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Abstract

Measuring the morphology of brain sulci has been recently proposed as a novel imaging approach in AD. We aimed to investigate the relevance of such an approach in AD, by exploring its (1) clinical relevance in comparison with traditional imaging methods, (2) relationship with amyloid deposition, (3) association with cognitive functions. Here, 51 patients (n=32 MCI/mild dementia-AD, n=19 moderate/severe dementia-AD) diagnosed according to clinical-biological criteria (CSF biomarkers and amyloid-PET) and 29 controls (with negative amyloid-PET) underwent neuropsychological and 3T-MRI examinations. Mean sulcal width (SW) & mean cortical thickness around the sulcus (CT-S) were automatically measured. We found higher SW and lower CT-S in AD patients than in controls. These differences were more pronounced at later stages of the disease and provided the best diagnostic accuracies among the imaging markers. Correlations were not found between CT-S or SW and amyloid deposition but between specific cognitive functions and regional CT-S/SW in key associated regions. Sulcal morphology is a good supporting diagnosis tool, that reflects the main cognitive impairments in AD. It could be considered as a good surrogate marker to evaluate the efficacy of new drugs.

Keywords: Alzheimer's disease, sulcal morphology, cortical thickness, sulcal width, data-driven science

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Introduction

Although positron emission tomography (PET) imaging now enables *in vivo* detection of amyloid (Klunk et al. 2004) and tau (Villemagne et al. 2015) lesions, these techniques are more invasive and expensive than magnetic resonance imaging (MRI) as well as less widely available. Furthermore, the ATN classification system ("A" (Aβ-amyloid), "T" (tau), and "N" (neuronal injury)) proposed recently by the United States' National Institute on Aging and Alzheimer's Association (NIA-AA) research framework reinforced the role of anatomic MRI as a marker of neurodegeneration (N), in addition to amyloid and tau (A, T) markers (Jack et al. 2018). This stresses the importance to refine the methods used to analyse structural brain MRI because of the supportive role they have in the diagnosis of neurodegenerative diseases such as Alzheimer's disease (AD).

As an example, hippocampal volume measurement has long been considered to be a supportive diagnostic feature of AD (Albert et al. 2011; Dubois et al. 2014). Indeed, hippocampal volume (HV) correlates with memory performance, (Sarazin et al. 2010) the density of neurofibrillary tangles at autopsy (Jack et al. 2002), and cerebrospinal fluid (CSF) levels of tau and phosphorylated tau (de Souza et al. 2012), which are all markers of the underlying pathophysiological processes of AD. However the overlap between healthy controls and AD patients on HV measures,(Frisoni et al. 1999; de Souza et al. 2013) limits its relevance for diagnostic purpose at the individual level (Frisoni et al., 2010). In addition, hippocampal atrophy is also observed in other neurodegenerative conditions such as frontotemporal dementia (de Souza et al. 2013; Hornberger et al. 2012; La Joie et al. 2013), warranting caution for considering this anatomical marker as specific of AD.

Other quantitative MRI techniques, such as voxel-based morphometry (VBM) and cortical thickness (CT) measures are additional potential tools for the diagnosis of AD as they reveal the involvement of neurodegeneration in the neocortex at an early stage of AD (Karas et al. 2004; Singh et al. 2006; Hämäläinen et al. 2007; Kinkinghéhum et al. 2008; Holland et al., 2009; Cuingnet et al. 2011). CT analyses led to the definition of a cortical atrophy signature of AD consisting in 9 regions showing significant cortical thinning from the early stages of the disease (Dickerson et al. 2009). This signature predicted the conversion from MCI to AD dementia (Bakkour et al. 2009) and the progression to AD among cognitively healthy older adults (Dickerson et al. 2011). Based on these methods, clinical classifiers have also been obtained by applying machine learning techniques to structural MRI data (Mateos-Pérez et al. 2018).

Beyond these approaches, measuring the morphology of sulcal cortical folds using three-dimensional processing techniques has been recently proposed as a novel approach to investigate the morphology of the cortical surface,(Mangin et al. 2004; Mangin et al. 2010) including in AD (Hamelin et al. 2015; Cai et al. 2017). In contrast to VBM or CT measurements, this method is not dependent on grey/white contrast, which weakens with age and disease progression, but on the contrast between the grey matter and the CSF, which is far less affected by these parameters. Sulcal morphology measures provide individual models of cortical anatomy rather than relying on a common stereotaxic space, potentially overcoming some biases induced by spatial normalisation (Mangin et al. 2004). Moreover, the sulcal abnormalities integrate not only atrophy of the cortical mantle around the sulcus but also atrophy of the surrounding gyral white matter, which could enhance the sensitivity to detect the

earliest stages of AD (Liu et al. 2013a; Liu et al. 2013b). These measures can lead to a high number of variables, by mapping the cortex into circumscribed and numerous regions of interest, which could have a true relevance in data-driven medicine in the era of big-data and precision medicine in addition to providing high spatial resolution.

