischl et al., 2004). Each T1-weighted scan was segmented into cortical and subcortical ROIs in each hemisphere. The CC was identified and divided into five subsections (anterior, midanterior, central, midposterior, posterior) by the `mri_cc` command of FreeSurfer. The five subsections were derived from evenly spaced partitions along the primary eigenaxis, closely corresponding to the longitudinal axis. Data from the FreeSurfer output, expressed in volumes (mm^3) for each ROI, were then converted to be exported into SPSS for analysis as described below.

Estimation of white matter lesions (WML) volume

WML volumes (in cm^3) were estimated using a semi-automatic method (Brickman et al., 2011; Gurol et al., 2006). Supratentorial WMLs appearing as hyperintensity areas were segmented on T2-weighted sequences using the MRIcro software (Rorden & Brett, 2000). This method was described in detail elsewhere (Mortamais et al., 2013). WML values were transformed by a $\log_{10}(x + 0.01)$ function given their highly asymmetric distribution and possible null values.

Intracranial volume (ICV) estimation

ICV was computed from T1-weighted anatomical images using the segment `m-file` of the SPM5 software (Wellcome Department of Cognitive Neurology, London, UK). The ICV (gray plus white matter plus cerebrospinal fluid) was used as a covariate in the models to minimize the effect due to global brain-size differences. All outputs were manually inspected to ensure accurate and valid data.

Statistical analyses

To assess the association between CH levels and sociodemographic, lifestyle, clinical and psychiatric variables, descriptive analyses were carried out using the χ^2 , analysis of variance (ANOVA), and Kruskal–Wallis tests, according to the variable characteristics. Multivariate Cox proportional hazards models with delayed entry and age as time-scale were used for the longitudinal analysis of dementia and AD onset, during the 8-year follow-up (Commenges, Letenneur, Joly, Alioum, & Dartigues, 1998). The assumption of hazard log-linearity with Schoenfeld partial residuals and residual normality (`dfbeta`) was checked for each CC area measure. The checks did not indicate a violation of the proportional hazard assumption and non-normality of residuals. The date of dementia onset was set half way between the date of the last follow-up visit, when the subject was classified as normal, and the date of diagnosis. The models were adjusted for sex, education level, and for potential confounders reported in the literature: MMSE, APOE $\epsilon 4$, history of cardiovascular disease, diabetes, hypertension, BMI, hypercholesterolemia, smoking status, alcohol use, depressive symptoms, and lifetime anxiety. The results of the Cox proportional hazards regression analyses were expressed as hazard ratios (HR) with 95% confidence intervals (CI). Additional sensitivity analyses were performed to assess the reliability of our findings. Specifically, the association between CH and dementia risk was re-examined after exclusion of all incident cases of dementia at phase 3 (4 years of follow-up). MRI brain ROIs were compared according to the CH level using ANOVA after adjustment for age, sex, educational level, and

ICV. False Discovery Rate (FDR) correction (Benjamini & Hochberg, 1995) was used for multiple comparisons in case of significance. Except for WML data that were transformed, MRI measures were normally distributed based on the Shapiro–Wilks test. Analyses were two-tailed and significance was set at $p \leq 0.05$.

We also performed a mediation analysis to examine the potential mediating role of white matter integrity on the relationship between CH and dementia. Age, sex, education, and APOE status were included as covariates in the models. The hypothesized mediation model was analyzed using the PROCESS macro for SPSS (Hayes, 2017), based on ordinary least squares (OLS) regression. The bias-corrected 95% CI was calculated with 5000 bootstrapping re-samples to estimate the conditional indirect effect (the indirect effect refers to the effect that is through the mediator under study). If the interval does not include zero, the effect is statistically significant at $p < 0.05$.

All statistical analyses were done with IBM SPSS Statistics (SPSS Inc., Chicago, Illinois, USA, version 20).

Results

Baseline characteristics of the study population

The mean age of the 1388 participants was 73.6 years (standard deviation = 4.7), and 782 (56.3%) were women. Among all participants, 291 (21%) did not have CH (score = 0), whereas 432 (31.1%) had moderate CH (score = 1), and 665 (47.9%) high CH (score = 2 or 3, score 2 = 411 subjects, score 3 = 254 subjects) (Table 1). Participants with moderate or high CH were more likely to have fewer years of formal education, current high depressive symptoms, and more lifetime anxiety disorders, especially lifetime generalized anxiety. Participants without MRI ($N = 880$ 63% of the individuals with CH evaluation) were older (72.5 v. 70.8 years, $p < 0.01$) and more often women (61.3% v. 47.8%, $p < 0.01$) than the other participants ($N = 508$).

