Predicting conversion from Mild Cognitive Impairment to Alzheimer's disease using cortical diffusivity analysis

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Background: Alzheimer's Disease (AD) is characterized pathologically by important neural architecture changes. Diffusion Tensor Imaging (DTI) has provided promising results for the investigation of microstructural changes of white matter, but its use in cortical grey matter is still limited. In the present study, we investigated the performance of our novel cortical diffusivity measurements [McKavanagh et al. 2019] for classifying patients with AD, healthy elderly subjects (HS), patients with mild cognitive impairment (MCI) who progress to probable-AD (MCI-converter, MCI-C), and those with MCI who do not progress to probable-AD (MCI-stable, MCI-S). The aim here was to test the classification power of our novel cortical diffusion measurements and to test their correspondence with the standard hallmarks of AD pathology measured in CSF (total-tau, phosphorylated-tau and amyloid beta).

Method: DTI and T1 structural scans and CSF data of 454 subjects (respectively 310 HS, 48 MCI-S, 45 MCI-C and 51 AD) from the National-Alzheimer's-Coordinating-Center (NACC) were used (Table 1).

Table 1 – Cohort description

	Age (years)	Gender (F/M)	Apoe4 (Yes/No)	MMSE Score	Cortical Grey Matter fraction	Hippocampal fraction
HS (n=310)	66.08 ±6.81	209/101	131/179	29.26 ±0.92	0.310 ±0.018	0.0053 ± 0.0005
MCI-S (n=48)	68.37 ±6.72#	22/26*	17/31#	27.97 ±1.78 *#	0.299 ±0.017*#	0.0049 ± 0.0006 *#
MCI-C (n=45)	71.46 ±6.53*°	12/33*	24/21	26.54 ±2.18*#°	0.281 ±0.017 *°	0.0043 ± 0.0007 *°
AD (n=51)	73.71 ±9.60*	25/26*	34/17*	20.97 ±3.89*	0.273 ±0.021°	0.0042 ± 0.0006 °

*= significantly different compared to HS; #= significantly different compared to AD; ° *= significantly different compared to MCI-S

Three novel whole brain cortical diffusivity measures (AngleR, PerpPD, and ParlPD) [McKavanagh et al. 2019], (Figure 1) and three standard measures (mean diffusivity [MD], cortical grey matter volume fraction and bilateral hippocampal volume fraction) were calculated for each subject. Receiver Operating Characteristics (ROC) curve analysis and the Area Under the Curve (AUC) were used to assess the group discrimination capability of our method.

Figure 1- Cortical diffusivity mask

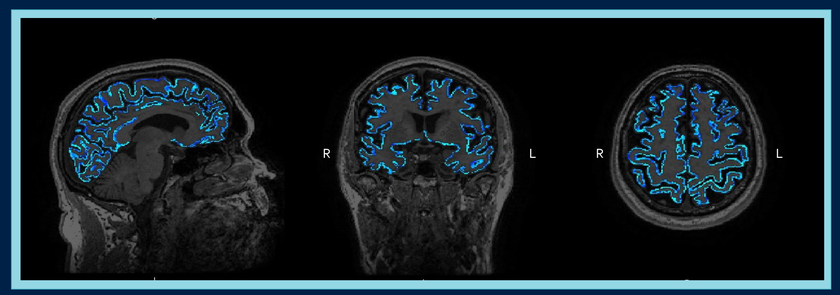
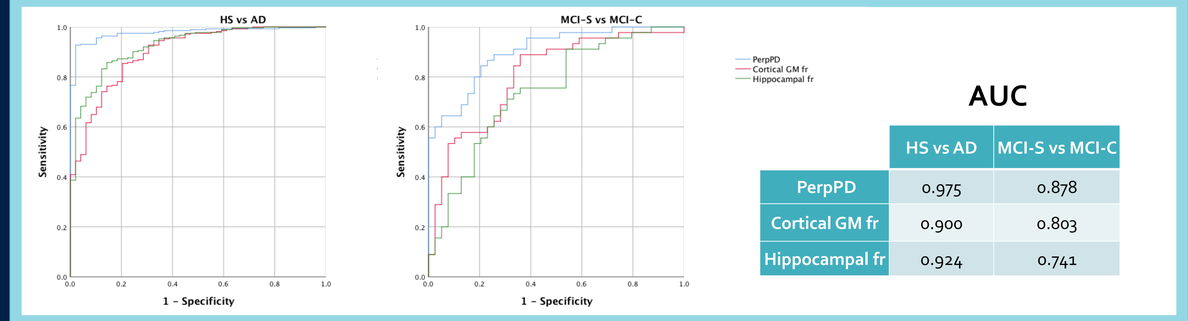


Figure 1. Blue voxels indicate the cortical diffusivity values from low (dark) to high (light))

Results: The results showed that the new DTI derived measures can detect altered quality of cortical grey matter in AD patients, distinguishing between these and HS with an AUC of 0.975, and between MCI-C and MCI-S with an AUC of 0.878 (Figure 2).