So far, only few studies have analysed sulcal morphology in AD. Despite conflicting results, findings suggest that sulcal morphology analysis provides insights into the structural brain changes in AD (Cai et al. 2017; Im et al. 2008; Liu et al. 2008; Reiner et al. 2012). To our knowledge, only one study based the inclusion of patients and controls on biological evidences of AD (Hamelin et al. 2015). In that study, we showed that sulcal width measures improved the diagnosis of early-onset AD. However, whether sulcal morphology measures improve AD diagnosis in comparison to more traditional MRI methods such as HV, regional cortical thickness or volumes measures remains unclear. Another unsolved question is how sulcal morphology relates to amyloid deposition and cognitive dysfunctions as so far, correlations between these measures and cognitive scores have never been performed.

The present study aimed to investigate sulcal morphology measurements in AD patients defined by clinical-biological criteria in order to (a) describe the sulcal morphology profile at both the MCI/mild dementia and moderate/severe dementia stages; (b) compare their accuracy to identify AD pathophysiology in comparison with more broadly used imaging methods; (c) explore their relationship with cortical amyloid deposition and; (d) with specific cognitive dysfunctions in AD.

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Methods

1.1 Participants

Eighty participants were included from the Biomage (NCT01095744) and ImaBio3 studies (NCT01775696) that were approved by the Ethics Committee of the Pitié-Salpêtrière Hospital. All participants provided signed informed consent and were followed-up for 24 months to improve the diagnostic accuracy. Exclusion criteria were: (a) any clinical or neuroimaging evidence of focal lesions; (b) severe cortical or subcortical vascular lesions (Fazekas score >1, evaluated on FLAIR sequences); (c) severe depression (Score at the Montgomery-Åsberg Depression Rating Scale <30); Montgomery et al. 1979).

Fifty-one typical (i.e., amnestic) AD patients were included according to these criteria: (a) memory impairment observed at the Free and Cued Selective Reminding Test (FCSRT), with or without another cognitive impairment (Sarazin et al. 2007); (b) biological evidence of AD-related pathophysiological process as defined by a CSF biomarker profile indicative of AD (Innotest Amyloid Tau Index (IATI) score <0.8) analysed in 86% (n=44/51) of patients (de Souza et al. 2011) and/or positive amyloid imaging on positron emission tomography using ^{11}C-labeled Pittsburgh Compound B (PiB-PET) defined by a global cortical index (GCI) > 1.4 (100%, n=51/51). IATI score was calculated following this formula: $(A\beta_{1-42})/(240+ 1.18*Tau)$. Patients were divided in two groups: mild cognitive impairment (MCI) due to AD or mild AD dementia (MCI/mildAD, n=32, 63%) and moderate to severe dementia patients (DemAD, n=19, 37%) according to the ability to function independently, following the NIA-AA guidelines (Albert et al. 2011; McKhann et al. 2011), and the MMSE score (≥20 or <20, respectively). Twenty-nine healthy controls were included according to these criteria: (a) normal neuropsychological assessment; (b) no history

of psychiatric/neurological conditions; (c) negative amyloid retention on PiB-PET (GCI<1.4).

1.2 Neuropsychological measures

All participants underwent a neuropsychological examination that included the MMSE (Folstein et al. 1975) and a standard evaluation of verbal (FCSRT) and visual long-term memory (recall of Rey complex figure), executive functions (Trail Making Task, Similarities from WAIS III), working memory (digit spans), language (word naming task), gesture praxis and visuo-constructive functions (copy of Rey figure).

1.3 Imaging parameters

1.3.1 MRI acquisition

MRI scans were obtained on a 3T Siemens Trio scanner (32 channels with a 12 channel head coil for signal reception) involving a 3D T1-weighted volumetric magnetisation-prepared rapid-gradient echo (MP-RAGE) sequence with repetition time=2300ms, echo time=2.98ms/3.43, inversion time=900, matrix=256x256 and slice thickness=1mm. This sequence provided a high grey/white matter contrast-to-noise ratio and allowed excellent segmentation and co-registration with the PET images.