Cynical hostility and Alzheimer's disease or all dementia

Analysis of the association between baseline CH status and the incident dementia and AD rates at the 8-year follow-up visit (adjusted Cox proportional HR values and 95% CI in Table 2) showed that compared with participants without CH, a high CH score was associated with higher rates of dementia ($p = 0.027$) and AD ($p = 0.030$). The results remained significant after the exclusion of participants with incident dementia ($N = 10$) at phase 3 (Table 2). Figure 2 shows AD incidence in the function of the CH status over time.

Cynical hostility and brain MRI markers

Analysis of the association (ANOVA) between CH levels and volumes of brain ROIs after adjustment for age, sex, educational level, and ICV (Fig. 3 and online Supplementary Table S1 for complete results) showed that CH was not associated with significant differences in grey matter ROIs. Conversely, for white matter ROIs, anterior CC volumes were smaller, and WML volumes were larger in individuals with high CH level than in those without CH. This last association did not remain significant after FDR correction for multiple comparisons in white matter volumes. The analyses performed after adjusting for depressive symptoms (model 2), lifetime anxiety disorders (model 3), and suicidal risk (model 4) gave similar results.

Table 1. Comparison of the baseline demographic and clinical characteristics in participants categorized according to their cynical hostility status

Characteristic	Cynical hostility								p value ^a
	Total sample N = 1388		None (score = 0) N = 291		Moderate (score = 1) N = 432		High (score = 2–3) N = 665		
<i>Socio-demographic and lifestyle characteristics</i>									
	Mean	s.d.	Mean	s.d.	Mean	s.d.	Mean	s.d.	
Body mass index	25.0	3.5	24.9	3.6	24.1	3.4	25.0	3.5	0.73
Age	73.6	4.7	73.2	4.5	73.7	4.8	73.7	4.7	0.31
	N	%	N	%	N	%	N	%	
Women	782	56.3	175	60.0	234	55.2	373	56.1	0.28
Educational level									<0.02
No formal education	279	20.0	42	14.4	92	21.3	144	21.7	
Primary	400	28.8	85	29.2	110	25.5	205	30.9	
Secondary	331	23.8	67	23.0	112	25.9	152	22.9	
Higher	378	27.2	97	33.3	118	27.3	163	24.5	
Living alone	349	25.2	80	27.5	107	24.8	162	24.4	0.60
Tobacco use (current or past)	605	43.6	115	39.5	186	44.1	304	45.7	0.20
Alcohol consumption ^b	556	40.1	109	38.0	173	41.1	274	42.1	0.50
<i>Clinical and biological characteristics</i>									
	Mean	s.d.	Mean	s.d.	Mean	s.d.	Mean	s.d.	
Triglycerides (mmol/L)	1.3	0.02	1.2	0.04	1.2	0.03	1.3	0.02	0.12
C-reactive protein (log) (N = 194)	0.3	0.03	0.3	0.05	0.3	0.05	0.4	0.04	0.49
Carotid intima-media thickness (mm)	0.7	0.00	0.7	0.00	0.7	0.00	0.7	0.01	0.60
	N	%	N	%	N	%	N	%	
Self-reported poor health	66	5.1	10	3.7	18	4.5	38	6.0	0.30
Asthma	80	5.8	18	6.2	26	6.0	36	5.4	0.87
Cardiovascular disease ^c	101	7.3	19	6.5	19	6.7	53	8.0	0.63
Stroke	34	2.5	3	1.0	10	2.3	21	3.2	0.15
Hypertension ^d	628	45.2	123	42.3	196	45.4	309	46.5	0.49
Diabetes ^e	151	10.9	34	11.7	49	11.4	68	10.3	0.75
Hypercholesterolemia ^f	761	55.1	157	54.1	235	54.5	369	55.8	0.86
APOE-4 allele carrier	239	17.2	50	19.4	71	19.5	118	21.1	0.78
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
MMSE	27	26–28	28	26–29	27	26–28	27	26–28	0.11