Figure 2– Receiver Operating Characteristics curves



AUC

	HS vs AD	MCI-S vs MCI-C
PerpPD	0.975	0.878
Cortical GM fr	0.900	0.803
Hippocampal fr	0.924	0.741

Figure 2. The ROC curves show the best areas under the curves to differentiate HS vs AD and MCI-S vs MCI-C.

All the cortical diffusivity measures were significantly correlated with CSF values (total-tau, phosphorylated-tau and amyloid-beta). (Table 2)

Table 2 – Correlation analysis CSF/ Cortical Diffusivity values

	Amyloid-Beta	Phosphorylated-Tau	Total Tau
AngleR	r=-0.223 *p*=0.004	r= 0.264 *p*=0.001	r= 0.323 *p*=0.000
PerpPD	r=-0.331 *p*=0.000	r= 0.486 *p*=0.000	r= 0.548 *p*=0.000
ParlPD	r=-0.278 *p*=0.000	r= 0.471 *p*=0.000	r= 0.535 *p*=0.000

Table 2. The table show the significant associations between CSF values and cortical diffusivity measures.

Conclusions: Our findings support using cortical diffusivity measurements as a surrogate of cortical microstructure quality for identification of the early stages of AD. These changes were consistent with CSF signature in which amyloid-beta was sensitive in the early stages and tau was elevated in the late stages (MCI-C and AD). Further development may aid early diagnosis, patient cohort selection, and quantification of the microstructural changes in response to therapies in clinical trials.

Reference:

-McKavanagh R, Torso M, Jenkinson M, Kolasinski J, Stagg CJ, Esiri MM, McNab JA, Johansen-Berg H, Miller KL and Chance SA (2019). Relating Diffusion Tensor Imaging measurements to microstructural quantities in the cerebral cortex in Multiple Sclerosis. Human Brain Mapping;DOI:10.1002/hbm.24711.

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Sex differences in cortical microstructural changes in asymptomatic individuals at risk for Alzheimer's disease

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Background: The preclinical phase of Alzheimer's disease (AD) is characterized by cortical microstructural changes before the appearance of clinical symptoms. Previous studies have shown that women can present significantly faster age-related decline than men [Filon et al., 2016; Barnes et al., 2005; Ferretti et al., 2018]. The aim of the present study was to investigate the impact of sex in whole brain cortical changes in an asymptomatic population at risk for AD.

Method: A total of 167 individuals (68 males and 99 females) recruited in the Investigation of Alzheimer's Predictors in Subjective Memory Complainers (INSIGHT-preAD) study, were included in the present work. The T1 structural and diffusion tensor imaging (DTI) scans acquired at baseline and after 24 months, were analysed to calculate 3 novel cortical diffusion measures (AngleR, PerpPD and ParlPD- Figure 1) [McKavanagh et al., 2019] and the mean diffusivity (MD).

An independent sample t-test was used to assess group differences in demographic, clinical and MRI values. A linear regression analysis was performed to investigate the role of sex, age and APOE genotype on baseline cortical values. The repeated measures ANOVA was used to assess cortical diffusion differences at baseline and follow-up.

Figure 1 – Cortical diffusion mask

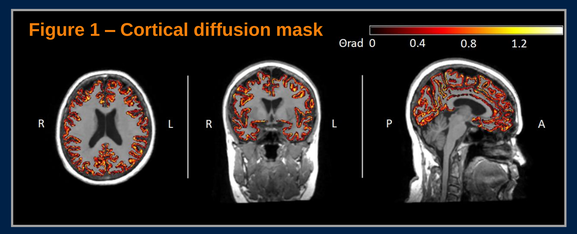


Figure 2. Red voxels indicate the values of AngleR from low (dark) to high (yellow))

Results: No demographic, clinical or brain volumetric differences between men and women were detected (Table 1). Men compared with women showed higher angle between the principal diffusion direction and the radial minicolumn direction across the cortex at the baseline (p=0.001).