1.3.2 Sulcal morphometry measures

For each participant, cortical sulci were reconstructed and automatically identified from each individual 3D T1-weighted MRIs. As performed in a previous study (Hamelin et al., 2015), the cortical sulci were extracted from T1-weighted scans via the following steps. First, a brain mask was obtained with the SPM8 skull-cleanup

tool, an automated skull stripping procedure. Second, segmentation of the images into grey and white matter as well as CSF was performed using histogram scale-space analysis and mathematical morphology (Mangin et al. 2004). Third, individual sulci were segmented and labelled using Morphologist from Brainvisa (http:// http://brainvisa.info/web/morphologist.html). For segmentation, a kind of crevasse detector was employed to reconstruct each fold geometry as the medial surface from the two opposing gyral banks that spanned from the most internal point of the fold to the convex hull of the cortex (Mangin et al. 2004). Then, a Bayesian-inspired pattern recognition approach relying on statistical probabilistic anatomy maps and multiscale spatial normalization was used to label the folds for 60 sulci (Perrot et al. 2011; Mangin et al. 2015). The sulcus width (SW) was quantified for each sulcus using the average distance between both banks of the pial surface. This average distance was computed as a ratio between the volume of CSF filling up the sulcus from the brain hull to the fold bottom, and the surface area of the sulcus estimated by half the sum of the areas of the triangles making up a mesh of the corresponding medial surface. A fast-marching algorithm applied to a voxel-based binary representation of the cortex grey matter was employed to compute the average thickness of the cortical mantle on both sides of the sulcus (CT-S). Both measures were computed in millimetres for each participant as individual values in each ROI for each hemisphere. Quality checks were performed at each step of the procedure. No manual corrections were needed. Additional details about this procedure and the quality checks performed are provided in the Supplementary material.

We defined 18 regions of interest (ROIs), which were extracted in each brain hemisphere (Figure 1). In the frontal lobe: the (**1**) anterior lateral sulci (superior,

middle, intermediate and inferior frontal sulci), (**2**) median frontal sulci (medial portions of the inferior-frontal sulcus, inferior-rostral-frontal sulcus and anterior calloso-marginalis fissure), (**3**) orbital sulci (polar-frontal, orbital and olfactory sulci), (**4**) internal frontal sulcus, (**5**) subcallosal sulcus (or corpus callosum sulcus, including its non-frontal parts), (**6**) precentral sulci (lateral portions of the superior, middle and inferior frontal sulci) and (**7**) central sulcus. Within the temporal lobe: the (**8**) temporo-polar, (**9**) superior temporal, (**10**) inferior temporal, (**11**) rhinal, (**12**) collateral and (**13**) temporo-occipital sulci, grouped with their branches. In the parietal lobe: the (**14**) lateral parietal sulci (intraparietal sulcus, superior and inferior post-central sulci, superior parietal sulcus and their intermediate branches), (**15**) precuneus and retrosplenial sulci (including the internal parietal and medial inferior parietal sulci), (**16**) posterior cingulate sulci (including the posterior calloso-marginalis and paracentral sulci) and (**17**) parieto-occipital sulcus. In the occipital lobe, we grouped all sulci into a unique ROI defined as (**18**) occipital sulci.

1.3.3 Regional cortical volumes (rVOIs)

Grey matter automated segmentation was performed from each individual 3D-T1-weighted MRI scan using the VBM8 package of SPM8 (Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). The automated anatomical labelling atlas was deformed to each individual MRI (deformation field extracted from VBM8) and intersected with the T1-MRI grey matter. We pooled the AAL VOIs into greater volumes of interest, i.e. (1) frontal; (2) anterior cingulate; (3) middle cingulate; (4) posterior cingulate; (5) precuneus & retrosplenial; (6) parietal; (7) temporal; (8) hippocampus; (9) and occipital VOIs. VOIs were computed for each hemisphere,

resulting in 18 rVOIs. Additional details about rVOIs are provided in the Supplementary material.

1.3.4 FreeSurfer cortical thickness (FCT)

A surface based cortical thickness estimation using the FreeSurfer analysis toolbox (version 5.3; http://surfer.nmr.mgh.harvard.edu/) was performed. A surface-based approach provides better reliability on two different same-day scans than voxel-based approaches, and morphometric procedures have been demonstrated to show good test-retest reliability (Han et al., 2006; Clarkson et al., 2011; Reuter et al., 2012). Detailed documentation is available on the FreeSurfer web page. These extracted values were considered for inter-group statistical comparisons. We visually inspected the FreeSurfer parcellation results to identify global segmentation abnormalities including non-cortical tissue labelling, missing structures and movement artefacts.

