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RESEARCH PAPER

Cortical atrophy in presymptomatic Alzheimer's disease presenilin 1 mutation carriers

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ABSTRACT

Background Sporadic late-onset Alzheimer's disease (AD) dementia has been associated with a 'signature' of cortical atrophy in paralimbic and heteromodal association regions measured with MRI.

Objective To investigate whether a similar pattern of cortical atrophy is present in presymptomatic presenilin 1 E280A mutation carriers an average of 6 years before clinical symptom onset.

Methods 40 cognitively normal volunteers from a Colombian population with familial AD were included; 18 were positive for the AD-associated presenilin 1 mutation (carriers, mean age=38) whereas 22 were non-carriers. T1-weighted volumetric MRI images were acquired and cortical thickness was measured. A priori regions of interest from our previous work were used to obtain thickness from AD-signature regions.

Results Compared to non-carriers, presymptomatic presenilin 1 mutation carriers exhibited thinner cortex within the AD-signature summary measure ($p<0.008$). Analyses of individual regions demonstrated thinner angular gyrus, precuneus and superior parietal lobule in carriers compared to non-carriers, with trend-level effects in the medial temporal lobe.

Conclusion Results demonstrate that cognitively normal individuals genetically determined to develop AD have a thinner cerebral cortex than non-carriers in regions known to be affected by typical late-onset sporadic AD. These findings provide further support for the hypothesis that cortical atrophy is present in preclinical AD more than 5 years prior to symptom onset. Further research is needed to determine whether this method could be used to characterise the age-dependent trajectory of cortical atrophy in presymptomatic stages of AD.

By the time a person has mild Alzheimer's disease (AD) dementia, a substantial burden of neurodegenerative AD neuropathology has devastated the structural and functional integrity of a distributed set of paralimbic and heteromodal regions of the cerebral cortex.[1] Autopsy studies of cognitively normal (CN) older adults[2 3] and recent studies of molecular imaging and cerebrospinal fluid (CSF) markers,[4 5] as well as longitudinal neuropsychological studies,[6] suggest that this process begins years before symptoms develop. Research diagnostic criteria have recently been published for preclinical AD that employ imaging and CSF biomarkers to identify asymptomatic individuals with cerebral amyloidosis and evidence of early neurodegeneration, one goal of which will be to screen older adults for silent AD neuropathology for potential intervention trials.[7 8] Recent proposals are calling for the field to plan for presymptomatic intervention trials in individuals at elevated genetic risk for AD.[9 10]

In addition to molecular imaging and CSF markers, in vivo MRI data have been analysed in increasingly sophisticated ways to identify anatomic changes consistent with early AD-related neurodegeneration.[11–14] Moving beyond the initially proposed markers of hippocampal and whole brain atrophy and ventricular enlargement, the field has begun measuring regional cortical atrophy. We recently demonstrated that a 'signature' pattern of multifocal paralimbic and heteromodal cortical atrophy can be reliably detected in patients with mild AD dementia and is a valid indicator of symptom severity.[15] This pattern has been translated into a single summary measure that can predict dementia in patients with mild cognitive impairment (MCI).[16] More relevant for preclinical AD, this marker is detectable in CN adults with imaging evidence of brain amyloid[15] and is predictive of time to AD dementia onset in CN adults an average of 8 years prior to dementia diagnosis.[17] CN individuals with this MRI marker are more likely to exhibit abnormal AD-like CSF.[18]

One challenge in using markers such as this to screen CN older adults for silent AD pathology is in finding a high-risk population to make this type of research more efficient. The rare families with autosomal dominant early-onset familial AD (EOFAD) are an ideal population in which to carry out such investigations, since presymptomatic carriers of disease-causing mutations can be studied from young adulthood through symptom onset. Recently, a number of studies have demonstrated that patients with EOFAD-causing gene mutations show evidence of presymptomatic changes compared to matched controls, including alterations in brain anatomy[19–21] and physiology.[22–26]

In the present study, we sought to determine whether the AD-signature MRI biomarker of cortical atrophy is detectable in a sample of presymptomatic presenilin 1 (PSEN1) E280A mutation carriers an average of 6 years prior to symptom onset and 11 years prior to dementia diagnosis. We used a strongly hypothesis-driven approach to focus specifically on this single measure as well as measures from individual regions of interest (ROI) that compose the distributed AD-signature pattern. In addition, we further investigated the data using an exploratory analysis surveying the entire cerebral cortex to try to determine whether

these genetically-determined EOFAD gene mutation carriers exhibited an atypical pattern of cortical atrophy compared to typical late-onset AD.

