

Disruption of gray matter microstructure in Alzheimer's disease continuum using fiber orientation

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Abstract

There have been several MR imaging biomarkers of Alzheimer's disease (AD) for early diagnosis. Cortical mean diffusivity (MD) is one of them for the study of the cortical microstructural change in AD. However, the feasibility of MD often remain in doubt as partial volume effects may overestimate the results. This study aims to investigate feasible gray matter microstructural biomarker with higher sensitivity for early AD detection. We propose diffusion tensor imaging (DTI) measure, 'radiality', for early AD biomarker. It is a dot product between cortical surface normal vector and primary diffusion direction, which reflects the fiber orientation within the cortical column. Here, we gathered neuroimages from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database; 78 cognitive normal, 50 early mild cognitive impairment (EMCI), 34 late mild cognitive impairment (LMCI), and 39 AD patients. Then, we evaluated cortical thickness (CTh), MD, amount of amyloid and tau accumulations using positron emission tomography (PET), which are conventional AD biomarkers. Radiality was projected on gray matter surface to compare and validate the changes along other neuroimage biomarkers. Results showed decreased radiality primarily in entorhinal, insula, frontal and temporal cortex as disease progress onward. Especially, radiality could delineate the difference between cognitive normal and EMCI group while other biomarkers could not. We looked into the relationship between the radiality and other biomarkers to validate its pathological evidence in AD. Overall, radiality showed high association with conventional biomarkers. Additional ROI analysis exhibits dynamics of AD related changes as stages onward. In conclusion, radiality in cortical gray matter showed AD specific changes and relevance with other conventional AD biomarkers with higher sensitivity. Besides, it could show group differences in early AD changes from EMCI which show advantage for early diagnosis than using conventional biomarkers. We provide the evidence of structure changes with cognitive impairment and suggest radiality as a sensitive biomarker for early AD.

1. Background

Alzheimer's disease (AD) is notorious for its long preclinical period where various pathophysiological changes occur before the main symptom. As progress of AD is not completely understood, early diagnosis and intervention remain hopeless [1, 2]. Repetitive failures of recent drug trials attribute to applying treatment to patients at the progressed stage [3-5]. Thus, identification of people at the earlier stage is critical in clinical trials and may be promising for controlling this devastating disease.

At present, there are several biomarkers to diagnose and monitor disease progression; amyloid and tau deposit through positron emission tomography (PET) imaging or from cerebrospinal fluid (CSF), volumetric and morphology analysis using T1 weighted magnetic resonance (MR) imaging and clinical assessments. Although the results from PET and CSF screening are promising, these interventions are more invasive than MR imaging. In the urge of finding suitable MR biomarkers, researchers have focused on characterizing early mild cognitive impairment (EMCI) and late mild cognitive impairment (LMCI) [6-7]. Although the criteria to separate EMCI and LMCI was based on the memory score, biomarkers from EMCI showed continuous spectrum to LMCI implying that EMCI as a transitional stage of AD [8]. Thus, evaluating the sequential changes of EMCI and LMCI should help understanding the early AD.

Diffusion tensor imaging (DTI) utilizes the diffusion of water molecules within tissues and provides axonal microstructural properties, thus widely applied for studying white matter integrity [9, 10]. Early AD studies using DTI have studied mainly on the white matter. However, since white-matter changes in AD may be the results of Wallerian degeneration, followed by the neurodegeneration in gray matter [11, 12], the destruction of white matter is a less sensitive change in AD.

The idea of measuring microstructural changes in gray matter using DTI has been demonstrated in both AD and frontotemporal dementia [13-15]. These studies showed that gray matter mean diffusivity (MD) is increased in patients compared with healthy control and MD could be a promising imaging biomarker. However, there is lasting notion that increased MD could be overestimated by CSF signal and this effect persisted even with rigorous correction such as partial volume effects correction [16].

To overcome this problem, we adopted radiality, which is presumably reflecting the integrity of tangential cortical fibers. This parameter has been applied to study neurodevelopment and could distinguish stages of aging [17-19]. Moreover, cortical microstructural changes are often observed with aging or neurodegeneration, which can be viewed as opposite of neurodevelopment [20-22]. Thus, changes of fiber orientation may suggest cortical alterations and could be used as a biomarker in the neurodegenerative diseases.

In this study, we hypothesized that the radiality within gray matter could be a microstructural measure of cortex and used as the early signature of AD. We performed a cross-sectional surface-based cortical analysis approach using DTI, amyloid PET, and Tau PET images to AD continuum. We evaluated whether gray matter radiality shows: i) early mesoscopic AD-related pathological change, and ii) compliment to conventional AD biomarkers while providing a distinct information regarding AD-related pathologies.