Mean cortical thickness indices for 68 ROIs were obtained. We performed quality control review of all cortical regions to ensure accurate labelling of grey-white matter boundaries. Please see the Supplementary material for additional detail about FreeSurfer segmentation and parcellation procedures, the ROIs considered and the full description of the quality check procedure regarding the ROIs approach. One-tailed student tests (controlled for age) were performed for each of the 68 ROIs testing the hypothesis that the average thickness in a given ROI is smaller in AD participants. We controlled for multiple comparisons by controlling the false discovery rate at 5%, using the Benjamini and Yekutiely procedure under the assumption of positive dependency between variables, to determine in which ROIs the differences between groups were significant (Benjamini et al, 2001).

In parallel to the ROI approach, we used FreeSurfer's built-in statistical tools for vertex-wise generalized linear models on the individual surfaces previously resampled into the common anatomic space and smoothed using a Gaussian smoothing kernel of 10mm. The group comparison (controlled for age) consisted of AD participants vs controls. The statistical significance of between-group cortical thickness differences was evaluated using a clusterwise correction for multiple comparisons (Hagler et al., 2006). Initial clusters of significant contiguous groups of vertices were obtained using a vertex-wise p-value threshold of $p<0.01$ (one-tailed) and were only reported if they met a cluster-wise forming threshold (Cluster Simulation Data probability) of $p<0.05$ (one-tailed), accounting for the probability of finding a given cluster by chance, given its surface area and the amount of smoothing applied to surface maps. Individual thickness averages were then obtained within each significant cluster and subsequently normalized by their surface area and averaged to arrive at an individual thickness index for each participant.

1.3.5 Hippocampal volume (HV)

Hippocampal segmentation was performed bilaterally for each participant using the validated software SACHA (Segmentation Automatisée Compétitive de l'Hippocampe et de l'Amygdale) (de Souza et al. 2013; Chupin et al. 2009). Briefly, this software segments the hippocampus and the amygdala on the basis of competitive region-deformation between these structures, relying on prior knowledge of the relative positions of these structures with respect to 11 sets of anatomical landmarks automatically identified at the border of the deforming objects. A quality check of the segmentation was performed and passed for all participants. Only the hippocampal volume was considered.

1.3.6 Regional amyloid load

[^{11}C]-PIB PET scans were performed on a high-resolution tomograph (CTI/Siemens Molecular Imaging, TN, USA). Quantitative analysis was performed as described previously (de Souza et al. 2011). Briefly, parametric images representing [^{11}C]-PIB uptake in each voxel was calculated as a region-to-cerebellum ratio of the radioactivity concentration over 40-60 min. The AAL VOIs defined above were applied on the PET parametric images after coregistration with the participant's MRI. The GCI of [^{11}C]-PIB uptake was defined as the participant's mean value in the neocortical regions cited above; see **1.3.3 Regional cortical volumes (rVOIs)**. Additional details are provided on PET imaging and the computation of regional amyloid burden values in the Supplementary material.

1.4. Statistical analyses

Data were analysed using SPSS20 (SPSS Inc., Chicago, Illinois).

1.4.1 Between-groups differences

Three-way then two-by-two differences between groups (controls, MCI/mildAD, demAD) were explored using a multivariate analysis of variance, with age set as a nuisance covariate. All imaging parameters (CT-S, SW, rVOIs and HV) were adjusted for each participant's intracranial volume derived from SPM8 segmentations preliminary to these analyses, except FCT, which is not affected by intracranial volume (Barnes et al., 2010). Differences were sought for clinical, neuropsychological, demographical and the imaging measures. False Discovery Rate (FDR) corrections was applied to account for multiple comparisons.

1.4.2 Prediction of AD diagnosis

A data-driven method was applied to identify the set of ROIs that was the best predictor (in %) of the presence/absence of AD (controls vs patients) diagnosis among the imaging measures that involved multiple regions (CT-S/SW/rVOIs/FCT). The same analysis was applied for HV measure. This automated procedure relied on a binary logistic regression where variables provided by each method were included in the analysis then removed stepwise from the model according to a probability of Wald statistic unless they yielded a significant contribution to the model ($p<0.001$). Bootstrap procedures were conducted (with a total of 1000 resamplings with a 95% confidence interval) to ensure the stability of each classification performed. This approach was complemented by the computation of sensitivity, specificity and (95%) confidence intervals, all calculated based on the number of true/false positive and true/false negative obtained with the logistic regression output. The application of Akaike's information criterion (AIC) allowed us to compare the accuracy of each imaging methods' prediction power, independently of the number of predictors.