METHODS

Participants and clinical evaluation

Forty volunteers were recruited from the University of Antioquia (Colombia) Registry, which currently includes more than 1500 living members with familial AD. Eighteen participants were positive for the AD-associated PSEN1 mutation E280A (carriers) whereas 22 were PSEN1 mutation negative and served as controls. All participants belonged to a single extended family. Family members who lived in close proximity to the University of Antioquia and the Instituto de Alta Tecnologia Medica were invited to participate. Potential participants were screened in advance for the presence of neurological and psychological disorders, drug use and MR scanner compatibility. Of 44 participants recruited, two were excluded because of claustrophobia, and two because of having metal in their bodies.

All participants underwent comprehensive clinical and neuropsychological assessments.[27] These assessments included a structured interview, which focused on identification of memory complaints and their effect on everyday life, family life, social life, and working life of participants, as well as a medical and neuropsychological examination. Clinical history was taken and medical and neurological examinations were done by a neurologist or a physician trained in dementia assessment. Neuropsychological tests were done by neuropsychologists and psychologists trained in neuropsychology. Medical history and neuropsychological assessments were systematised with the Systematised Information System for the Neuroscience Group of Antioquia. The neuropsychological protocol included the Mini-Mental State Examination (MMSE) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery, which has been adapted to this Colombian population.[28] Normative data were previously generated for this battery from PSEN1 E280A non-carriers from the same kindred.[27] In addition, activities of daily living (ADL) were assessed with the Barthel index and the Lawton instrumental ADL (IADL) scale. The Global Deterioration Scale (GDS) was also used to rate level of impairment.

For the present study, participants were selected based on the following criteria: (1) no clinically significant cognitive decline (based on the full clinical assessment, including no cognitive impairment within any domain as indicated by the most recent CERAD neuropsychological assessment, which was done within 6 months prior to the time of the scanning session, and GDS=1); (2) no impairment in ADL or IADL (Barthel=50; Lawton=8). All subjects were screened for MRI compatibility.

All subjects provided written informed consent before participating in accordance with the regulations and approval of the local ethics committee of the University of Anitoquia (Colombia). The Colombian protocol allowed de-identified data collected in Colombia to be analysed by researchers in the USA.

Genetic analysis

For genetic analyses, genomic DNA was extracted from blood by standard protocols, and PSEN1 E280A characterisation was done as previously described.[29] Genomic DNA was amplified with the primers PSEN1-S 5′ AACAGCTCAGGAGAGGAATG 3′ and PSEN1-AS 5′ GATGAGACAAGTNCCNTGAA 3′. We used the restriction enzyme BsmI for restriction fragment length polymorphism analysis. Each participant was classified as a PSEN1 E280A carrier or non-carrier. Investigators were blind to the genetic status of the participants during data collection and analysis.

MRI data acquisition

For each subject, two 3D T1-weighted MRI images (T1-FFE; TR=2530 ms, TE=3.39 ms; flip angle=7°; field of view, 256×256; 1.0×1.0×1.0 mm; 176 slices) were acquired using a Philips 1.5T Achieva MR scanner at the Instituto de Alta Tecnología Médica in Medellin, Colombia. Automatic shimming procedures were performed.

MRI morphometric data analysis

The data were analysed using the fully automated cortical surface procedures in FreeSurfer V.4.5, detailed elsewhere[30] (http://surfer.nmr.mgh.harvard.edu). Data were visually inspected for errors; in this sample, none were identified.

Very briefly, the T1 acquisitions for each participant were motion corrected and averaged. The resulting averaged volume was used to segment cerebral white matter and multiple subcortical grey matter and ventricular regions and to estimate the location of the grey/white boundary. Topological defects in this boundary were corrected, and it was used to find the pial surface with submillimetre precision. Cortical thickness measurements were obtained by calculating the distance between those surfaces at each of approximately 160 000 points/hemisphere. The surface representing the grey–white border was 'inflated', differences among individuals in the depth of gyri and sulci were normalised, and each subject's reconstructed brain was then morphed and registered to an average spherical surface representation that optimally aligns sulcal and gyral features across participants. Thickness measures were then mapped to the inflated surface of each participant's reconstructed brain and the data were smoothed on the surface using an iterative nearest-neighbour averaging procedure (n=100 iterations). The procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimising geometric distortion.