2. Methods

2.1 Demographics

Data used in this study were obtained from Alzheimer's Disease Neuroimaging Initiative (ADNI) (adni.loni.usc.edu). Among ADNI database, we analyzed the subjects who took both MRI and PET (amyloid, AV 45 and tau, AV 1451); 78 cognitive normal (CN), 50 EMCI, 34 LMCI, and 39 AD. Subjects were sampled with following criteria; age around 60 to 90-year-old, education year 12 to 20, and gender match within group. To assess AD continuum, amyloid negative CN and amyloid positive EMCI, LMCI, and AD subjects were selected. A total of 201 subjects' T1 and DTI images were gathered from ADNI. To increase sample size, multi-center approach was used as discussed in [13]. The amyloid positivity of the subjects was determined by whole brain PET AV45 standardized uptake value ratio (SUVR) with 1.11 cut-off. **Table 1.** shows the demographics of the subjects used in this study; note that subjects who underwent AV1451 tau PET imaging were 44 in CN, 9 in EMCI, 5 in LMCI, and 3 in AD. Additional 28 CN subjects who showed amyloid positive were gathered to identify earliest AD pathological changes as presented in **Supp. Table 1.**

2.2 Image processing

T1 weighted images were processed with Freesurfer package v6.0 (<http://surfer.nmr.mgh.harvard.edu>) as previously reported in [13]. Cortical thickness (CTh) maps were registered to Freesurfer average sphere through spherical registration for group comparison. DTI and PET images were registered with their respect to T1 images using boundary-based algorithm for further process. DTI images were processed using FSL package as followed: eddy current correction, rotate gradient vectors from the results of eddy correction, and tensor fitting to produce mean diffusivity map and primary eigenvector map. DTI metrics were further processed to avoid partial volume effect using Koo et al [24]. PET images were partial volume corrected using `mri_gtmpvc` which is built in Freesurfer package. PET images were normalized by mean signal from whole cerebellum and converted to SUVR for amyloid and tau PET, AV45 and AV1451 respectively. Then images were boundary-based registered to corresponding T1 structural images. To avoid any partial volume effects, the center parts of the cortical column were sampled for surface analysis. Lastly, CTh was smoothed with 10 mm while other modalities were smoothed with 15 mm full width half maximum Gaussian kernel. **Fig. 1** shows the overall scheme of the process.

2.3 Calculation of radially

A surface normal vector was obtained from individual gray matter surface to define cortical orientation. Vertex-wise dot product between primary diffusion direction, primary eigenvector of diffusion tensor, and the surface normal vector was quantified as a radially index; r . where v represents surface normal vector and e_1 represents primary diffusion direction [20]. (see Equation in the Supplementary Files)

It ranges from 0 to 1, where $r = 0$ indicates tangential diffusion and $r = 1$ indicates radial diffusion to cortex. Subject's principal eigenvector map was projected onto the individual surface reconstruction to calculate vertex-wise radially as discussed in [20].

2.4 Statistical analysis

We first compared the differences between groups for radially, CTh, MD, AV45 and AV1451 with a general linear model, which is available in Freesurfer. The results were cluster-wise corrected for family-wise error (FWE) corrected p -value < 0.05

To test the associations between radially and other neuroimage biomarkers, we calculated set of vertex-wise partial correlations with the radially as the dependent variable and CTh, MD, AV45, and AV1451 as the independent variable. Age, gender, year of education, and MRI center were set as covariates of cluster analyses. Permutation test was applied to resolve multiple comparisons problem through a Monte Carlo simulation with 10,000 repeats, which is built-in function of Freesurfer.

To test the linear relationship between radially and other neuroimage biomarkers, we quantified mean metrics within AD specific ROIs. ROIs include entorhinal, fusiform, insula, inferior, middle, and superior

temporal cortex. Mean metrics within ROIs were plotted in a box and whisker plots and presented in **Fig. 4(e)** and **Fig. 5**. Significance between groups was tested with one-way ANOVA.

3. Results

3.1 Group comparison along AD continuum

We first compared radially, CTh, and MD differences between groups; CN vs EMCI, CN vs LMCI, CN vs AD as respectively. The results were cluster-wise corrected for FWE corrected p -value < 0.05 . **Fig. 2** shows significant group different clusters range from p -value 0.05 to 10^{-5} . Only radially could delineate the difference from EMCI to CN. Compared to CN, all groups showed decreased radially, decreased CTh, and increased MD. There was no group difference of radially between EMCI and LMCI.

3.2 Partial correlation between radially and other image biomarkers

We then found vertex-wise correlation between radially and other image biomarkers as shown in **Fig. 3**. CTh showed mostly positive correlations that decrease in cortical thickness accompanied with decrease in radially. MD showed mostly negative correlation that increase in MD accompanied with decrease in radially. Amyloid and tau levels showed negative correlation with radially.

3.3 Correlations between radially and other image biomarkers

In order to find progressive changes in radially as disease progression, AD specific ROIs mask was used to calculate mean biomarker data. Each subject's mean data were scatter plotted and used to calculate Pearson correlation as shown in **Fig. 4**. CTh showed $R = 0.641$, MD showed $R = -0.677$, AV45 showed $R = -0.490$, and AV1451 showed $R = -0.412$ with radially.

3.4 Radially dynamics from AD specific ROIs

To find generative changes in radially as disease progresses, mean radially in AD ROIs was calculated for direct comparison among groups. Radially within AD specific ROIs were plotted in a box and whisker plot as shown in **Fig. 5**. The results showed decreasing radially with disease progression. Significance was tested with one-way ANOVA with p -value < 0.05 , 0.01 , 0.001 . Insula, middle and superior temporal cortex showed most radially reduction with disease onward.