1.4.3 Correlations with amyloid load and cognitive performance

Principal component analyses (PCA) were run in AD patients (all) with CT-S and SW values as well as with neuropsychological scores, after a z-score transformation in order to reduce the datasets. Correlations between sulcal (CT-S or SW) components and amyloid deposition or neuropsychological components were sought with age as a nuisance covariate. Automated linear modelling was also performed to quantify the percentage of variance of the different neuropsychological components explained by the variation of the different sulcal components.

Results

1.1 Demographics, clinical, biological (Table 1)

Age, education and gender did not differ across the three groups (all p>0.10). No differences were observed between MCI/mildAD and DemAD on CSF levels of phospho-tau, total-tau, and beta-amyloid, or amyloid load GCI measured by PET. For the last analysis, the delay between the lumbar puncture and the PET was set as a covariate.

	Controls	MCI/mildAD	DemAD
N (M/F)	29 (15/14)	32 (13/19)	19 (8/11)
Age	65.82 (7.59)	66.59 (10.03)	68.10 (11.60)
Education	12.70 (3.05)	13.47 (3.59)	11.59 (4.00)
CDR	0	0.5	1 (n=17), 2 (n=2)
MMSE	29.22 (0.93)	23.59 (2.9) *#	15.84 (4.19) *#
Biomarkers			
CSF Ab42	N.A.	334.52 (95.46)	262.81 (106.82)
CSF Tau	N.A.	657.48 (208.18)	618.73 (319.41)
CSF pTau	N.A.	94.70 (23.37)	91.23 (42.82)
Amyloid PET (GCI)	1.22 (0.07)	2.64 (0.42) *	2.57 (0.51) *

Table 1 – Demographics, clinical and diagnostic biomarker measures for controls, MCI or mild AD (MCI/mildAD) and moderate/severe (demAD) patients. GCI=global cortical index. * Significant difference in comparison with controls; # Significant difference between AD groups.

1.2 Neuropsychological comparisons (Supplementary Table 2)

As expected, ANOVA showed significant differences between the three groups on the MMSE and all neuropsychological scores, following the expected pattern controls>MCI/mildAD>demAD.

1.3 Inter-group comparisons on imaging measures

All the analyses were conducted with age as a nuisance covariate and were FDR corrected.

*For **CT-Ss**,* the comparisons between MCI/mildAD or DemAD and controls are shown in Supplementary Table 3 and Figure 2. When contrasting AD subgroups, no significant results survived after FDR correction but uncorrected decreases were observed in the left precuneus and right rhinal sulcus (all p's<.01) in DemAD.

*For **SW**,* the comparisons between MCI/mildAD or DemAD and controls are shown in Supplementary Table 3 and Figure 3. When contrasting AD subgroups, no significant results survived after FDR correction but SW was higher in the left precuneus, collateral fissure, right occipito-temporal, central sulci and anterior lateral fissure in DemAD (all p's<.05).

*For **rVOIs*** (Supplementary Table 4)*,* MCI/mildAD showed lower cortical volume in the bilateral frontal, bilateral hippocampus, right precuneus, right parietal and right temporal regions (p<.05) in comparison to controls. DemAD showed lower cortical volume in the bilateral parietal (p<.0005), left middle cingulate, right anterior cingulate, right precuneus, right temporal and right occipital regions (p<.05) compared to controls. Results of the contrast between the AD groups are presented on Supplementary Table 5.

For **FCT**, the comparisons between MCI/mildAD or DemAD and controls are shown in Supplementary Table 6. Between the AD groups (Supplementary Table 7), DemAD showed lower FCT than MCI-AD in the following ROIs: bilateral superior, inferior (including supramarginal gyrus) and medial (precuneus) parietal, extending to the right isthmus of the cingulate cortex and the lateral occipital. DemAD also showed lower FCT than MCI/mildAD in lateral (left inferior, bilateral middle, left superior and right transverse), inferior (right fusiform) and medial (parahippocampal) temporal ROIs. Lower FCT in the left precentral and pars opercularis ROIs was also observed in DemAD.

*For **HV**,* MCI/mildAD and DemAD showed smaller left, right and mean HV (all p<.0001) compared to controls. No differences were observed between AD subgroups (p>.27).

1.4 Automated identification of the best imaging predictors (Table 2)

An automated binary logistic regression (stepwise) analysis was employed to identify the group of measures that was the best predictor of an AD diagnosis within each set of measures (CT-S, SW, rVOIs, FCT), independently from the patients' disease stages. This automated and whole-brain approach allowed an analysis independent from any *a priori* hypothesis.

