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Sulcal Span in Alzheimer's Disease, Amnestic Mild Cognitive Impairment, and Healthy Controls

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Abstract. Differences of cortical morphology between healthy controls (HC), amnestic mild cognitive impairment (MCI), and Alzheimer's disease (AD) have been repeatedly investigated using voxel-based morphometry (VBM). However, the results obtained using mainly VBM remain difficult to interpret as they can be explained by various mechanisms. The aim of the present study was to evaluate the differences of cortical morphology between HC, MCI, and AD patients using a new post-processing method based on reconstruction and identification of cortical sulci. Thirty HC, 33 MCI, and 30 AD patients were randomly selected from the ADNI database. For each subject, cortical sulci were reconstructed and automatically identified using Brainvisa software. Depth and fold opening of nine large sulci were compared between HC, MCI, and AD patients. Fold opening of parietaloccipital fissure and intraparietal sulcus on both sides strongly differed between the 3 groups, with gradual increase from HC to MCI of about 1 mm and from MCI to AD of about 2 mm (right intraparietal: $p = 0.005$; left intraparietal: $p = 0.004$; right parietaloccipital: $p = 0.003$; left parietaloccipital: $p = 0.0009$). Results were left unchanged after adjustment for age, gender, and level of education. These variables were also strongly linked to neuropsychological scores, independent of age, gender, and level of education. In the present study, we found important regional differences of cortical morphology with gradual deterioration from HC to MCI to AD. The most important differences were found in parietaloccipital fissure and intraparietal sulcus. Further studies are needed to understand the involved underlying mechanisms.

Keywords: Alzheimer's disease, cortex, cortical sulci, mild cognitive impairment, MRI

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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INTRODUCTION

The global and regional differences of brain structure between healthy aging, amnestic mild cognitive impairment (MCI), and Alzheimer's disease (AD) have been assessed repeatedly [1]. Both the extent of global brain atrophy and regional measures obtained using voxel-based morphometry (VBM) methods or measures of cortical thickness were found to differ between these populations [1]. At the cortical level, the results obtained using VBM techniques remain difficult to interpret as they can be related to actual modifications of cortical thickness, changes of gray/white matter contrast, or differences of cortical morphology [2–4].

Recently, new markers of cortical morphology have been developed for magnetic resonance imaging (MRI) studies [5]. Particularly, cortical sulci can now be automatically reconstructed and identified over the whole brain and thereafter compared between individuals. For each sulcus, various parameters, such as its depth or width can be extracted [6]. More globally, the total folding of the brain surface can be assessed through the gyrification index (GI), namely the ratio of the total sulcal surface areas to that of the exposed brain surface [6].

The evaluation of morphological descriptors of cortical sulci offers potential advantages over voxel-based methods for investigating the cortex during aging or dementia [7]. Particularly, alterations of cortical morphology can be evaluated separately from modifications of cortical thickness [7]. Technically, the post-processing is made in the native space of acquisition and each step can be visually checked, thus reducing the sources of errors. The methodology has been also validated in the context of aging or in presence of cerebrovascular lesions [8, 9] when other image segmentation algorithms appear inaccurate.

According to some pathological studies, the cortical atrophy in AD may be the result of a loss of cortical surface rather than of cortical thickness [10]. Following this hypothesis, the reduction of cortex length (potentially secondary to the loss of local columnar organization) would result in changes of sulcal depth and of sulcal width. In the present study, we evaluated the global and regional sulcal morphological differences between healthy aging, MCI and AD subjects selected from the ADNI database (http://adni.loni.ucla.edu/).