3.5 Cut-off analysis using Radially

To further test feasibility of radially as AD biomarker, we performed cut-off analysis to distinguish CN with other AD stages as shown in **Supp. Table 2**. We sought to find the cost-effective point where it minimizes the difference between sensitivity and specificity. With varying cut-off, we could quantify ROC curve and calculated AUC. Classification of CN vs EMCI showed 70.5% accuracy with 70.2% sensitivity, 72.7% specificity, and 0.766 AUC. Subsequent analysis to distinguish between CN and LMCI, MCI group (EMCI+LMCI), AD, and patient group (EMCI+LMCI+AD) also showed similar results.

4. Discussion

In this study, we tried to investigate the early features of EMCI using cortical radiality, which reflects mesoscopic structural changes. By leveraging the radiality in the gray matter, we could detect the changes in EMCI which were not detected by conventional MRI biomarkers. We found progressively larger regions of decreased radiality as disease progresses, starting from medial temporal cortex in EMCI to whole brain in AD. While, CTh or MD did not show significant differences between CN and EMCI.

We investigated the relationship of radiality with other image measures. Association between radiality and CTh showed strong positive correlation on widespread regions of the brain as shown in **Fig. 3**. It is clear that higher CTh indicate deeper cortical structure and fiber orientation tend to have radial orientation. Cortical depth profile analysis showed that thicker the cortical thickness larger the radiality [25]. In addition, MD showed strong negative correlation on mostly temporal, parietal, and frontal cortices. Radiality may sensitive to CTh but reflecting microstructural feature as well. With AV45 and AV1451, radiality showed association that widely overlapped with both CTh and MD. Thus, radiality may also reflect changes due to accumulation of pathologic protein accumulation within the cortex.

Although microstructural changes associated with radiality is unclear, one plausible feature is the disorganization of tangential cortical fibers. It has been reported that the tangential cortical fibers develop at the stages of neurodevelopment and aging [20]. There are several events that lead to increase in tangentially oriented fibers including dendritic elaboration [26], formation of local circuits [27], expansion of thalamo-cortical fibers [28] and disappearance of radial glia [29, 30]. Decrease in radiality may indicate contrary to those of neurodevelopment. For instance, synaptic loss, neuronal soma changes and neurite disorganization occurs along with the neuronal loss may lead to decrease in radiality. These changes may concurrent with net loss of macromolecule that affect diffusivity, increasing free water in extracellular space. However, radiality provide evidence of neuronal density that explain concurrent cortical atrophy. Furthermore, accumulation of amyloid or tau proteins may also participate in the disruption of microstructure. Given radiality can delineate the EMCI, we can further speculate that these microstructural changes occur in the earlier stage of AD which are not apparent in macroscopic investigation.

To test the sensitivity of radiality, we sought to find earliest stage of AD. Interestingly, our CN vs EMCI cluster analysis did not show biphasic trajectory as discussed in previous work [31]. Thus, we conducted additional analysis on amyloid negative CN and amyloid positive CN (**Supp Fig. 1**). We could observe biphasic behavior of CTh and MD where biomarkers showed opposite direction of changes. While CTh showed increased and MD decreased, radiality showed monotonous decrease in amyloid positive CN. This distinct behavior of radiality could characterize the changes in EMCI while CTh and MD could not. Both the CTh increase and MD decrease in early stage of AD was thought to be caused by an amyloid-induced inflammatory response [13]. However, radiality seems to decrease whenever there are microstructural changes in the tissue. From preterm study, occipital cortex showed decrease in radiality as in early development [17-19]. In the case of multiple sclerosis, decreased radiality was observed in

dorsolateral prefrontal cortex, Heschl's gyrus, and primary visual cortex possibly due to cortical alterations [32].

There were several limitations of the current study. First, relatively poor resolution of DTI images compared to structural T1 could lead to inaccurate results. Although surface analysis was employed to mitigate registration or segregation error, higher resolution of DTI would be needed to observe precise cortical changes. Second, use of multi-protocol DTI images could influence the observation of progressive changes in MCI. We sought to control age, gender, year of education, and MRI center variance among the group while applying harmonization to minimize the variation between subjects [33]. Third, number of subjects who took tau PET imaging were not enough to show the relationship with tau pathology. In order to focus on progressive changes, not only showing relationship with amyloid but also with tau is an important aspect [34]. However, several subjects in this study underwent screening only once without follow up or only MRI data were available.

5. Conclusions

In conclusion, we investigated the cortical changes in EMCI using structural MRI and DTI as well as PET imaging markers. Only radiality could delineate the changes in EMCI while cortical thickness and MD could not. In addition, radiality changes in frontal cortex as simultaneously with amyloid deposit in continuum. These results indicate that multimodal approach, atrophy and microstructure, may illuminate early changes in AD. However, further study is needed to support the relationship between cortical structure alterations and diffusion orientation changes.

