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Reduced fractional anisotropy of genu of corpus callosum as a predictor of longitudinal cognition in MCI

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ABSTRACT

Our goal was to evaluate the utility of diffusion tensor imaging (DTI) for predicting future cognitive decline in mild cognitive impairment (MCI) in conjunction with AD biomarkers (amyloid PET and AD signature neurodegeneration) in 132 MCI individuals ≥60 years old with structural MRI, DTI, amyloid PET, and at least one clinical follow-up. We used mixed effect models to evaluate the prognostic ability of fractional anisotropy of genu of the corpus callosum (FA-Genu), as a cerebrovascular disease (CVD) marker, for predicting cognitive decline along with AD biomarkers. We contrasted the value of white matter hyperintensities, a traditional CVD marker as well as FA in the hippocampal cingulum bundle (FA-HCB) with the FA-Genu models. FA-Genu significantly predicted cognitive decline even after accounting for AD biomarkers. WMH was not associated with cognitive decline in the model with WMH and FA-Genu. DTI specifically FA-Genu provides unique complementary information to AD biomarkers and has significant utility for prediction of cognitive decline in MCI.

Keywords

Diffusion tensor imaging; mild cognitive impairment; cerebrovascular disease; genu of corpus callosum

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1. INTRODUCTION

Mild Cognitive Impairment (MCI) is often a prodrome of dementia(Petersen, 2009) with a progression rate of 10–15% per year (Bruscoli and Lovestone, 2004; Petersen et al., 2001) and many of those with MCI who progress to AD dementia have elevated levels of Aβ (Quigley, Colloby and O'Brien, 2011). Because a significant proportion of variability in progression to dementia from MCI is not explained by brain Aβ levels, there is a need for additional biomarkers to aid in the prediction of future cognitive decline in MCI.

Diffusion tensor imaging (DTI) is a promising marker for cerebrovascular disease (CVD)(Tu et al., 2017; Williams et al., 2017). Studies have shown that reduction of fractional anisotropy (FA) or directionality and increase in overall mean diffusivity (MD) are associated with cognitive decline (Croall et al., 2017; Tuladhar et al., 2015). We recently reported that the FA of the genu of the corpus callosum (FA-Genu) is a useful biomarker of CVD because the loss of microstructural integrity in the genu was associated with worsening of systemic vascular health and cerebrovascular injury even after accounting for AD pathologies (Vemuri et al., 2018). This was supported by several studies that have found disconnection of the white matter (WM) tracts in MCI in the context of CVD (Catani and ffytche, 2005; O'Sullivan et al., 2001). Our primary aim was to test if poor WM microstructural health, as captured by FA-Genu, was predictive of faster cognitive decline and to evaluate its clinical utility in the presence of AD biomarkers (amyloid and neurodegeneration).

Using DTI, we investigated the interrelationships between FA-Genu, amyloid pathology, neurodegeneration (cortical thickness in AD signature regions) and cognitive decline among MCI participants, aged 60 years and older, and enrolled in the population-based Mayo Clinic Study of Aging (MCSA). In addition, we also compared the effectiveness of DTI measures from a different region, FA in the hippocampal cingulum bundle (FA-HCB), a tract that has been known to be vulnerable to AD pathology.

2. MATERIALS AND METHODS

2.1. Selection of Participants

The MCSA was designed to investigate the epidemiology of MCI and risk factors for MCI and dementia among the residents of Olmsted County Minnesota. The MCSA sample population was enumerated from the Olmsted county population using the Rochester Epidemiology Project (REP) medical records -linkage system (Rocca et al., 2012; St Sauver et al., 2012). The MCI participants were diagnosed based on the published consensus criteria (Petersen et al., 2010) that were described previously. In the current analyses, we included participants ≥60 years of age who had a diagnosis of MCI at the time of their structural MRI, DTI, FLAIR-MRI, and amyloid PET scans that had sufficient quality and had detailed neuropsychology evaluation at the imaging visit, and at least one clinical follow-up.