The primary analytic approach employed here made use of 'AD-signature' ROIs generated from a previous study and applied a priori. In the previous study in which these ROIs were identified, cortical thickness in patients with mild AD dementia was compared to that of age-matched CN adults, and regions of thinner cortex were identified[15] (this prior study involved an entirely independent sample of subjects). The analysis generated nine ROIs/hemisphere that were reliably affected across four samples of mild AD patients.[15] In addition to these nine AD-signature ROIs, an ROI from the primary visual cortex was used as previously, as a control region (not atrophied in AD vs CN adults). Figure 1A shows the ROIs.

For each subject, mean cortical thickness within each ROI was calculated by deriving an average of all the thickness estimates at vertices that fell within the labelled ROI. A single summary measure was then derived from the average thickness across all 18 (9/hemisphere) ROIs, the 'AD-signature' ROI summary measure.

Statistical analysis

Pearson correlation analyses were done to investigate the association between age, gender, education, cognitive measures and cortical thickness. A χ^2 test was used to test gender distribution. An analysis of variance was constructed to compare the groups using the AD-signature summary measure as well as individual regions, adjusting for age. Statistical analyses were

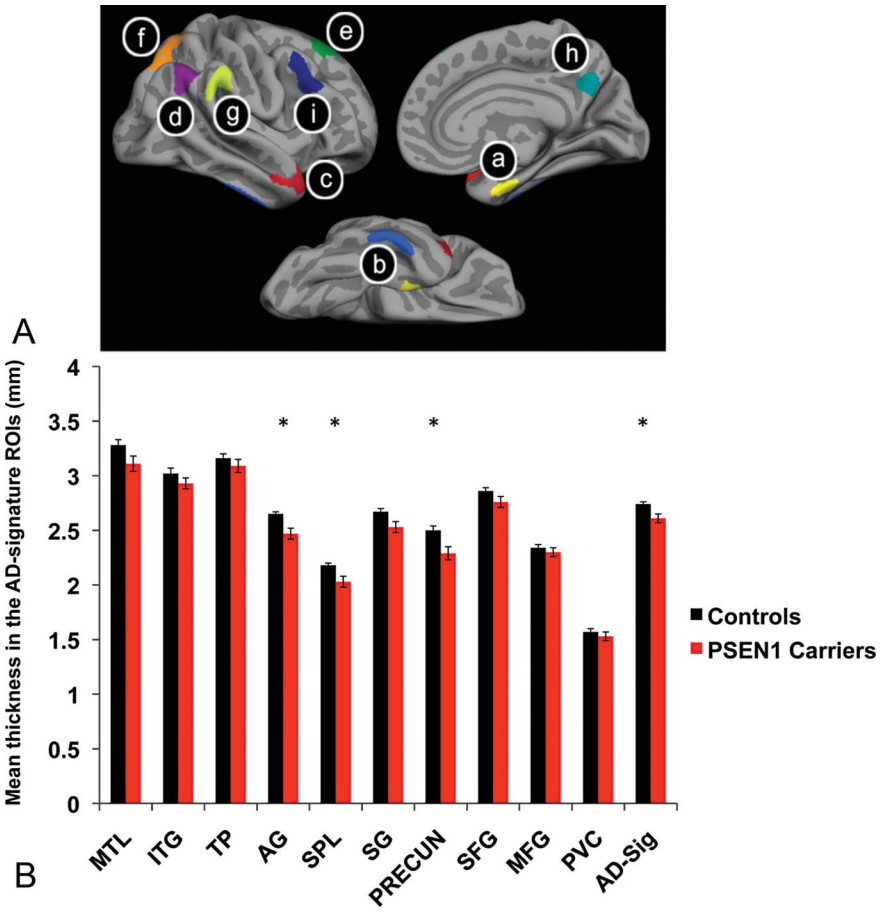

Figure 1 Comparison between presenilin 1 (PSEN1) mutation carriers and non-carriers in cortical thickness from a priori regions of interests (ROIs) that compose the 'Alzheimer's disease (AD)-signature' set of regions. (A) Localisation of regions of interest in AD-signature: (a) Medial temporal lobe (MTL), (b) inferior temporal gyrus (ITG), (c) temporal pole (TP), (d) angular gyrus (AG), (e) superior frontal gyrus (SFG), (f) superior parietal lobule (SPL), (g) supramarginal gyrus (SG), (h) precuneus (Precun), (i) medial frontal gyrus (MFG), primary visual cortex (PVC), AD-signature (AD-sig). (B) Bar graphs show mean cortical thickness within each ROI in the PSEN1 mutation carriers and non-carriers, averaged across hemispheres ($p<0.005$). Error bars depict 1 SE of the mean. See table 2 for additional details.