List Of Abbreviations

AD Alzheimer's disease

MD Mean diffusivity

ADNI Alzheimer's Disease Neuroimaging Initiative

EMCI Early mild cognitive impairment

LMCI Late mild cognitive impairment

CTh Cortical thickness

PET Positron emission tomography

CSF Cerebrospinal fluid

MR Magnetic resonance

DTI Diffusion tensor imaging

CN Cognitive normal

GCDR Global clinical dementia ratings

MMSE Mini Mental State Examination

MADAS-Cog Modified Alzheimer's disease Assessment Scale cognitive subscale

SUVR Standardized uptake value ratio

ROI Region of interest

Declarations

Ethical approval and consent to participate

The study procedures were approved by the institutional review boards of all participating centers (https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf), and written informed consent was obtained from all participants or their authorized representatives. Ethics approval was obtained from the institutional review boards of each institution involved: Oregon Health and Science University; University of Southern California; University of California—San Diego; University of Michigan; Mayo Clinic, Rochester; Baylor College of Medicine; Columbia University Medical Center; Washington University, St. Louis; University of Alabama at Birmingham; Mount Sinai School of Medicine; Rush University Medical Center; Wien Center; Johns Hopkins University; New York University; Duke University Medical Center; University of Pennsylvania; University of Kentucky; University of Pittsburgh; University of Rochester Medical Center; University of California, Irvine; University of Texas Southwestern Medical School; Emory University; University of Kansas, Medical Center; University of California, Los Angeles; Mayo Clinic, Jacksonville; Indiana University; Yale University School of Medicine; McGill University, Montreal-Jewish General Hospital; Sunnybrook Health Sciences, Ontario; U.B.C.Clinic for AD & Related Disorders; Cognitive Neurology—St. Joseph's, Ontario; Cleveland Clinic Lou Ruvo Center for Brain Health; Northwestern University; Premiere Research Inst (Palm Beach Neurology); Georgetown University Medical Center; Brigham and Women's Hospital; Stanford University; Banner Sun Health Research Institute; Boston University; Howard University; Case Western Reserve University; University of California, Davis—Sacramento; Neurological Care of CNY; Parkwood Hospital; University of Wisconsin; University of California, Irvine—BIC; Banner Alzheimer's Institute; Dent Neurologic Institute; Ohio State University; Albany Medical College; Hartford Hospital, Olin Neuropsychiatry Research Center; Dartmouth-Hitchcock Medical Center; Wake Forest University Health Sciences; Rhode Island Hospital; Butler Hospital; UC San Francisco; Medical University South Carolina; St. Joseph's Health Care Nathan Kline Institute; University of Iowa College of Medicine; Cornell University; and University of South Florida: USF Health Byrd Alzheimer's Institute. Upon accessing the database, we have received administrative approval for access to the ADNI database.

Consent for publication

Not applicable

Availability of data and materials

The MRI and PET data were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu/>). Application for access to the ADNI data can be submitted by anyone at <http://adni.loni.usc.edu/data-samples/access-data/>. The process includes completion of an online application form and acceptance of Data Use Agreement.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PL, YJ, and HK contributed to the study conception and design. Material preparation, data collection and analysis were performed by PL. The first draft of the manuscript was written by PL. YJ and HK commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.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.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Table 1

Table 1. Demographics

	CN (n=78)	EMCI (n=50)	LMCI (n=34)	AD (n=39)	Post hoc
Female, n (%)	42 (53.8)	19 (37.2)	15 (44.1)	17 (43.6)	--
Age (SD) (y)	72.7±5.9	74.7±5.3	73.9±5.6	74.7±7.17	--
Education (SD) (y)	16.7±2.5	15.2±2.6	16.1±2.8	15.4±2.9	--
GCDR (SD)	0.0	0.5	0.5	0.8±0.3	CN<EMCI=LMCI<AD
MMSE (SD)	29.3±1.5	28.2±1.2	27.6±1.4	24.4±4.0	CN>EMCI=LMCI>AD
MADAS-Cog (SD)	9.7±6.8	13.6±5.9	14.6±4.8	26.3±14.2	CN<EMCI=LMCI<AD
Logical memory I: Immediate recall (SD)	14.2±2.9	10.4±3.4	6.4±3.3	3.8±2.0	CN>EMCI>LMCI>AD
Logical memory II: Delayed recall (SD)	12.8±3.4	8.6±2.0	3.1±2.7	1.3±1.6	CN>EMCI>LMCI>AD
MRI center	30/48	41/10	28/6	36/3	
Florbetapir+, n (%)	0 (0)	50 (100)	34 (100)	39 (100)	--
Subjects with AV1451 image, n (%)	44 (68.8)	9 (14.1)	5 (7.8)	3 (4.7)	--

Data are n (%) or mean±SD values. There were no gender, age, or year of education intergroup differences. GCDR, MMSE, and MADAS-Cog scores in EMCI and LMCI did not show significant differences. Analysis of variance with Tukey test was used for post hoc analysis with p -value < 0.05. For MRI data, two major scanners were used: GE and SIMENS and delineated as MRI center GE/SIMENS.

AD: Alzheimer's disease, CN: cognitive normal, EMCI: early mild cognitive impairment, GCDR: global Clinical Dementia Rating, LMCI: late mild cognitive impairment, MADAS-Cog: Modified Alzheimer's Disease Assessment Scale-Cognitive subscale, MMSE: Mini Mental State Examination.