*For **CT-S**,* the binary logistic regression identified a set of seven ROIs that was the best significant predictor of an AD diagnosis (90.8%; -2log-likehood=26.94; p<.000001); it included the left inferior temporal, left central, right superior temporal,

right polar temporal, right inferior temporal, right rhinal and right medial frontal sulci. This set of imaging variables provided a sensitivity of 94.2% (CI(95%): 87.7 – 100.6) and a specificity of 85.2% (CI: 71.8 – 98.6).

For SW, the set of regions that was the best significant predictor of an AD diagnosis (92.1%; -2log-likehood=24.89; p<.000001) was composed from eight regions including the left inferior temporal, internal frontal, anterior lateral frontal and the right rhinal, polar temporal, internal frontal, collateral and anterior lateral frontal sulci. This result was associated with a sensitivity of 94.1% (CI: 87.7 - 100.6) and a specificity of 88.9% (CI: 77.0 – 100.7). When both (CT-S and SW) types of measures were considered in a single model, the regression overfitted and failed to provide results.

For rVOIs, the identified group (82.1%; -2log-likehood=49.49 p<.000001) was composed of the left anterior cingulate and the right frontal, middle & posterior cingulate gyri, precuneus, parietal, temporal and posterior rVOIs. This provided a sensitivity of 90.2% (CI: 82.0 – 98.4) and a specificity of 66.7% (CI: 48.9 – 84.5).

For FCT, due to the large number of ROIs considered (n=68) and the relatively small sample size (n=80) the regression model overfitted and failed to provide any results. A different approach was then employed to ensure a comparison with FreeSurfer's data: we considered the regions in which the cortical thickness was decreased in AD (vs controls) based on the vortex-wise comparison made. During this analysis, 6 regions (namely the left inferior temporal, isthmus cingulate, superior frontal and the right supramarginal, inferior parietal and precuneus) were identified by FreeSurfer (Raw data presented on Supplementary Table 8; Results showed on Figure 2). These

regions were then included in the logistic regression model using enter method. This group reached an accuracy of 80.8% (-2log-likehood=61.98 p<.000001). This provided a sensitivity of 83.3% (CI:70.2 – 91.6) and a specificity of 75.0% (CI:52.9 – 89.3).

For HV, the regression reached 78.9% of accuracy (-2log-likehood=61.764 p<.00005), with a sensitivity of 86.0% (CI:73.3 – 94.2) and a specificity of 65.4% (CI:44,3 – 82.8).

To ensure the stability of these classifications analyses, we performed bootstrapping and obtained identical results for all sets of imaging variables considered. As shown in Table 2, despite high accuracy for all methods considered, AIC values indicate that sulcal measures are better predictors of AD.

Imaging measures	Accuracy to predict AD
Sulcal cortical thickness (CT-S)	90.8% (42.94)
Sulcal width (SW)	92.1% (42.89)
Regional cortical volumes (rVOIs)	82.1% (67.49)
FreeSurfer cortical thickness (FCT)	80.8% (75.98)
Hippocampal Volume (HV)	78.9% (65.76)

Table 2 – Prediction accuracy (in %) with Akaike's information criterion (AIC) value in bracket of the diagnosis of AD for sulcal morphometry (sulcal cortical thickness and width), regional cortical volume, FreeSurfer cortical thickness and hippocampal volume measures. Higher percentages and lower AICs indicate better prediction accuracy.

1.6 Correlations with amyloid load

There was no correlation between regional amyloid load or GCI (PiB binding) and any sulcal measure in both AD subgroups and AD group as a whole.

1.7 Neuropsychological correlates (in AD patients)

In order to explore the neuropsychological correlates of sulcal morphology we ran a PCA on all neuropsychological scores, then on all CT-S or SW measures separately in order to reduce the dimensions of the dataset. Four neuropsychological components were identified with labels deducted from the PCA structure: (1) verbal memory, (2) executive functioning, (3) instrumental and (4) orientation components (considering the eigenvalue on the scree plot). Reduction of data procedures were also performed for sulcal measures. More specifically, bilateral sulcal data of each lobe for each parameter (CT-S or SW) were considered separately and a PCA was conducted in setting the number of components to extract to 1. Therefore, we obtained frontal, temporal and parietal components (only a single occipital value was available and thus the PCA was not conducted for this lobe) for each type of parameter. Then, correlations (controlled for age) were sought between the neuropsychological and the CT-S or SW lobar components. These analyses revealed a significant correlation (corrected for multiple comparisons) between (a) the verbal memory and temporal sulcal components (R=.48; p<.0001 for CT-S and R=-.30; p<.05 for SW components); (b) the instrumental and parietal components (R=.39; p<.005 for CT-S

and R=-.51; p<.00005 for SW); (c) the executive and both frontal and parietal SW components (R=-.50; p<.0001; R=-.57; p<.000005 respectively).