Standard protocol approvals, registrations, and patient consents: The study was approved by the Mayo Clinic and Olmsted Medical Center institutional review board and written informed consent was obtained from all participants.

2.2. Imaging Biomarkers

All MRI scans were obtained on a 3T GE scanner with an eight channel phase array coil (GE, Milwaukee, WI).

2.2.1. DTI acquisition and processing: DTI acquisition was performed using a single-shot echo-planar imaging sequence with an isotropic resolution of 2.7 mm. The DTI data consisted of 46 images for each set with 41 diffusion-encoding gradient directions (b=1000 s/mm^2) and 5 non diffusion-weighted images (b=0 s/mm^2). The diffusion data were preprocessed using the in-house developed pipeline. Briefly, the images were skull stripped (Reid et al., 2018), denoised (Veraart et al., 2016), corrected for head motion and eddy current distortion (Andersson et al., 2016), Gibbs ringing (Kellner et al., 2016), and then Rician noise bias correction was performed (Koay et al., 2009). Diffusion tensors were then fitted by nonlinearly minimizing the squared residuals (Garyfallidis et al., 2014), and FA and MD maps were calculated from the tensors. Advanced normalization tools –Symmetric Normalization (ANTS-SyN) (Avants et al., 2011) was used to non-linearly register FA image of the JHU "Eve" atlas to each participant's FA image (Oishi et al., 2009) and the median values of FA in each region were obtained. The atlas was slightly modified by fusing the left and right portions of structures spanning the left-right mid-plane, such as the genu and pons.

2.2.2. Neurodegeneration Assessment from structural scans: The cortical thickness measurements were performed from MPRAGE scans using the FreeSurfer version v5.3, and estimated the average cortical thickness of AD signature regions including the entorhinal cortex, inferior temporal, middle temporal and fusiform gyrus. A derived single measure was used as the surrogate marker of neurodegeneration (Schwarz et al., 2016).

2.2.3. Amyloid Assessment from PET scans: The detailed descriptions of acquisition, processing and summary measure calculation for amyloid PET scans were published previously (Jack et al., 2017). A cortical global Pittsburgh compound B positron emission tomography (PiBPET) standardized uptake value ratio (SUVR) was computed by calculating the median uptake over voxels in the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus ROI values for each participant normalized by the cerebellar crus grey matter of the in house atlas modified from (Lopresti et al., 2005) and used as a global amyloid load measure.

2.2.4. Cerebrovascular Pathology Assessment from FLAIR scans: The acquisition and analysis of FLAIR-MRI images on the study participants were described in detail by Graff-Radford et al (Graff-Radford et al., 2019). Briefly, all subjects MPRAGE and FLAIR images were co-registered to template space using Statistical parametric Mapping. Then FLAIR images were masked using the segmented WM mask from MPRAGE image to remove the non-brain tissue and voxels other than WMH. WMH voxels on FLAIR images were segmented using semi-automated clustering technique as described in (Graff-Radford et al., 2019). These custom made masks were further visually inspected and manually edited by the trained analysts to exclude the artifacts from the WMH volume. We used the WMH fraction as ratio of WMH to the total intracranial volume as our outcome measure.

2.3. Cognitive Performance Measures

A detailed neuropsychological evaluation was performed on all MCSA participants as described previously (Petersen et al., 2010; Roberts et al., 2008). We assessed four cognitive domains using nine tests: executive (Trail Making Test Part B and Wechsler Adult Intelligence Scale–Revised (WAIS-R) Digit Symbol), language (Boston Naming Test and category fluency), Memory (Wechsler Memory Scale–Revised (WMS-R) Logical Memory-II (delayed recall), WMS-R Visual Reproduction-II (delayed recall), Auditory Learning Verbal Test delayed recall) and Visuospatial performance (WAIS-R Picture Completion and WAIS-R Block Design). In this study, we used a global cognitive function standard score that was derived from the z-transformation of the average of the four standardized cognitive domain scores: memory, language, attention/executive, and visuo-spatial function (Vemuri et al., 2014).