MATERIALS AND METHODS

Subjects

Participants were selected from the ADNI database (see below). Healthy controls (HC, $n = 30$) were individuals with Mini-Mental Status Examination (MMSE) scores between 24 and 30 and a Clinical Dementia Rating scale (CDR) score of 0 [11]. MCI patients ($n = 33$) had MMSE scores between 24 and 30, a subjective memory complaint verified by an informant with an objective memory loss as measured by education-adjusted performance on the Logical Memory II subscale (delayed paragraph recall) of the Wechsler Memory Scale-Revised, [12] a CDR of 0.5, no significant impairment in other cognitive domains, and essentially preserved activities of daily living with absence of dementia. Only individuals classified as having the amnestic subtype of MCI, based on the revised MCI criteria, [13] were selected. Thirty AD patients, defined as individuals with MMSE scores between 20 and 26, a CDR scale of 0.5 or 1, and fulfilling the NINCDS/ADRDA criteria for probable AD were finally selected. All subjects included in the study had a Geriatric Depression Scale score of less than 6 [14].

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. For up-to-date information, see http://www.adni-info.org.

Cognitive testing

All subjects underwent extensive cognitive testing detailed elsewhere (http://www.adni-info.org/). The delayed recall performance in the Auditory Verbal Learning Test [15] (AVLT) and in the Alzheimer's disease Assessment Scale score (ADAS-Cog) 10-Word

list [16] were selected from the cognitive measures included in the ADNI database because delayed recall has been shown to be a strong predictor of AD [17]. Complementary to memory performance, executive functions were evaluated by Trail Making Test B (time to complete, TMTB) and a measure of global functioning was provided by the MMSE score.

MRI acquisitions

MRI scans at baseline were downloaded from the ADNI database. All sequences were acquired on a 1.5 Tesla scanner. In ADNI, specific efforts were made to ensure for comparability of results from different centers, using certifications protocols and identical sequences across centers detailed elsewhere (http://www.adni-info.org/).

Post processing of MRI

Determination of the global brain volume was performed as previously described [9]. The brain parenchymal fraction (BPF) was defined as the ratio of brain tissue volume to the intracranial cavity volume [9]. BrainVisa (http://brainvisa.info) was used for the reconstruction of cortical sulci, as previously reported [6]. Briefly, the medial surface area of cortical folds was obtained using an erosion procedure after brain segmentation [18]. Sulcal structures, defined as medial surfaces from the two opposing gyrus banks that span from the most internal point of sulcal fold to the hull of the cortex, were constructed automatically by the software [18]. The GI was calculated as the ratio of the sum of the fold surface areas to the closed surface of both hemispheres [6].

A dedicated procedure detailed elsewhere allows the identification of a large number cortical sulci on each hemisphere (Fig. 1) [19]. Only a limited number of sulci, namely primary and secondary sulci are present in all individuals [20]. We selected 9 different sulci for analyses in the present study: the anterior and posterior cingulate, intraparietal, central, superior frontal, orbital, superior temporal and rhinal sulci as well as the parietaloccipital fissure (Fig. 2). They were chosen for the following reasons: 1) they are present in all individuals; 2) they are large with highest probability of accurate identification [19]; and 3) they are located in different cerebral lobes, particularly in areas known to be affected in AD (temporal, parietaloccipital, and frontal regions). At each step of the procedure, the data were visually checked. Corrections were needed only in less than 5% of the subjects. Mean depth and fold opening (mean distance between the two walls of pial surface defining the cortical sulci) were measured (in millimeters) for each sulcus on both sides. Cortical thickness was assessed for every sulcus in its immediate neighborhood, as previously reported [7].

Statistical analyses

Between group differences were tested according to variable type and distribution. Numerical variables with normal distribution and similar variances across groups were tested using ANOVA. Chi-square tests were used for categorical variables. Due to multiple statistical tests, level of significance was set to 0.01. Results were checked after adjustment for age, gender, and level of education.