Psychiatric characteristics	N		%		N		%		p
	N	%	N	%	N	%	N	%	
Current high depressive symptoms (CESD>16)	213	15.4	37	12.8	57	13.2	119	18.0	0.04
History of past major depressive disorder (MINI)	334	25.1	70	25.3	95	22.8	169	26.4	0.40
Suicidal risk (MINI)	181	13.0	36	12.4	48	11.1	97	14.6	0.13
Lifetime anxiety disorders(MINI)	337	27.2	53	20.6	107	28.2	177	29.3	<0.03
Lifetime agoraphobia (MINI)	197	15.9	34	13.2	60	15.8	103	17.1	0.37
Lifetime generalized anxiety (MINI)	134	10.1	16	5.8	42	10.1	76	11.9	<0.02
Lifetime psychotic syndrome (MINI)	67	4.8	12	4.1	16	3.7	39	5.9	0.22

CESD, Center for Epidemiologic Studies Depression; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MINI, Mini International Neuropsychiatric Interview, MMSE, Mini-Mental State Examination. ^a χ^2 , analysis of variance or Kruskal-Wallis tests, according to the variable characteristics.

^bAlcohol consumption ≥ 12 g/day.

^cHistory of stroke, myocardial infarction, angina pectoris, arteritis or cardiovascular surgery (coronary surgery/angioplasty, endarterectomy).

^dSystolic blood pressure ≥ 160 or diastolic blood pressure ≥ 95 mm Hg, or use of antihypertensive medication.

^eTreatment for diabetes, or glucose ≥ 6.2 mmol/L.

^fTotal cholesterol ≥ 6.2 mmol/L.

Role of white matter on the relationship between CH and dementia (mediation analysis)

The β total effect of CH on white matter integrity was 0.0522 with S.E. = 0.2971. The β indirect effect was 0.00428 with the CI (-0.112 to -0.1518). The mediating effect of white matter integrity (anterior CC) on the relationship between CH and dementia was not significant.

Discussion

This study shows that CH is significantly related to dementia and AD. Specifically, a high CH score was associated with a greater incidence of dementia and AD over an 8-year follow-up, and with MRI white matter alterations, particularly smaller anterior CC volume.

Only one previous study on 622 elderly subjects found an association between higher cynical distrust level and incident dementia (Neuvonen et al., 2014). The risk of dementia was higher in people with the highest level of cynical distrust compared with people with low cynical distrust, after accounting for age, sex, cardiovascular risk factors, socioeconomic factors, lifestyle, health status, and APOE-4 carrier status. However, AD was not differentiated from other types of dementia due to the overall smaller number of dementia cases. Consistent with this study, in our sample, higher CH levels were not associated with higher mortality (online Supplementary Table S2), which was entirely explained by behavioral and socioeconomic confounding factors. More recently, a study on a cohort of 99 013 community-dwelling older adults also reported that hostility, and also anxiety, pessimism, hopelessness, and perceived constraints, were associated with a 20–30% increased risk of dementia during a 6–8-year follow-up, independently of depressive symptoms, history of mental disorders, and common behavioral and vascular risk factors, such as obesity, diabetes, hypertension, smoking, and physical activity (Sutin et al., 2018). However, this study did not use clinical criteria for the diagnosis of dementia. In our study, a high level of CH was significantly associated with more lifetime anxiety disorders, and this could have biased our findings. Nevertheless, after adjustment for potential confounding factors, including anxiety disorders, our results remained similar. Our study brings new data to the small, but growing literature on the links between personality and dementia, specifically highlighting the potential role of early structural brain alterations. The present study suggests that CH-associated white matter alterations, particularly in the CC, the main white matter interhemispheric commissure, might be early pathological markers of cognitive decline and subsequent dementia. These findings are in line with a set of neuroimaging studies. A growing body of evidence suggests that white matter degeneration is an early neuropathological process of AD pathogenesis (Sachdev, Zhuang, Braidy, & Wen, 2013) preceding grey matter degeneration and thereby contributing to more differentiated pre-AD diagnoses (Amlien & Fjell, 2014). In the present study, we did not show a significant mediating effect of white matter integrity (anterior CC) on the relationship between CH and dementia. However, this negative result might be explained by the small number of subjects in the analysis ($n = 508$ with only 14 dementia cases) when combining the personality and brain imaging samples.