performed using statistical software (SPSS V.16.0; SPSS Inc, Chicago, Illinois, USA). Percent atrophy and Cohen's d effect size were calculated using standard methods as previously described.[15]

RESULTS

The presymptomatic PSEN1 mutation carriers and non-carriers did not differ in age, gender, education or MMSE (table 1). Furthermore, they did not differ in any of the CERAD neuropsychological battery tests.

There was no significant correlation between cortical thickness and cognitive measures, or between cortical thickness and years of education or gender. There was a significant ($r=-0.63$, $p=0.006$) inverse correlation between the summary AD-signature cortical thickness measure and age in the PSEN1 carrier group but not in the non-carrier group. This indicates that the closer an individual with a PSEN1 mutation is to the estimated age of clinical onset, the thinner the cortex within the AD-signature set of ROI, a relationship that likely reflects early neurodegeneration based on the fact that it is not observed in non-carriers.

Mean cortical thickness in the AD-signature summary measure was 4.75% thinner in presymptomatic carriers than non-carriers (carriers: 2.61 (SD=0.18) mm; non-carriers: 2.74 (SD=0.10) mm; $F(1,37)=6.92$, $p=0.012$).

Analyses of individual AD-signature ROIs demonstrated the largest atrophy effects in the right angular gyrus ($F(1,38)=8.56$, $p=0.006$), left angular gyrus ($F(1,38)=4.47$, $p=0.041$), right precuneus ($F(1,38)=13.28$, $p=0.001$) and left superior parietal lobule ($F(1,38)=8.59$, $p=0.006$) in carriers compared to non-carriers. Similar trend-level effects were found in several other ROIs, including right medial temporal lobe (MTL) ($F(1,38)=3.40$, $p=0.07$), left temporal pole ($F(1,38)=3.07$, $p=0.08$), left supramarginal gyrus ($F(1,38)=2.96$, $p=0.09$) and right supramarginal gyrus ($F(1,38)=3.69$, $p=0.06$). Other ROIs showed

Table 1 Demographic and neuropsychological data

	Controls (n=22)	PSEN1 carriers (n=18)	p Value
Gender	18 females	12 females	0.27
Age, years	39.5 (6.2)	38.2 (4.5)	0.70
Education, years	10.2 (3.7)	9.7 (2.6)	0.70
MMSE, /30	29.6 (0.6)	29.7 (0.4)	0.63
CERAD tests			
Verbal fluency	19.6 (5.1)	17.5 (2.6)	0.12
Naming, /15	13.3 (1.5)	13.3 (1.7)	0.90
Memory words			
Total correct, /30	19.8 (3.4)	18.5 (5.0)	0.42
Total intrusions	1.5 (2.6)	1.6 (1.4)	0.81
Recall of words			
Total correct, /10	7.2 (1.3)	6.0 (2.6)	0.13
Total intrusions	0.3 (0.6)	0.3 (0.5)	0.73
Recognition of words			
Correct 'yes', /10	9.6 (0.6)	9.4 (0.8)	0.56
Correct 'no', /10	9.9 (0.2)	9.8 (0.5)	0.56
Constructional praxis, /11	9.6 (1.0)	9.6 (1.0)	0.85
Recall of drawings, /11	9.1 (1.9)	8.4 (2.2)	0.30

Values denote mean (±SD).
CERAD, Consortium to establish a registry for Alzheimer's Disease; MMSE, Mini-Mental State Examination; PSEN1, presenilin 1.