RESULTS

There was no demographic difference between the three groups. Particularly age, gender, and level of education did not differ between the 3 groups (see Table 1). By definition, MMSE scores largely differed between the three groups (HC median MMSE score: 29; MCI median MMSE score: 28; AD median MMSE score: 23.5), as well as AVLT delayed recall ($p < 10^{-4}$), ADAS-cog 10-word list

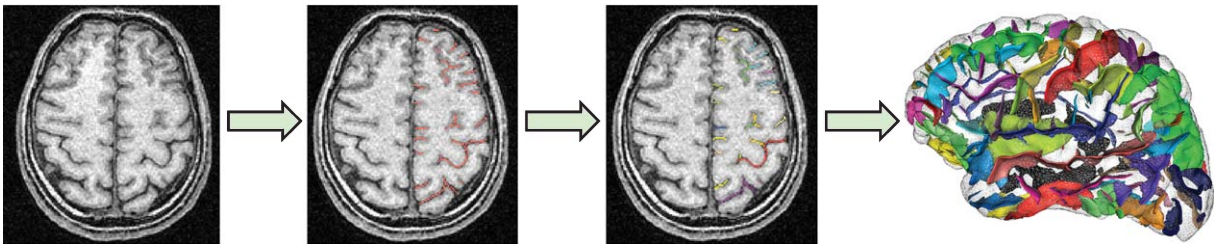

Fig. 1. Main steps involved in the reconstruction or cortical sulci. For each subject, cortex sulci are reconstructed after several steps detailed elsewhere [7] and thereafter identified. Visualization in 2D and 3D allows checking of both sulcal reconstruction and identification.

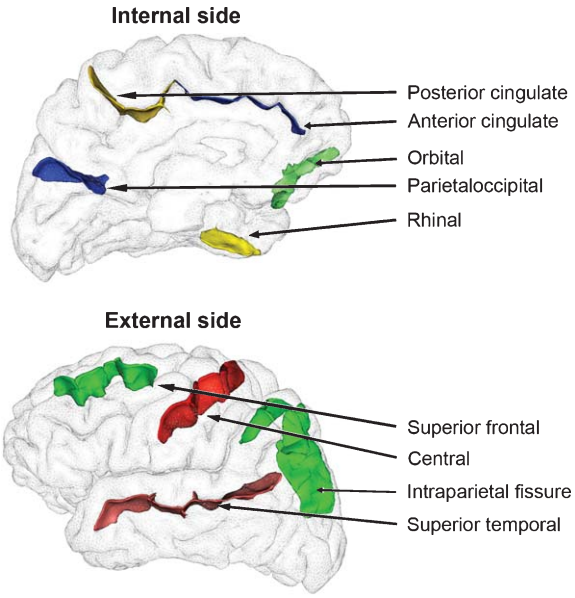

Fig. 2. Sulci evaluated in our study. Example from one subject of our sample, for which the nine sulci considered for analyses are reconstructed and projected over the cortical surface.

delayed recall ($p < 10^{-4}$) and time to complete TMTB ($p < 10^{-4}$).

BPF strongly differed between the three groups ($p < 10^{-4}$), by contrast to the GI that did not ($p = 0.11$). Depth of right superior temporal and parietaloccipital sulci significantly differed between the three groups, with progressive reduction from HC to MCI to AD (right superior temporal: HC: 16.79 ± 1.7, MCI: 15.83 ± 2.3, 14.83 ± 2.2, $p = 0.0006$; parietaloccipital: HC: 17.74 ± 2.9, MCI: 16.68 ± 2.1, AD 15.41 ± 2.6, $p = 0.006$) (Table 2). Depth of left anterior cingulate and parietaloccipital sulci also significantly differed between the three groups (anterior cingulate: HC: 8.33 ± 2.1, MCI: 9.19 ± 1.3, AD: 9.56 ± 1.4, $p = 0.006$; parietaloccipital: HC: 18.36 ± 2.3, MCI: 15.45 ± 2.4, AD: 16.33 ± 3.3, $p = 0.0008$).