Supplementary Table 1

Supplementary Table 1. Results of cut-off analysis

	N	Accuracy	Sensitivity	Specificity	AUC
CN vs EMCI	78 vs 50	70.5%	70.2%	72.7%	0.766
CN vs LMCI	78 vs 34	67.9%	70.6%	66.7%	0.757
CN vs (EMCI+LMCI)	78 vs 84	70.5%	69.4%	66.7%	0.766
CN vs AD	78 vs 39	78.6%	79.5%	78.1%	0.867
CN vs (EMCI+LMCI+AD)	78 vs 123	72.8%	72.3%	73.1%	0.798

Supplementary Figure Legend

Supplementary Figure 1. Comparison of amyloid negative CN and amyloid positive CN

Group difference in radially, cortical thickness and mean diffusivity from cognitive normal amyloid negative and positive. Radially showed decrease in postcentral, CTh showed increase in insula, and MD

showed decrease in postcentral cortex. Color bar indicates p -value interval of 0.05 to 10^{-5}

Figures

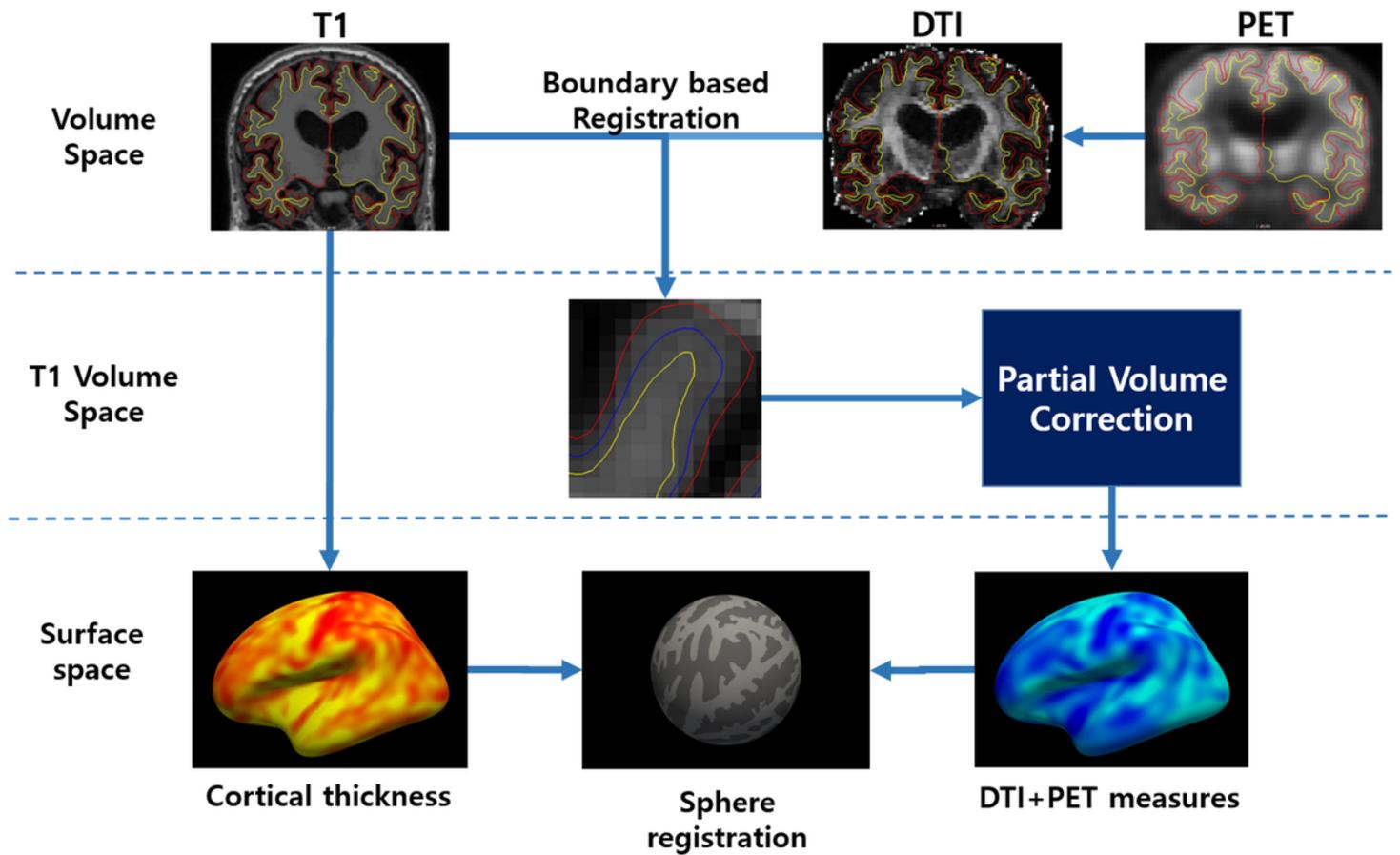


Figure 1

Overall scheme for surface projection analysis. DTI and PET images were boundary-based registered to T1 image and projected to fsaverage surface for group comparison.