The biological mechanisms by which CH may predispose to AD and more generally to dementia are still unknown. However, elevated pro-inflammatory activity may constitute a

Table 2. Association between baseline cynical hostility level and incidence of dementia and Alzheimer's disease during the 8-year follow-up

Level of cynical hostility	All dementia types				Alzheimer's disease			
	Dementia diagnoses (n)	p value	Hazard ratio ^a	95% CI	Alzheimer's disease diagnoses (n)	p value	Hazard ratio ^a	95% CI
None (0) (reference)	11		1.00		8		1.00	
Intermediate (score = 1)	26	0.234	1.64	0.72–3.72	17	0.308	1.71	0.60–4.85
High (score = 2–3)	47	0.027	2.30	1.10–4.80	29	0.030	2.74	1.10–6.85
Sensitivity analyses without participants with dementia identified at phase 3								
None (0) (reference)	11		1.00		6		1.00	
Intermediate (score = 1)	23	0.384	1.47	0.61–3.50	14	0.418	1.55	0.43–4.48
High (score = 2–3)	37	0.042	2.20	1.03–4.73	24	0.043	2.61	1.02–6.62

^aHazard ratios were calculated using the Cox proportional hazard models with delayed entry, age as a time-scale, and after adjustment for sex, educational level, baseline MMSE, APOE ε4, history of cardiovascular disease, diabetes, hypertension, BMI, hypercholesterolemia, smoking status, alcohol use, depressive symptoms, and lifetime anxiety.

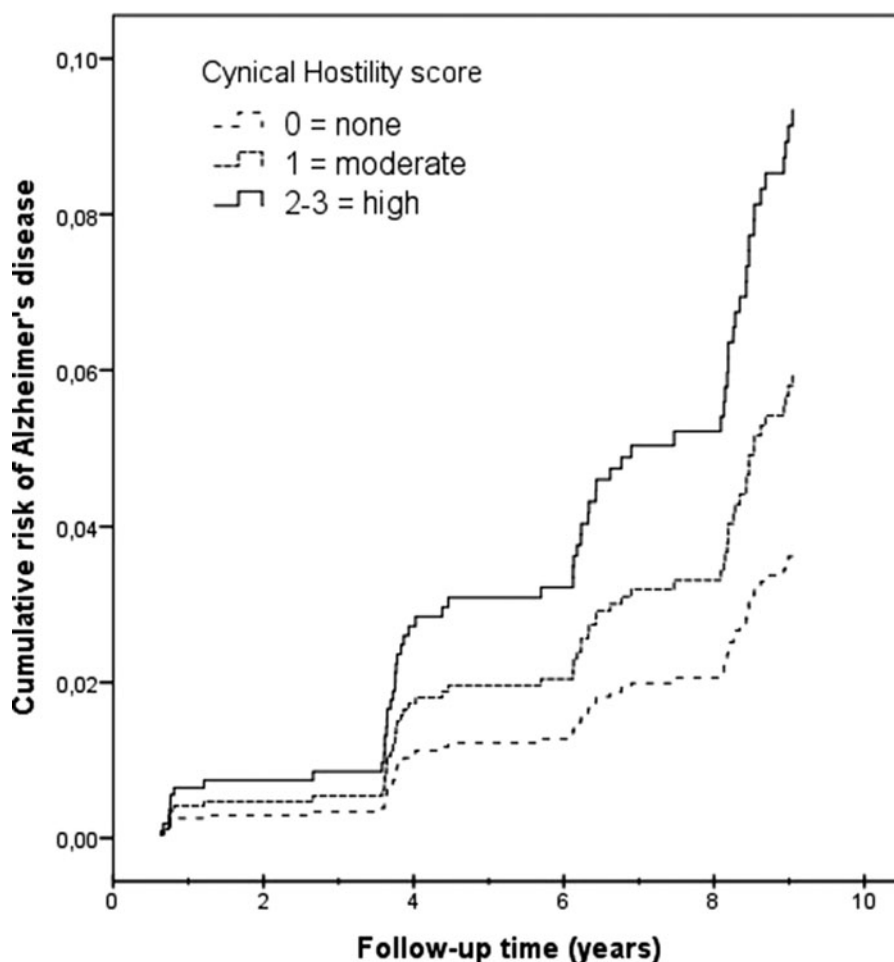


Fig. 2. Survival curve obtained from a Cox regression analysis to assess the association between the levels of cynical hostility (CH) and incident Alzheimer's disease (AD). The cumulative risk of AD is shown along the y-axis with follow-up time on the x-axis. The risk of incident dementia over 10-year follow-up is significantly higher in individuals with high CH (—) than moderate (—) or no CH (---).