Fold opening significantly differed between the three groups on both side for intraparietal and parietaloccipital sulci, with a progressive augmentation from HC to MCI to AD (right intraparietal sulcus: HC: 1.74 ± 0.3, MCI: 1.76 ± 0.4, AD: 2.06 ± 0.6, $p = 0.005$; right parietaloccipital, HC: 1.49 ± 0.3, MCI 1.68 ± 0.6, AD 1.88 ± 0.5, $p = 0.003$; left intraparietal sulcus: HC: 1.74 ± 0.3, MCI: 1.85 ± 0.4, AD: 2.06 ± 0.6, $p = 0.004$; left parietaloccipital sulcus: HC: 1.47 ± 0.3, MCI: 1.62 ± 0.3, AD: 1.79 ± 0.5, $p = 0.0009$).

Fold opening of right posterior cingulate and of superior temporal as well as that of left superior frontal sulcus also significantly differed between the three groups, still with a progressive augmentation from HC to MCI to AD (right posterior cingulate: HC: 2.29 ± 0.4, MCI: 2.37 ± 0.6, AD: 3.02 ± 1.5, $p = 0.004$; right superior temporal: HC: 1.66 ± 0.3, MCI: 1.75 ± 0.3, AD: 1.90 ± 0.3, $p = 0.002$; left superior frontal: HC: 2.20 ± 0.4, MCI: 2.35 ± 0.6, AD: 2.65 ± 0.6, $p = 0.002$).

All p-values remained significant after adjustment for age, gender, and level of education. After further adjustment for BPF, only depth of right superior frontal and parietaloccipital as well as that of left anterior cingulate remain significantly different between the 3 groups. By contrast, cortical thickness did not differ between the three groups for either of the sulci (data not shown).

There were strong relationships between the different parameters that differed across the 3 groups and the clinical variables, after adjustment for age, gender, and level of education (Table 3).

Table 1
Clinical and radiological characteristics of the three samples in our study

	Healthy controls ($n = 30$)	MCI subjects ($n = 33$)	AD patients ($n = 30$)	p
Mean age, sd, range	75.9, 74.0, 62.0–90.0	75.4, 76.0, 61.0–89.0	76.6, 76.5, 60.0–89.0	0.69
Gender, male, %	17 (56)	17 (52)	14 (47)	0.74
Years of education	15.7 ± 2.6	16.6 ± 2.8	15.4 ± 2.6	0.64
Right handedness, n, %	27 (90)	32 (97)	29 (97)	0.40
Cognitive scores				
MMSE, mean, median, range	29, 29, 26–30	27.5, 28, 24–30	23.2, 23.5, 20–26	$<10^{-4}$
AVLT delayed recall	6.9 ± 3.2	3.0 ± 4.1	0.6 ± 2.1	$<10^{-4}$
ADAS-Cog 10-word list delayed recall	7.1 ± 1.4	3.8 ± 2.6	1.2 ± 1.8	$<10^{-4}$
TMTB time to complete (s)	87.0 ± 46.0	109.9 ± 65.6	180.3 ± 102.0	$<10^{-4}$
MRI markers				
BPF	0.77 ± 0.03	0.75 ± 0.04	0.73 ± 0.03	$<10^{-4}$
Gyrification Index	1.29 ± 0.11	1.25 ± 0.18	1.21 ± 0.15	0.11

Table 2
Differences of cortical morphological markers between HC, MCI, and AD. Results of ANOVA tests between the three groups for depth and fold opening on both sides. Results were unchanged after adjustment for age, gender, and level of education