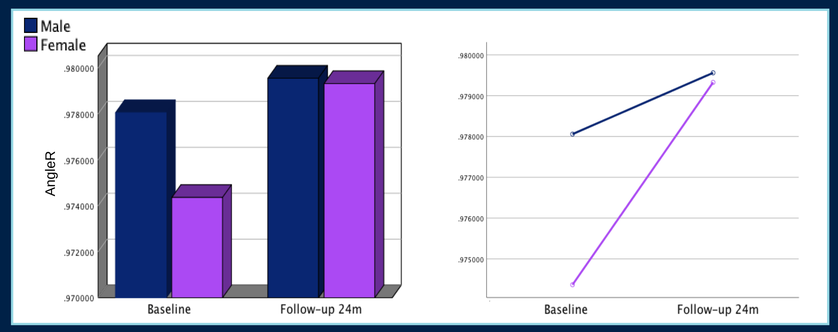
Table 1 – Cohort description at baseline

Baseline	Age (years)	APOE -4 (Yes/No)	MMSE Score	Cortical Grey Matter fraction	Hippocampal fraction	AngleR	PerpPD	ParlPD	MD
Male (n=68)	75.81 ±3.78	7/61	28.60 ±0.95	0.298 ±0.023	0.0050 ± 0.00006	0.978 ±0.010*	0.541 ±0.027	0.366 ±0.013	0.946 ±0.041
Female (n=99)	75.50 ±3.05	22/99	28.77 ±0.90	0.293 ±0.034	0.0066 ± 0.00007	0.974 ±0.007	0.534 ±0.021	0.365 ±0.013	0.937 ±0.029

*significant difference

The linear regression analysis revealed that only sex explains differences in AngleR values (p=0.001). The repeated measures ANOVA showed a significant effect of time (p=<0.001) and a significant interaction between time and sex (p=0.013), with a higher progression rate in women compare to men (Figure 2).

Figure 2 – Repeated measures ANOVA



The figure 2 shows the difference of AngleR between males and females at baseline and in the progression rate.

Conclusions: These findings indicate that sex has a significant effect on cortical changes and in their progression rate. The DTI measures could have a central role in enabling individual's specific characterization and may be informative for the development and assessment of potential drug targets that are specific for each subgroup.

Reference:

-Filon JR, Intorcia AJ, Sue LI, Vazquez Arreola E, Wilson J, Davis KJ, ... & Woodruff BK (2016). Gender differences in Alzheimer disease: brain atrophy, histopathology burden, and cognition. Journal of Neuropathology & Experimental Neurology, 75(8), 748-754.

- Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, & Bennett DA (2005). Sex differences in the clinical manifestations of Alzheimer disease pathology. Archives of general psychiatry, 62(6), 685-691.

- Ferretti MT, Iulita MF, Cavedo E, Chiesa PA, Dimech AS, Chadha AS, ... & Depypere H (2018). Sex differences in Alzheimer disease—the gateway to precision medicine. Nature Reviews Neurology, 14(8), 457-469.

- McKavanagh R, Torso M, Jenkinson M, Kolasinski J, Stagg CJ, Esiri MM, McNab JA, Johansen-Berg H, Miller KL and Chance SA (2019). Relating Diffusion Tensor Imaging measurements to microstructural quantities in the cerebral cortex in Multiple Sclerosis. Human Brain Mapping;DOI:10.1002/hbm.24711.

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Cortical microstructural changes and Amyloid Beta burden in cognitively intact subjective memory complainers

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Background: The aim of the present study was to investigate the association between brain amyloid β (Aβ) accumulation and cortical microstructural changes in cognitively intact individuals with subjective memory complaints.

Method: A total of 258 individuals (100 males,158 females) from the Investigation of Alzheimer's Predictors in Subjective Memory Complainers (INSIGHT-preAD) study [Dubois et al., 2018], were included (Table 1). The 18F-florbetapir PET images were used to compute whole brain and regional standard uptake value ratios (SUVr), while T1 structural and diffusion tensor imaging (DTI) scans were analysed to calculate 3 novel cortical grey matter diffusion measures (AngleR, PerpPD and ParlPD) and the mean diffusivity (MD) [McKavanagh et al., 2019]. A linear regression model was used to study the association between the global SUVr value and whole brain cortical diffusion measures, by including the diffusion measure as the dependent variable, and age, sex, APOE genotype and global amyloid SUVr as independent predictors. Partial correlation analysis, controlling for sex, was used to investigate regional associations between SUVr and diffusion values in 6 regions of interest (bilateral anterior cingulate, posterior cingulate, frontal superior orbital, inferior parietal, precuneus, middle temporal cortex). Results were considered statistically significant after false discovery rate correction (FDR <0.05).