pathway linking CH to AD and dementia *via* white matter alterations. Indeed, it has been demonstrated that CH may influence inflammation by promoting cytokine production by helper T lymphocytes (Th1) (Janicki-Devverts et al., 2010). In the whole ESPRIT cohort, we found a significant association between CRP and CC volume, suggesting that low-grade inflammation is

associated with CC structural integrity alterations during aging (Cyprien et al., 2019). Moreover, CC atrophy extent has been associated with the degree of cognitive decline: atrophy in the anterior portion in patients in the prodromal stage of dementia, and anterior and posterior atrophy in patients with AD (Wang et al., 2015). These results are consistent with our findings of a

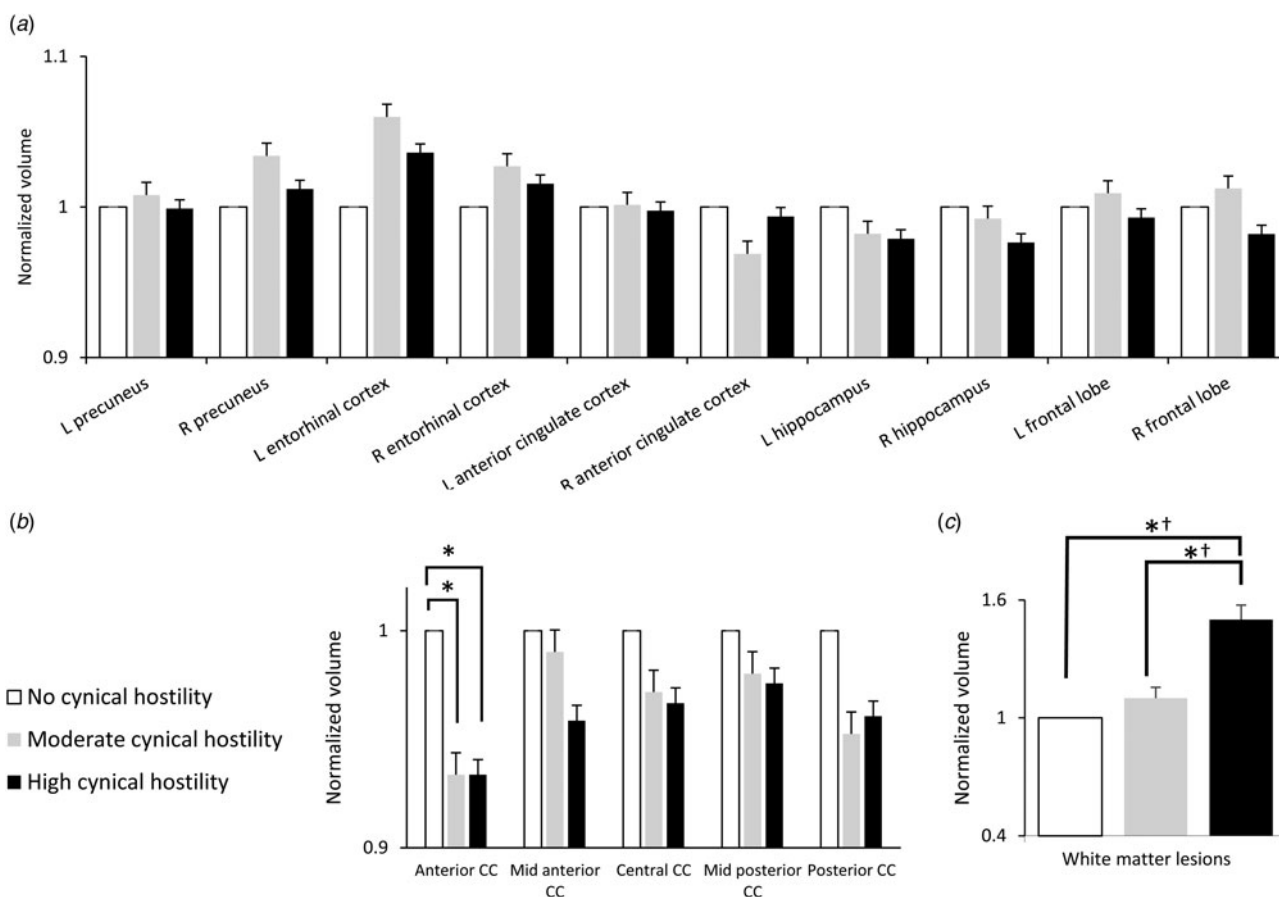


Fig. 3. Association between cynical hostility levels and MRI volumes of brain regions of interest (ANOVA). Analyses were performed after adjustment for age, sex, educational level, and intracranial volume. (a) Grey matter volumes. (b) Corpus callosum volumes. (c) White matter lesions (log) volumes. * $p < 0.05$. †Non-significant level after False Discovery Rate (FDR) correction $q^* = 0.0083$ (Benjamini & Hochberg, 1995). CC, corpus callosum; L, left; R, right.

smaller anterior CC volume among participants with high CH. Hence, inflammatory mechanisms could provide a plausible link between CH with AD. The association of CH and dementia with cardiovascular risk factors could provide an alternative explanation for our findings. However, in our analysis, CH emerged as an independent risk factor of dementia after controlling for these factors. Consequently, it is unlikely that cardiovascular risk factors mediate the association between high CH level and incident AD.

The results of this study are strengthened by the large sample size, the population-based design, and the relatively long follow-up, supporting the robustness of the association between baseline CH and incident dementia that was evaluated with a strict procedure by neurologists. The fact that the population was well characterized allowed us to take into account a large number of potential confounding factors.

Some potential limitations need to be acknowledged. Participants who were prospectively diagnosed with dementia could have been already in the prodromal phase when completing the assessments (protopathic bias). This might have overestimated the association between CH and AD risk. To overcome this bias, sensitivity analyses were also conducted to eliminate participants with incident dementia at phase 3 (i.e. 4 years after the baseline assessment), and the association still remained significant. Although the 4-year lag time should be sufficient to correct for the reverse causation bias, this latter cannot be formally ruled out because AD can have a very long prodromal