	Right								Left							
	Depth				Fold opening				Depth				Fold opening			
	HC	MCI	AD	*p*	HC	MCI	AD	*p*	HC	MCI	AD	*p*	HC	MCI	AD	*p*
Orbitofrontal	5.13 ± 3.8	5.90 ± 3.6	6.51 ± 3.4	0.14	2.32 ± 2.1	2.39 ± 2.3	2.49 ± 1.5	0.75	7.68 ± 2.6	6.66 ± 3.5	6.87 ± 3.2	0.33	2.41 ± 1.2	2.15 ± 1.4	2.27 ± 1.3	0.59
Superior frontal	12.96 ± 1.1	12.15 ± 1.9	12.96 ± 2.0	0.98	2.19 ± 0.4	2.41 ± 0.6	2.51 ± 0.6	0.02	12.89 ± 1.7	12.24 ± 1.7	11.89 ± 1.8	0.03	2.20 ± 0.4	2.35 ± 0.6	2.65 ± 0.6	**0.002** (0.28; 0.04; 0.001)
Anterior cingulate	8.47 ± 3.2	8.49 ± 2.6	8.23 ± 2.6	0.75	2.36 ± 1.1	3.77 ± 2.5	3.20 ± 1.5	0.08	8.33 ± 2.1	9.19 ± 1.3	9.56 ± 1.4	**0.006*** (0.06; 0.29; 0.01)	3.38 ± 2.7	3.17 ± 1.2	2.96 ± 1.1	0.42
Posterior cingulate	12.17 ± 2.2	11.58 ± 1.4	11.07 ± 1.6	0.02	2.29 ± 0.4	2.37 ± 0.6	3.02 ± 1.5	**0.004** (0.57; 0.02; 0.01)	11.79 ± 1.4	12.00 ± 1.7	11.20 ± 1.6	0.16	2.30 ± 0.5	2.35 ± 0.6	2.66 ± 0.8	0.02
Rhinal	8.30 ± 2.4	7.75 ± 2.0	8.37 ± 2.4	0.89	3.23 ± 1.3	4.11 ± 2.1	3.78 ± 2.2	0.28	9.11 ± 3.0	7.09 ± 3.0	7.69 ± 2.3	0.06	2.98 ± 1.5	3.10 ± 2.1	3.36 ± 1.7	0.39
Superior temporal	16.79 ± 1.7	15.83 ± 2.3	14.83 ± 2.2	**0.0006*** (0.07; 0.10; 0.0005)	1.66 ± 0.3	1.75 ± 0.3	1.90 ± 0.3	**0.002** (0.21; 0.06; 0.002)	16.08 ± 2.2	15.34 ± 1.7	16.52 ± 2.0	0.42	1.67 ± 0.2	1.79 ± 0.3	1.78 ± 0.2	0.09
Central	15.52 ± 1.3	14.82 ± 1.5	15.28 ± 1.7	0.58	2.02 ± 0.2	2.04 ± 0.3	2.25 ± 0.5	0.02	15.5 ± 1.4	14.94 ± 1.4	15.55 ± 1.7	0.98	2.04 ± 0.2	2.11 ± 0.4	2.18 ± 0.3	0.08
Intraparietal	14.54 ± 1.4	13.87 ± 1.3	13.92 ± 1.3	0.09	1.74 ± 0.3	1.76 ± 0.4	2.06 ± 0.6	**0.005** (0.78; 0.01; 0.003)	14.49 ± 1.4	13.98 ± 1.7	13.79 ± 1.7	0.10	1.74 ± 0.3	1.85 ± 0.4	2.06 ± 0.6	**0.004** (0.28; 0.08; 0.006)
Parietaloccipital	17.74 ± 2.9	16.68 ± 2.1	15.41 ± 2.6	**0.0006*** (0.10; 0.05; 0.003)	1.49 ± 0.3	1.68 ± 0.6	1.88 ± 0.5	**0.003** (0.10; 0.22; 0.001)	18.36 ± 2.3	15.45 ± 2.4	16.33 ± 3.3	**0.008** ($<10^{-4}$; 0.24; 0.009)	1.47 ± 0.3	1.62 ± 0.3	1.79 ± 0.5	**0.0009** (0.02; 0.15; 0.006)

Significant results are shown in bold. Significant results after adjustment for age, gender, level of education, and global brain volume are denoted by *. For significant results, post-hoc pairwise comparisons of individuals study groups are given in parentheses following the order HC versus MCI, MCI versus AD, and HC versus AD.