Table 2 Quantitative metrics of cortical atrophy by region

Region	Mean thickness, mm (SD)				Group mean difference	% atrophy	Cohen's d effect size
	Non-carriers		PSEN1 carriers				
Right medial temporal	3.40	(0.29)	3.21	(0.35)	0.19	5.59	0.59
Left medial temporal	3.16	(0.28)	3.01	(0.33)	0.15	4.75	0.49
Right inferior temporal	3.17	(0.33)	3.05	(0.40)	0.12	3.79	0.33
Left inferior temporal	2.88	(0.22)	2.81	(0.22)	0.07	2.43	0.32
Right temporal pole	3.07	(0.28)	3.08	(0.25)	−0.01	−0.33	−0.03
Left temporal pole	3.24	(0.21)	3.09	(0.31)	0.15	4.63	0.57
Right angular gyrus	2.60	(0.17)	2.37	(0.31)	0.23	8.85	0.92
Left angular gyrus	2.68	(0.16)	2.55	(0.21)	0.13	4.85	0.7
Right superior parietal	2.06	(0.17)	1.94	(0.30)	0.12	5.83	0.49
Left superior parietal	2.29	(0.16)	2.12	(0.19)	0.17	7.42	0.97
Right supramarginal	2.63	(0.20)	2.50	(0.25)	0.13	4.94	0.57
Left supramarginal	2.70	(0.17)	2.55	(0.30)	0.15	5.56	0.61
Right precuneus	2.42	(0.19)	2.11	(0.33)	0.31	12.81	1.15
Left precuneus	2.57	(0.24)	2.45	(0.19)	0.12	4.67	0.55
Right superior frontal	2.99	(0.24)	2.84	(0.32)	0.15	5.02	0.53
Left superior frontal	2.72	(0.13)	2.67	(0.21)	0.05	1.84	0.29
Right middle frontal	2.43	(0.17)	2.41	(0.22)	0.02	0.82	0.1
Left middle frontal	2.24	(0.18)	2.18	(0.17)	0.06	2.68	0.34
Primary visual cortex	1.57	(0.16)	1.53	(0.18)	0.04	2.55	0.23
AD-Signature summary measure	2.74	(0.10)	2.61	(0.18)	0.13	4.74	0.89

AD, Alzheimer's disease; PSEN1, presenilin 1.

effects that were all in the same direction but did not reach statistical significance. See figure 1B and table 2 for additional details. Asymmetries observed in table 2 should be interpreted with caution and are likely a reflection of relatively small sample size.

An exploratory analysis of cortical thickness across the entire brain (figure 2) revealed a pattern of atrophy in the PSEN1 mutation carriers compared to non-carriers generally consistent with the AD-signature identified in late-onset sporadic AD but with notably more prominent effects in the posterior cingulate/precuneus and frontal, parietal and lateral temporal regions and less prominent effects in the medial, ventral, and polar temporal cortical regions ($p<0.01$ uncorrected). Group differences in the precuneus and the superior temporal gyrus remained after using a more stringent multiple comparisons correction method (false discovery rate, FDR).

DISCUSSION

It is now well established that AD neuropathology accrues years before symptoms appear. This fact offers the hope that we may be able to intervene in the process while individuals are still asymptomatic, hopefully delaying the emergence of symptoms.[9 10] The maturation of AD biomarker research over the past decade led to proposals for new diagnostic criteria for preclinical AD.[7 31 32] The major challenge to the field now is: Whom do we screen? One ideal population for proof-of-concept intervention trials is presymptomatic carriers of deterministic genetic mutations associated with EOFAD.

In this study, we showed that carriers of the E280A PSEN1 mutation express an MRI biomarker of AD-related neurodegeneration—the 'signature of AD-related cortical atrophy'—approximately 6 years prior to symptom onset and 11 years prior to dementia diagnosis. We have previously shown that this imaging biomarker is a valid correlate of symptom severity[15] and an indicator of elevated risk for AD-like molecular pathology.[15 18] It is highly reliable in symptomatic patients[15 16] and increasing evidence indicates that it is reliable in CN adults,[17 18] although this latter population deserves further investigation. The present results provide further support for this point.

The PSEN1 mutation carriers in this study were cognitively intact based on clinical examination at the time of MRI scanning, as evidenced here by absence of cognitive symptoms reported on a structured interview and normal functional assessment, instrumental ADL, and neuropsychological test performance. Nevertheless, there was evidence from quantitative MRI of subtle neurodegeneration within the AD-signature cortical regions. These findings are nearly identical to those from two prior datasets. In one of these prior studies, we showed that, in two independent samples of CN older adults who were longitudinally followed for an average of 8 years, those who developed AD dementia exhibited quantitative MRI evidence AD-signature regional atrophy at baseline which predicted time-to-onset of dementia.[17] In the other study, we showed that CN older adults who expressed this AD-signature MRI biomarker were more likely than those without it to harbour AD-like CSF and early indicators of cognitive decline over 3 years.[18] In sum, these three independent datasets provide convergent support for the consistency of this MRI biomarker of preclinical AD and demonstrate that subtle evidence of neurodegenerative change in the structure of the brain can be present prior to evidence of symptoms or signs of cognitive impairment.