An automated linear model was conducted to investigate the respective contribution of CT-S decrease and SW increase within all ROIs to the neuropsychological component's variance in patients. Results are detailed in table 3.

Neuropsychological component	Regions of CT-S decrease	Regions of SW increase	% of variance explained
Episodic memory	Left superior temporal, right occipito-temporal, left central sulci and bilateral rhinal sulci	Bilateral internal frontal, left superior temporal, right polar temporal and parieto-occipital sulci	64.4% (all sulcal predictors p<.01)
Executive functions	Left lateral parietal, left frontal subcallosal, left precentral and central, right rhinal and right orbitofrontal sulci	Left superior temporal and right orbito frontal sulci	70.0% (all sulcal predictors p<.01)
Instrumental functions	Right precentral, left central and left lateral parietal sulci	Superior temporal and polar temporal sulci	67.0% (all sulcal predictors p<.01)

Table 3 - Respective correlation between CT-S decrease and SW increase within all sulcal ROIs with the neuropsychological components' variance in AD.

Discussion

In this study, we investigated sulcal morphology in AD at MCI/mild dementia and moderate/severe dementia stages. We found lower CT-S and higher SW in temporal,

parietal and frontal regions in patients, the differences being more pronounced with the severity of the disease. When we compared the different MRI measures considered in this study, the best diagnostic accuracy to predict AD was obtained with sulcal SW. The more broadly used MRI measures such as HV, regional cortical volumes or FreeSurfer cortical thickness achieved lower prediction power. In addition, sulcal morphology was not correlated with amyloid load but was associated with specific cognitive deficits. These investigations were conducted in patients/controls with biological confirmation/exclusion of AD diagnosis to confirm/exclude the AD pathophysiological process. In addition, all images were acquired within a standardized protocol on a single MRI machine enabling increased image quality and homogeneity in comparison to multicentre studies (Cuingnet et al. 2011; Plant et al. 2010).

The few studies that have previously analysed sulcal morphology in AD were based on heterogeneous methods. Some analysed sulcal changes by averaging all sulcal measures in each lobar region, while others chose to consider only a limited number of sulci, selecting the largest ones from different lobes to increase their identification while reducing the inter-individual variability. These different studies brought significant evidence for the potential that sulcal measures have for improving the diagnosis of AD. By averaging the bilateral sulcal measures in 18 ROIs and centering our investigation on SW in early and late-onset AD, we previously observed that SW increase in temporo-parietal regions characterized early onset AD and was a better diagnostic maker than HV in this population (Hamelin et al. 2015).

In the present study, we chose to increase the spatial resolution by defining 18 ROIs in each brain hemisphere and to investigate both CT-S and SW in mild and

moderate/severe AD patients. The benefit of such higher spatial resolution approach was counterbalanced by the number of variables to consider statistically. Given the high number of measures that were included in the analyses, we chose to present some neuropsychological correlation results that were not corrected for multiple comparisons. Those were only presented as exploratory results and should be confirmed in an independent sample. In parallel, data reduction strategies such as PCA were adopted to decrease the number of variables (Ming et al. 2015).

Our results confirm that sulcal modifications appear at an early stage during the course of AD and are not circumscribed to limbic structures despite the absence of language, visuospatial or praxis impairment, as if sulcal changes in some regions precede cognitive deficits, and then increase as the disease progresses. In this framework, the precuneus and retrosplenial cortex, in which we found a significant difference between mild and more severe patients for both SW and CT-S measures, could play a critical role as a marker of disease severity, in accordance with previous work showing that the atrophy of the precuneus was associated with a faster clinical progression of AD (Kinkinghéhum et al. 2008).

In order to determine the group of sulcal ROIs that could predict the more accurate classification of participants into the AD or control groups, thus reflecting the diagnosis accuracy, we used classification algorithms that led to the automatic identification of a specific set of frontal and temporal regions for CT-S and SW measures, independently from any a priori hypothesis. With the aim of determining which imaging method provided the best accuracy to predict AD, we compared the accuracy attained with sulcal measurements with the one attainted with more broadly-used approaches such as regional cortical volumes, FreeSurfer cortical thickness and

HV. As we were not able to rule out some relative collinearity among our variables during these regression procedures, we completed these analyses by the computation of sensitivity and specificity rates. CT-S and SW provided the best accuracy to identify AD patients as compared with classical methods. The cortical thickness measures provided by FreeSurfer remained less powerful to identify AD, although we had to employ an alternative method to provide results with this particular data set as the model overfitted due to the large number of values considered. While a similar approach was adopted in past studies to identify AD-signature cortical thickness (e.g. Dickerson et al. 2009), therefore providing an interesting trans-methodological comparison, this specific analysis cannot be considered as purely data-driven and the superiority of sulcal morphological parameters over FreeSurfer cortical thickness should be confirmed in larger populations in a full data-driven study.