DISCUSSION

In the present study, we found important regional differences of cortical morphology rather than of regional cortical thickness between HC, MCI, and AD subjects. By contrast to global cortical folding, namely the GI, which did not differ significantly between the three groups, we identified several regional parameters that were statistically different between the three groups. Particularly, fold opening of the parietaloccipital fissure and intraparietal sulcus on both sides were the parameters that most differed across the 3 groups. Indeed, the results suggest a progressive opening of these folds from HC to MCI and then to AD (see Fig. 3). Globally, they were 1 mm wider in MCI compared to HC and 2 mm wider in AD than in MCI patients. Fold opening of the right posterior cingulate and superior temporal sulci and of the left superior frontal sulcus also progressively increased from HC to MCI and then to AD. Moreover, depth of superior temporal and parietaloccipital sulci on the right side were significantly different between the three groups, with a mean reduction of 1 mm between HC and MCI and between MCI and AD. We also observed a significant difference between the 3 groups for left anterior cingulate and parietaloccipital sulci. There was a gradual increase of sulcal depth between HC, MCI, and AD groups for left anterior cingulate while for parietaloccipital sulcus AD showed intermediate depth values compared to HC and MCI patients. By contrast, we found no difference of cortical thickness in the vicinity of all sulci evaluated in the present study. We also observed important relationships between cortical morphology of those sulci that differed between the three groups and neuropsychological scores (see Table 3).

The differences of sulcal morphology have been scarcely investigated so far. In a previous study, Im et al. reported differences of sulcal morphology between HC, MCI, and AD subjects [21]. Their approach, however, was quite different as analyses were made at the lobar level and not relatively to the different sulci after their identification. Some of the parameters reported in the present study exhibited gradual changes between HC, MCI, and AD subjects, which has not been reported so far in other structures than the medial temporal lobe [1]. Of course, structural differences have already been reported between HC, MCI, and AD patients. In a previous study using VBM, gray matter loss differed between HC and MCI in the medial temporal lobe, while gray matter loss in parietal and posterior cingulate cortices differed between MCI and AD subjects [22]. Some authors have paralleled these findings with the observed temporal spreading of cortical pathology in AD [23]. In a previous study comparing AD patients with slow or fast cognitive decline, authors have reported more gray matter tissue loss in parietaloccipital areas, particularly in the cunueus, precuneus, and more generally in the cortex surrounding the parietaloccipital fissure in fast decliners compared to slow decliners [24]. Our results are in line with these data, which altogether suggest a progressive fold opening of the parietaloccipital fissure with increasing severity of AD pathology. By contrast to our approach, VBM identifies intergroup differences which can be due to differences of gray matter quantity but also to differences of cortical folding [2].

Beyond the observed variability of cortical morphology in normal aging, [25, 26] it may seem obvious that cortical morphology changes are related to the cortical thinning related to underlying AD pathol-