Table 1 – Cohort description

	Age (years)	Sex (F/M)	APOE-4 (Yes/No)	MMSE Score	Cortical Grey Matter fraction	Hippocampal fraction
Cohort	76.01 ±3.52	158/100	50/208	28.62 ±0.95	0.295 ±0.018	0.00048 ± 0.00005

Results: Linear regression revealed that whole brain amyloid SUVr values were positively associated with whole brain AngleR (the angle between the principal diffusion direction and the radial minicolumn direction within the cortical grey matter) (β = 0.23, p<0.001). Figure 1

Figure 1 - Regression plot

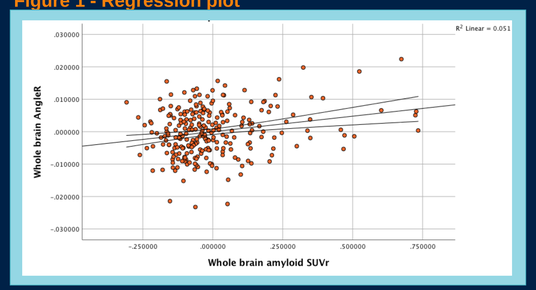

Figure 1. The regression plot shows there is a relationship between amyloid and cortical microstructure that is also influenced by other variables.

Regional partial correlations indicated significant associations between SUVr and AngleR regional values (Figure 2) in left anterior cingulate cortex (r=0.168;p=0.010) and bilateral precuneus (left r=0.173;p=0.005; right r=0.178;p=0.004).

Figure 2 - Partial regional correlations between regional SUVr and AngleR values

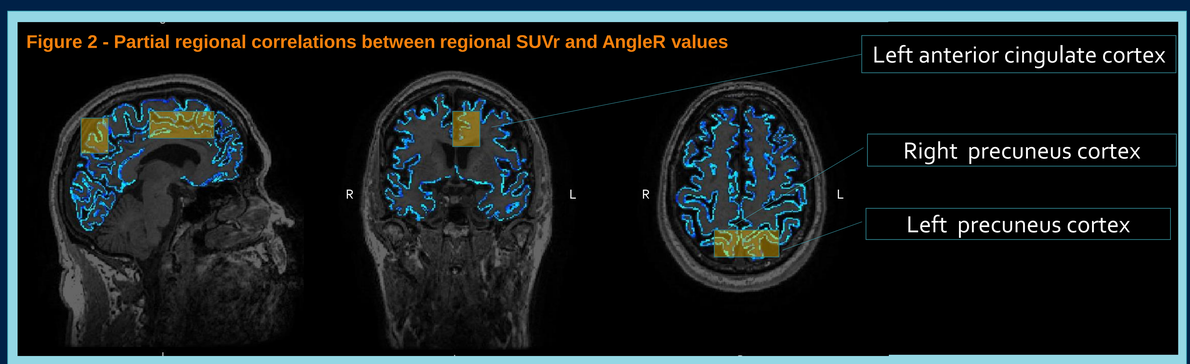

Figure 2. The yellow boxes show brain regions with a significant association between regional PET SUVr and AngleR values. (Blue voxels indicate the values of AngleR from low (dark) to high (light))

Conclusions: These results showed a significant relationship between Aβ accumulation and cortical architectural change in subjective memory complainers. The regional associations revealed the presence of microstructural changes in key regions commonly affected in the early stage of AD [Palmqvist et al., 2017]. Our novel cortical DTI measures could offer additional information about cortical changes, playing a potential role as index of "neurodegeneration" in the ATN framework [Jack et al., 2018] of Alzhiemer's biomarkers.

Reference:

- Dubois B, Epelbaum S, Nyasse F, Bakardjian H, Gagliardi G, Uspenskaya O, ... & Bertrand A (2018). Cognitive and neuroimaging features and brain β-amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study. The Lancet Neurology, 17(4), 335-346.
-McKavanagh R, Torso M, Jenkinson M, Kolasinski J, Stagg CJ, Esiri MM, McNab JA, Johansen-Berg H, Miller KL and Chance SA (2019). Relating Diffusion Tensor Imaging measurements to microstructural quantities in the cerebral cortex in Multiple Sclerosis. Human Brain Mapping;DOI:10.1002/hbm.24711.
- Palmqvist S, Zetterberg H, Mattsson N, Johansson P, Minthon L, Blennow K, ... & Swedish BioFINDER Study Group (2015). Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease. Neurology, 85(14), 1240-1249.
-Jack Jr, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., ... & Liu, E. (2018). NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia, 14(4), 535-562.

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