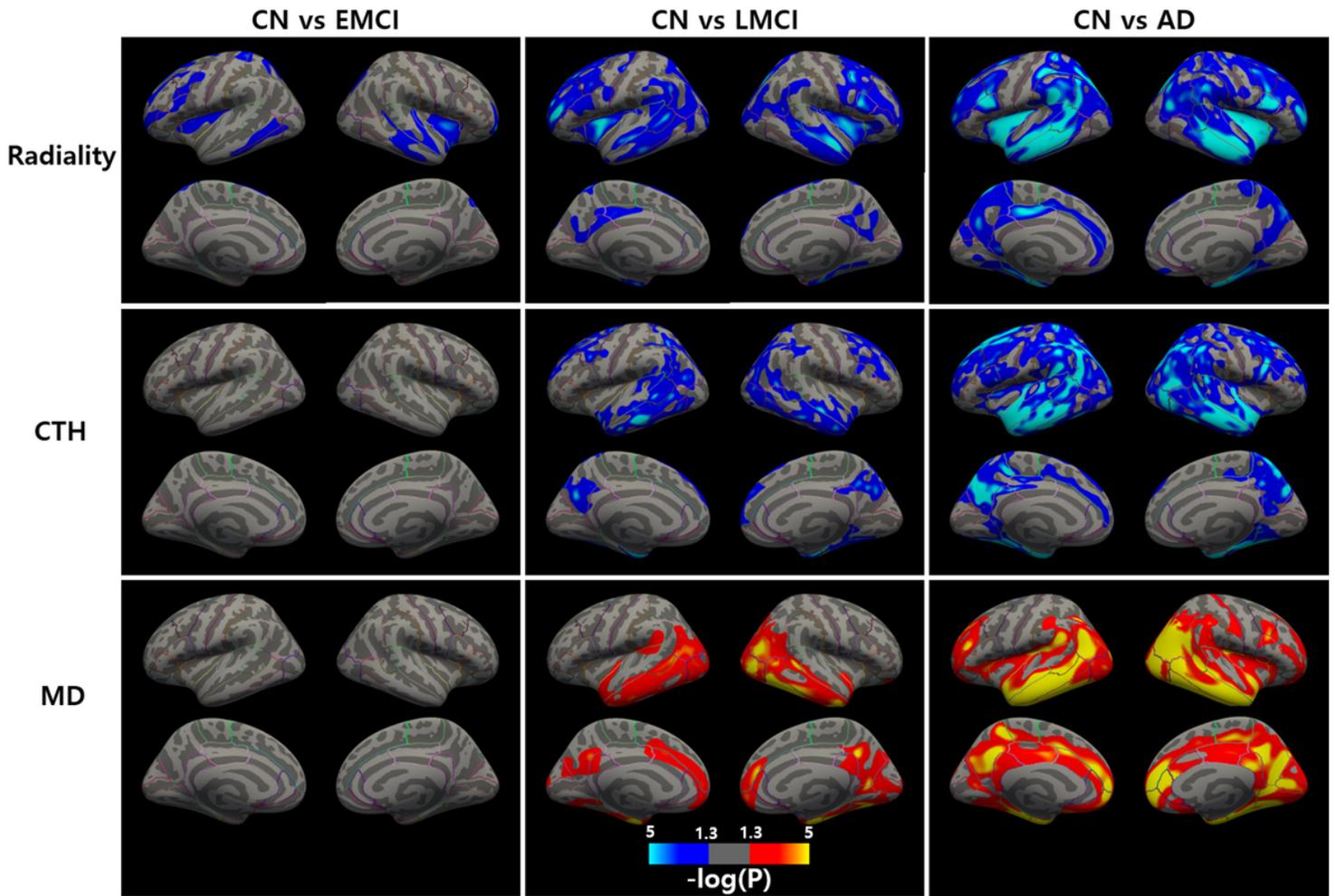


Figure 2

Group differences in radiality, cortical thickness, and mean diffusivity From left to right: CN vs EMCI, CN vs LMCI, and CN vs AD. Blue cluster shows decrease in metrics and red cluster shows increase in metrics. All the cluster were multiple corrected for p-value <0.05. Heat map indicate p-value interval of 0.05 to 10^{-5}