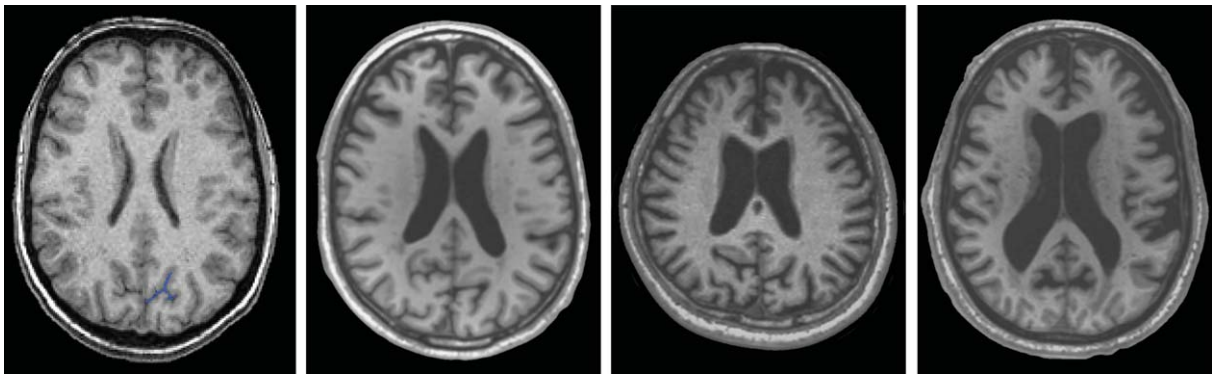

Fig. 3. Extent of morphological variations of the parietaloccipital fissure. 3DT1 MRI sequences registered in bi-commissural plane through caudate body for, from left to right, a young healthy subject with left parietaloccipital sulcus outlined on MRI (in blue), a healthy control (HC), a MCI subject, and an AD patient, illustrating the extent of depth reduction and sulcal widening.

Table 3
Relationship between sulcal measures and clinical scores. Linear regression modeling of clinical scores (dependent variables) by sulcal measures, after adjustment for age, gender, and level of education

	MMSE			Auditory Verbal Learning Test, delayed recall performance			Trail Making Test version B, time to complete			ADAS-Cog 10-Word list		
	Estimate	s.d.	*p*	Estimate	s.d.	*p*	Estimate	s.d.	*p*	Estimate	s.d.	*p*
Superior frontal fold opening, left	−1.03	0.52	0.05	−1.74	0.7	0.02	29.36	14.1	0.04	**−1.41**	**0.6**	**0.01**
Anterior cingulate depth, left	−0.33	0.2	0.07	−0.28	0.3	0.29	−1.50	5.0	0.76	−0.38	0.2	0.05
Posterior cingulate fold opening, right	−0.50	0.31	0.11	−0.86	0.4	0.05	9.17	8.3	0.28	**−0.90**	**0.3**	**0.006**
Superior temporal												
depth, right	**0.35**	**0.1**	**0.01**	**0.47**	**0.2**	**0.01**	−6.40	3.7	0.09	**0.41**	**0.1**	**0.005**
fold opening, right	**−2.65**	**1.0**	**0.01**	−3.59	1.5	0.02	49.90	28.7	0.09	**−2.91**	**1.1**	**0.01**
Intraparietal												
fold opening right	**−1.82**	**0.7**	**0.007**	−1.67	1.0	0.09	28.87	18.6	0.12	**−1.83**	**0.7**	**0.01**
fold opening left	−1.34	0.7	0.06	−2.25	1.0	0.02	22.59	19.0	0.24	**−2.12**	**0.7**	**0.005**
Parietaloccipital												
depth, right	**0.29**	**0.1**	**0.01**	**0.44**	**0.2**	**0.007**	−4.30	3.2	0.18	**0.38**	**0.1**	**0.002**
depth, left	0.17	0.1	0.11	0.20	0.1	0.18	−5.55	2.8	0.02	0.23	0.1	0.04
fold opening, right	−1.40	0.6	0.03	**−2.21**	**0.9**	**0.01**	**53.45**	**16.4**	**0.002**	**−1.98**	**0.7**	**0.004**
fold opening, left	−1.67	0.8	0.04	−1.35	1.2	0.25	27.92	22.3	0.21	−1.78	0.9	0.05

Significant results are shown in bold.