We hypothesized that our investigations could have been limited by a possible direct effect of amyloid deposits in the sulci, leading to artificially increased CT-S or decreased SW because of increased amyloid load. This hypothesis would have implied a positive correlation between CT-S and amyloid deposition and a negative correlation between SW and amyloid deposition. However, no significant correlation was found between sulcal measures and total or regional cortical PiB binding, suggesting that amyloid plaques density does not exert a mechanical effect on sulcal morphology.

Finally, the correlations between sulcal morphology and specific cognitive domains were explored. Given the large number of cognitive and sulcal variables, these analyses involved a data reduction through PCA. Results showed significant

correlations between verbal memory and temporal sulcal components (with both CT-S and SW), instrumental (denomination and gestural praxis) and parietal (CT-S and SW) components and executive and both parietal and frontal SW components. These analyses were confirmed by automated linear models showing that different sulcal modifications significantly predicted the variance of neuropsychological components. In sum, specific cognitive impairments were associated with regional CT-S decrease and SW increase in key regions involved in memory (temporal cortex), instrumental (parietal cortex) and executive (fronto-parietal cortex) processing. These exploratory analyses, relying sometimes on uncorrected results that could limit their generalizability, highlight the clinical interest of sulcal measures. Although these results would need further confirmation through studies that should be specifically designed to assess these relationships with cognitive performance (and thus would require more participants), this is the first time that sulcal morphology modifications are related to cognitive decline. This is of particular importance as markers of neuronal injury have the potential to provide pathologic staging information. In the context of the ATN classification system proposed by the NIA-AA research framework, sulcal morphology measures could provide relevant prediction of future cognitive decline when considered with amyloid and tau biomarkers (Jack et al. 2018). In this perspective, future studies should also assess the ability of sulcal morphology measures to discriminate Aβ+ from Aβ- patients.

Taken together, these results highlight the usefulness of sulcal morphology analyses in AD. They show that sulcal morphology is an efficient imaging marker of AD diagnosis, and related to its cognitive deficits. In addition, the comparisons with controls revealing that sulcal morphology modifications being more severe and more

broadly distributed in the brain in later stages of AD suggest that sulcal measures could be sensitive to the severity of the disease. Sulcal morphology could provide a new surrogate marker to evaluate the efficacy of future disease modifying strategies. As comprehensive and almost fully automatically extracted dataset of an individual's brain anatomy, sulcal measures also have relevance for precision medicine and should be considered as new data to be implemented in the clinical projects of big-scale initiative such as Human Brain Project or BRAIN Initiative.

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Contribution of each author to the study

MB, LH, OC, MS: design of the study. MB, LH, FC, MC: acquisition of experimental data. JL, LH, MB, MS: acquisition of clinical data. MB, FC: statistical analysis; MB, JL, MB, OC, MS: interpretation of results. MB, JL, MS: manuscript writing. all: manuscript editing.

Figure legends

Figure 1: Representation of the main sulci analysed, pooled into the 18 regions of interest defined (lateral, medial and inferior views of the right hemisphere).

Figure 2: CT-S reduction (in mm) in MCI/mildAD and DemAD patients compared with controls in each of the 18 ROIs of each hemisphere. Grey stars above MCI/mildAD bars represent significant differences (p<0.05 FDR corrected) between MCI/mildAD patients and controls, black stars above DemAD bars represent significant differences (p<0.05 FDR corrected) between DemAD patients and controls, and red circles represent significant but uncorrected differences (p<0.05) between MCI/mildAD and DemAD patients.

Figure 3: SW increase (in mm) in MCI/mildAD and DemAD patients compared with controls in each of the 18 ROIs of each hemisphere. Grey stars above MCI/mildAD bars represent significant differences (p<0.05 FDR corrected) between MCI/mildAD patients and controls, black stars above DemAD bars represent significant differences (p<0.05 FDR corrected) between DemAD patients and controls, and red circles represent significant but uncorrected differences (p<0.05) between MCI/mildAD and DemAD patients.