phase, even more than a decade (Amieva et al., 2008). However, only a lifetime cohort study would provide a definitive answer to the question whether hostility is a stable personality trait contributing to dementia or an early neuropsychiatric symptom of a developing neurodegenerative disease.

MRI imaging was performed at phase 1 (baseline), whereas the BDHI for the assessment of CH was completed at phase 2 (2 years of follow-up). This could have biased CH data collection. However, personality traits are considered to be stable patterns across adult life (Damian, Spengler, Sutu, & Roberts, 2019; Roberts, Wood, & Caspi, 2008). Therefore, it is highly unlikely that a change in CH occurred between baseline and phase 1. Moreover, the BDHI is not a conventional tool for CH assessment, like the Cook-Medley Hostility Scale or its derived eight-item Cynical Distrust Scale. However, the CH score used for this study was based on three related questions extracted from factor analyses that showed good internal reliability. Thus, the construct of the CH score is statistically valid, and our results are consistent with the findings by Neuvonen et al. (2014) with the Cynical Distrust Scale. Finally, longitudinal MRI data were not available to monitor brain changes in relation to CH.

In summary, the present study provides evidence to support an association between higher CH and incident AD rate in agreement with previous research. Furthermore, our findings suggest that in subjects with vulnerable personality (high CH score), white matter changes, particularly in the anterior CC, occur

before grey matter loss during the neurodegenerative process that leads to AD. Additional long-term epidemiological studies with repeated administration of the CH scale, or implementation of a history of CH reported from a family member or from medical records, are needed to extend these findings and explore the relationship between CH and longitudinal white matter changes at AD onset. We also need to identify lifestyle and biological factors that mediate the detrimental effect of CH on AD that might give insights into AD physiopathology and might be used to develop prevention strategies.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291721000416>.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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