ogy. However, some data suggest that other processes may be involved. In one pathological study, Duyckaerts et al. found no difference in cortical thickness between severely affected AD patients and HC but instead a reduction of cortical length, which they attributed to disappearance of cortical columns [10]. Additionally, the opening of the folds of parietaloccipal and intraparietal sulci on both sides observed in the present study may not be necessarily related specifically to AD. These features may also reflect a specific fragility of this area related to changes of global mechanical constraints of the brain related to physical tissue changes. We already observed this finding in patients with Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy (CADASIL) in the absence of AD, which is difficult to explain by specific neuronal loss localized in this area (personal data, unreported). Global folding did not differ between HC, MCI, and AD while most results did not remain significant after adjustment for global brain atrophy, further supporting the hypothesis that local modifications of cortical morphology may reflect global brain alterations rather than specific local processes. However, the absence of between-group differences for GI must be interpreted with caution as it could also reflect a wider variability of this measure compared to that of BPF.

Our study has limitations. The sample size of 93 subjects in total was relatively small. However, this choice was deliberate to detect only large differences with potential relevance in clinical setting. Also, although we used a far lower number of tests than in massive univariate approaches at the voxel level, we tested 2 parameters on each side for each of the 9 sulci, yielding 36 statistical tests. This number of tests can raise the probability of finding statistically significant associations only due to chance. However, this appears unlikely in this study. First, we found 9 p-values inferior to 0.01 in our sample, while one would expect less than one over the 36 tests if p-values were randomly distributed. Second, our results are quite homogeneous over the different sulci. Additionally, one variable, namely fold opening, represents more than two third of p-values < 0.01. Another important limitation of the present study is that, by contrast to other methods, our approach only gives minimal information about medial temporal lobe, a key structure in MCI and AD, through the reconstruction of the rhinal sulcus. Because of the proximity of air-bone-brain interfaces, of the architecture of the medial temporal structures and of lower regional gray to white contrast, we observed a significant variability of the reconstruction of the rhinal sulcus. Moreover, AD patient may show different patterns of sulcal structure than HC [27]. These elements may have hampered the detection of some differences between HC, MCI, and AD. Additionally, the absence of difference of cortical thickness between the three groups observed in the present study must be inter-

preted with caution as our method only computes one average value for cortical thickness for each sulcus in its neighborhood, and is thus possibly less sensitive than other approach for very localized differences. Finally, we found intriguing results for the depth of the left anterior cingulate sulcus, which was increased from HC to MCI and then to AD. Although possibly due to chance alone, this result may also reflect a recruitment bias. As MMSE scores were not related to age in any of the 3 groups, it is probable that the global brain "health" of a 90-year-old AD patient with a MMSE score of 23 (mean value in the AD group) is better than that of a 60-year-old AD patient with the same MMSE score. Some unexpected findings when comparing HC to AD patients may be related to the fact that some healthy brain areas compensate others in the oldest AD patients compared to the youngest.

This study has also several strengths. Our methodology relies on post-processing methods using MRI sequences in the native space of acquisition. Reconstruction and identification of cortical sulci was visually checked for each subject in both 2D and 3D modes using ad-hoc in house developed software, thus strongly limiting the potential sources of errors [7]. Our method has already been validated in the context of severely diseased brain and has been shown reliable even in the context of important brain atrophy and severe white matter lesions [8]. Our approach disentangles several phenomena that may be impossible to differentiate in voxel-based analyses [2].

In summary, we report in the present paper differences of cortical morphology between HC, MCI and AD subjects, which are strongly and independently linked to the neuropsychological scores. Our results provide a possible alternative explanation for the differences previously reported between MCI and AD patients using VBM in parietaloccipital and intraparietal areas. Moreover, some of the observed cortex parameters exhibited truly gradual changes from HC to MCI and to AD, further supporting the hypothesis of MCI as an intermediate stage between HC and AD. Cortical morphology probably does not reflect the same brain alterations than cortical thickness or gray matter density or volume. It is probably a better marker of the global mechanistic properties of brain tissue that are eventually altered by underlying pathological phenomenon such as neuronal loss or gliosis [10]. Further studies are needed to better delineate the mechanisms of cortical morphological changes in healthy aging and AD.

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