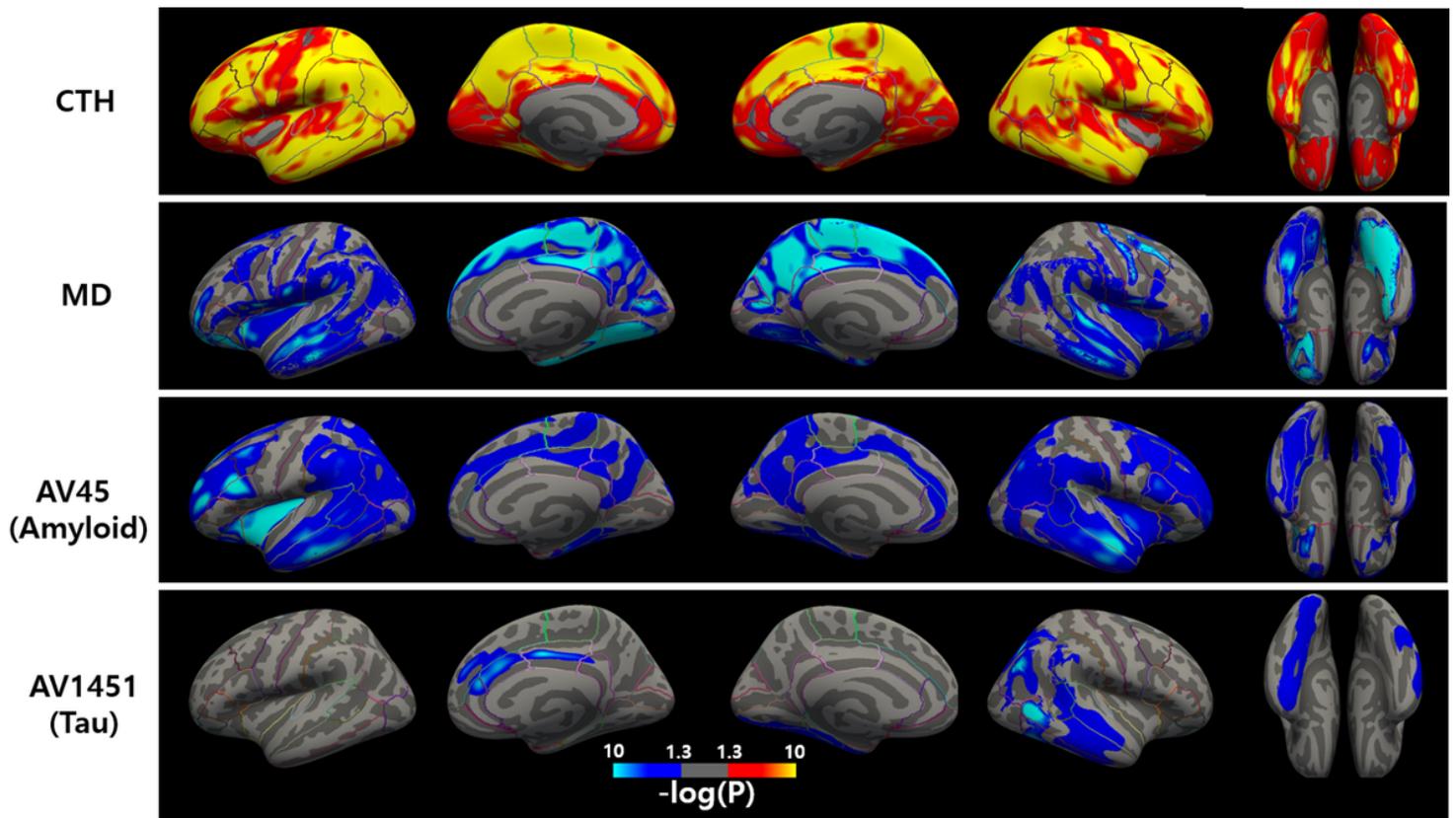


Fig 3. Partial correlation with Radiality

Figure 3

Partial correlation between image biomarkers and radiality. Red cluster shows positive correlation with radiality and blue cluster shows negative correlation. Cortical thickness showed positive correlations, mean diffusivity, AV45, and AV1451 showed negative correlations. Heat map indicate p-value interval of 0.05 to 10-10