Prior studies of EOFAD genetic mutation carriers have revealed evidence for the presence of atrophy in the presymptomatic stage of AD. Fox *et al* have reported a series of studies of a cohort of nine PSEN1 mutation carriers. In their first study,[33] hippocampal volume was measured and demonstrated mild atrophy in the 2 years prior to diagnosis of dementia. The second study conducted by this group[21]—measuring

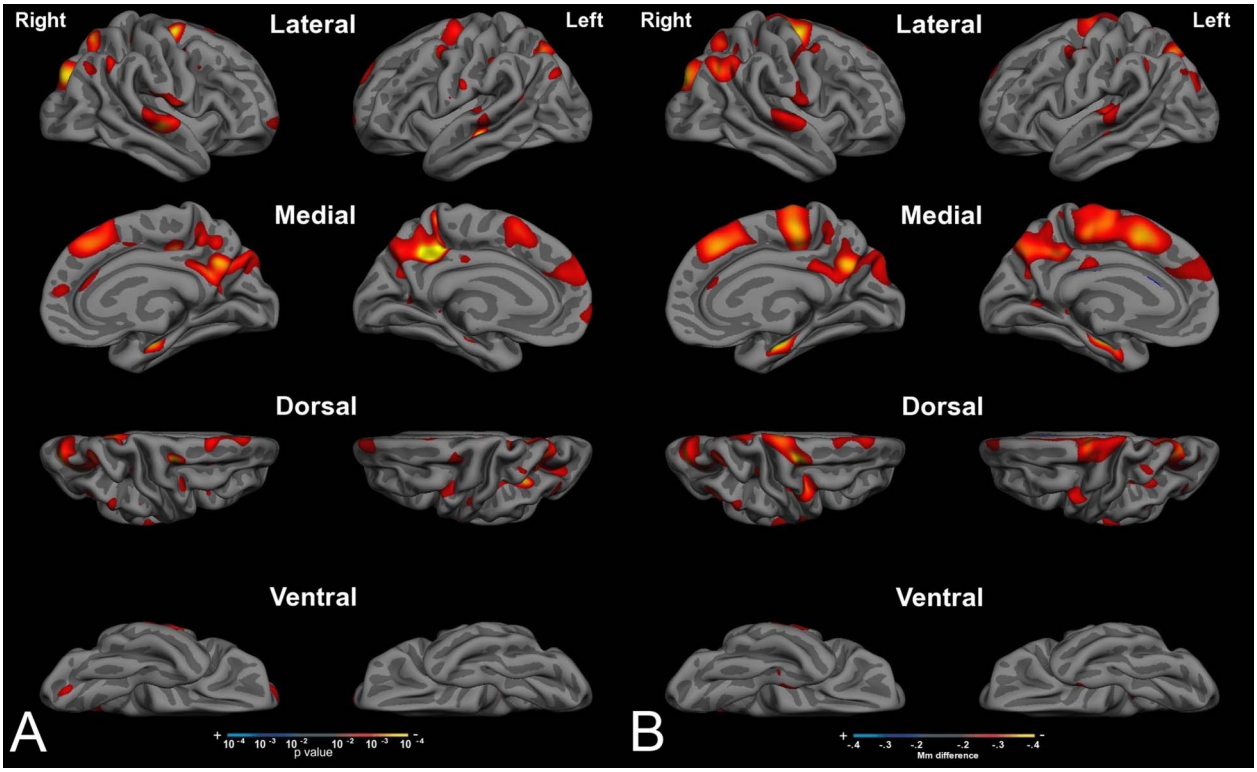

Figure 2 Exploratory map of cortical atrophy across hemispheres in presymptomatic presenilin 1 (PSEN1) E280A mutation carriers compared to matched non-carriers. An exploratory analysis was conducted across the entire cortical surface to identify regional atrophy in PSEN1 mutation carriers compared to matched non-carriers. Maps are presented on the semi-inflated cortical surface template (FreeSurfer *fsaverage*). Dark grey regions represent sulci and light grey regions represent gyri. Non-neocortical regions and midline regions that are not part of the cortical mantle (such as the corpus callosum and thalamus) have been excluded from the analysis. The colour scale represents: (A) the statistical significance of the comparison thresholded at $p<0.01$, uncorrected; and (B) the mean difference between the two groups in cortical thickness thresholded at 0.2 mm.

longitudinal rates of hippocampal and whole brain atrophy—demonstrated that while there were trends towards cross-sectional differences between carriers and controls prior to the development of symptoms (the presymptomatic phase), a difference in hippocampal volume was not present until the MCI phase and a difference in whole brain volume was not present until AD dementia was diagnosed. Nevertheless, rates of atrophy in both measures were greater in the mutation carriers than controls in the presymptomatic phase and accelerated with each clinical phase of the illness. A very recent investigation of the same nine mutation carriers identified cortical atrophy of the posterior cingulate 1.8 years and precuneus 4.1 years prior to diagnosis; the entorhinal cortex did not demonstrate statistically significant atrophy until the time of dementia diagnosis.[34]

Other reports have provided conflicting data. One recent study of 22 presymptomatic carriers of PSEN1 or APP mutations found no evidence of cortical or hippocampal atrophy.[35] Another investigation of six PSEN1 mutation carriers showed increased cortical thickness in the precuneus and parietotemporal regions compared to controls.[36] Possible contributors to these differences include genetic heterogeneity, differences in the age of participants or preclinical stage of the disease, or differences in MRI measurement techniques.

As previously described in presymptomatic EOFAD cases,[34] the posteromedial cortices including cingulate cortex and ventral precuneus demonstrate the most prominent atrophy in our sample, with approximately 8% atrophy in the precuneus. In the present analysis, lateral parietal regions in both inferior and superior parietal lobule also show relatively prominent effects (5–6% atrophy); these regions were not investigated in the Knight *et al* study.[34] In prior studies of CN older adults with brain amyloid, the MTL has also been reported to be relatively less affected (5% atrophy in this study) than posteromedial and lateral temporoparietal cortices[15 37]; in contrast, we previously showed that CN older adults who developed AD dementia approximately 8 years after scanning did show relatively prominent MTL cortical atrophy (12% atrophy).[17] The present findings are consistent with other evidence in sporadic early-onset AD, suggesting that younger age of onset is associated with less prominent MTL pathology and more prominent pathology in the lateral parietal cortex, precuneus, and posterior cingulated.[38] Future cross-sectional investigations of age effects and longitudinal studies with larger samples will be helpful to further characterise the pattern of cortical atrophy in EOFAD. We hypothesise based on the data reviewed above that the localisation of the earliest atrophy in preclinical AD is dependent in part on age and in part on other genetic modifiers (eg, apolipoprotein E[39]).

Limitations of the present study include a relatively small sample compared to studies of sporadic AD (although this is one of the largest samples of presymptomatic EOFAD carriers studied with any neuroimaging technique to date). More importantly, we have not yet compared the quantitative MRI measures to other widely used AD biomarkers, including fluorodeoxyglucose PET or measures of amyloid derived from imaging or spinal fluid. Collection of these data is in progress, and we plan to directly compare the markers to investigate sensitivity and specificity as well as temporal sequence of abnormalities. Another limitation of this study is that we do not know whether the findings are

generalisable to other genetic forms of autosomal dominant EOFAD since we only studied individuals with a single mutation. Ultimately, clinical trials of interventions aimed at preclinical AD will likely hinge—at least in part—on imaging and biofluid outcome measures; studies of EOFAD samples will probably contribute valuable information towards efforts to identify the strengths and weaknesses of various biomarkers for this purpose.[40]

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Contributors YTQ: designed the study, collected data, analysed the data, drafted the manuscript. CES: designed the study, drafted the manuscript, obtained funding to support study. EMR: designed the study, drafted the manuscript, obtained funding to support study. MB: analysed the data, drafted the manuscript. AR: designed the study, collected data. RAS: none, drafted the manuscript. FL: designed the study, collected data, drafted the manuscript, obtained funding to support study. BCD: designed the study, analysed the data, drafted the manuscript, obtained funding to support study.

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Notes