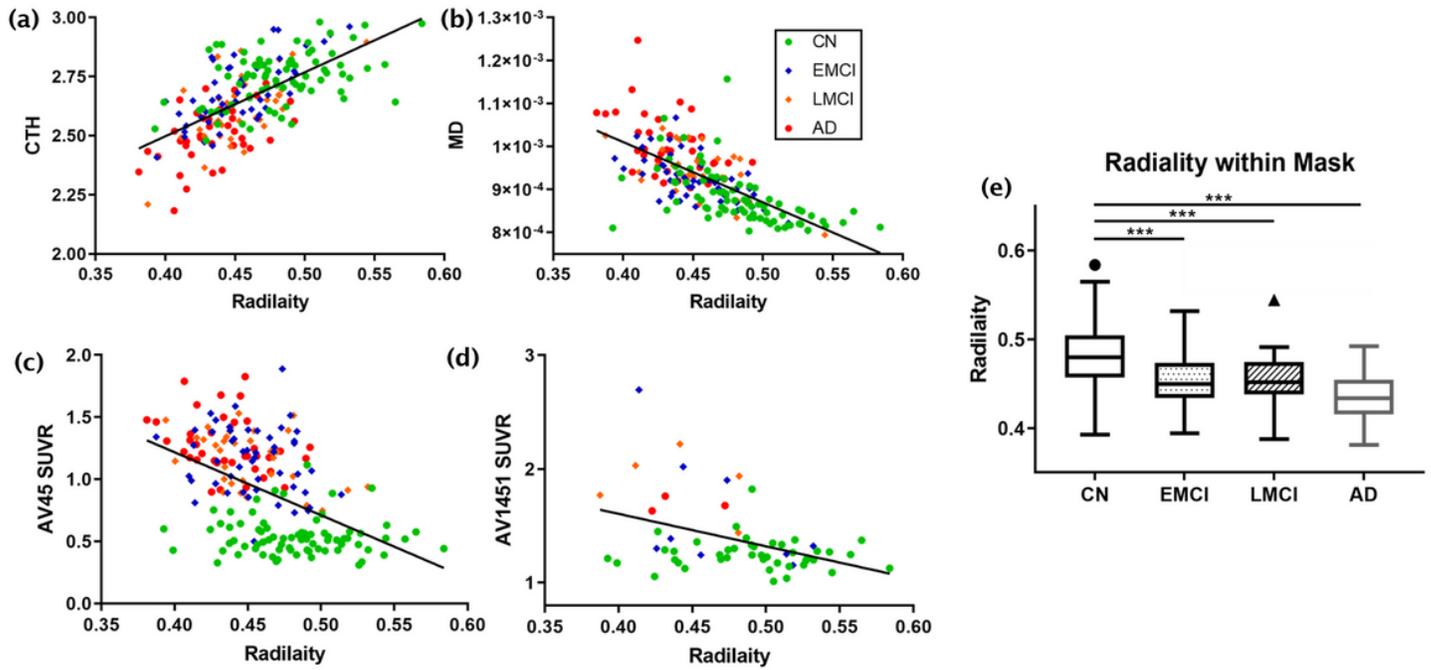


Figure 4

Correlation between radiality with other biomarkers (a) ~ (d) Scatter plot between image biomarkers and radiality. Radiality showed high association with conventional biomarker, indicating that it reflects neuropathology of AD (a) CTh, (b) MD, (c) AV45, (d) AV1451 respectively. (e) Box plot of group radiality comparison within AD specific ROI. Radiality from CN showed significant differences with EMCI, LMCI, and AD with p-value <0.001. There were no differences between EMCI and LMCI.

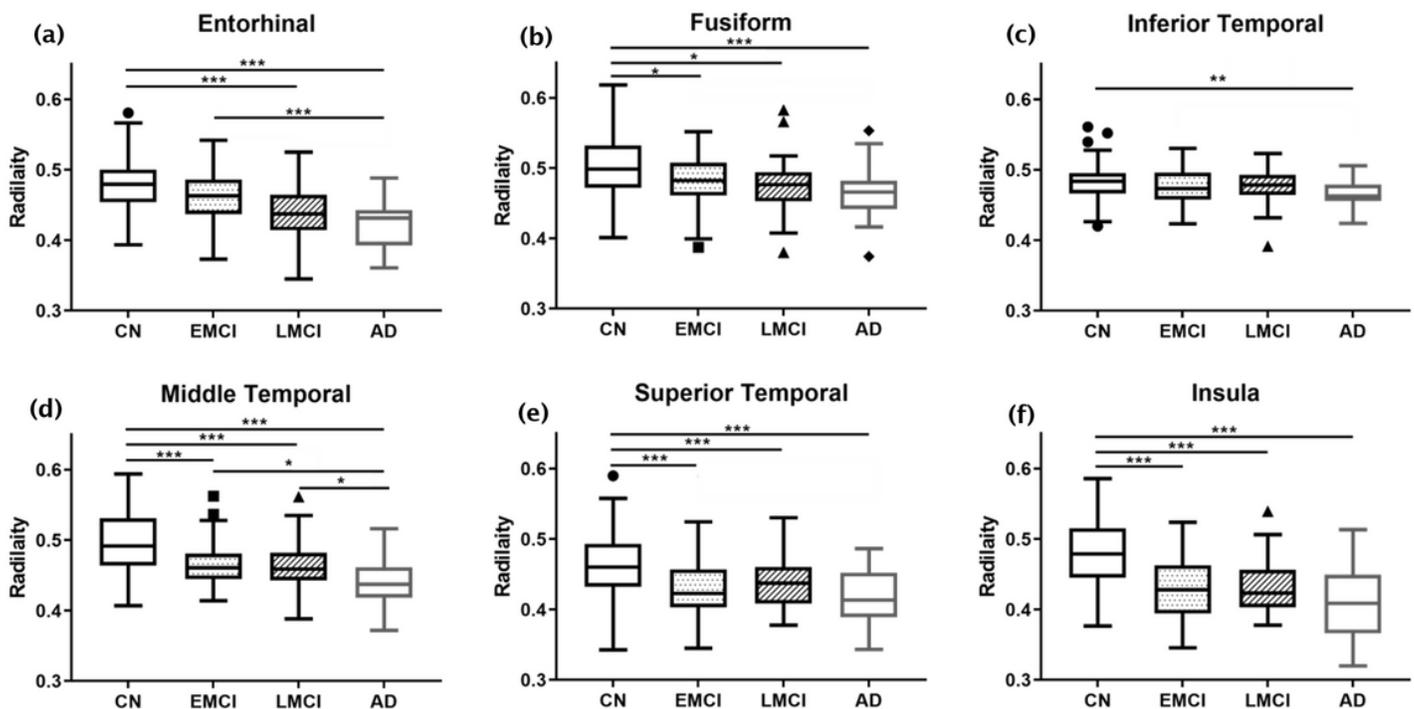


Figure 5

Box plot of group radiality comparison within AD specific ROI. (a) Entorhinal, (b) fusiform, (c) inferior temporal, (d) middle temporal, (e) superior temporal, (f) insula cortex. Significance was tested using one-way ANOVA with * p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001.

Supplementary Files

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- [Supplementarymaterials.pdf](#)