2.4. Statistical Analysis

All statistical analyses were performed using R statistical software, version 3.4.2 (RFoundation).

2.4.1. Evaluation of the DTI biomarker and education/occupation variables for predicting global cognition—We examined the effect of each of the DTI markers (FA-Genu) in the primary models and FA-HCB in the sensitivity analyses) and AD markers on longitudinal global cognitive performance using linear mixed effect models. We fit three separate linear mixed effect models for the DTI marker with global cognition as the dependent variable, and follow-up time, age, sex, education/occupation and various imaging biomarkers as fixed predictors. In the first model, we only used the DTI marker, in the second model the DTI marker in conjunction with amyloid and in the third model the DTI marker in conjunction with amyloid and neurodegeneration. In these models we considered all the main effects as well as the interactions of interest with time. We also tested for interactions of age, sex and education/occupation with the DTI marker. The models were fit with random intercepts and slopes. We did not test for three way interaction because of limited power. Among the three separate models for our predictors of interest, we compared the goodness-of-fit using Akaike information criteria (AIC). Lower AIC suggests greater prediction of variance in the data. The non-significant terms were removed from the model one at time, accounting for nested effects, until the final parsimonious models were reached. All models were tested and controlled for within-subject autocorrelation of the repeated measures.

The final parsimonious model included all main effects as well as all significant two-way interactions of potential predictors with time. We tested specifically for: interactions of the DTI imaging biomarker, other imaging biomarkers (PIB and cortical thickness), education/occupation, age and time. The global amyloid values used in the model were log transformed. A significant interaction of predictor with time would estimate the rate of change of global cognition over time based on the values of predictor variables.

2.4.2. Assessing the utility of DTI biomarker in conjunction with WMH—We estimated the added value of DTI marker for prediction of longitudinal cognition in MCI after accounting for WMH. The WMH was analyzed as percentage of total intracranial volume (TIV) in the model and values were log transformed. We fitted linear mixed effect models with global cognition as the outcome variable and with age and time as fixed effects. The final parsimonious model included all significant interactions of imaging biomarkers with time, main effects nested within those interactions, and other significant main effects.

3. RESULTS

The demographics, APOE4 status, intellectual enrichment variables, cognitive measures, vascular and AD biomarker values are provided in Table 1. As depicted in Table 1, out of 132 MCI participants, 51 (39%) were APOE4 positive and 73 (55%) amyloid-positive. Participants had a mean education level of 13.8 years and an education/occupation mean score of 11.7. The baseline global cognition z-scores were normally distributed among the participants. The mean follow-up time was 4.05 years (SD).

3.1. FA-Genu for prediction of longitudinal cognitive decline

The results of the three linear mixed effect models: 1) FA-Genu alone; 2) FA-Genu and PIB combined; and 3) FA-Genu, PIB and cortical thickness are presented in Table 2. In all three models with FA-Genu, higher education/occupation scores were associated with better baseline cognitive performance ($p<0.01$). In the model of FA-Genu alone, age was a predictor of baseline cognitive performance and had a faster rate of cognitive decline. Sex was not a significant predictor of cognition in any of the models and dropped out from further analysis. In model 3, all three biomarkers (FA-Genu, PIB, and cortical thickness) significantly predicted the rate of cognitive decline ($p<0.05$). The significant interaction between FA-Genu and time indicated that MCI participants with higher FA declined more slowly over time. In the third model with all three imaging predictors, the AIC was lower providing evidence that including all imaging predictors improved prediction of longitudinal cognition. A plot of predicted global cognition categorized by the imaging biomarkers and a spaghetti plot of global cognition as a function of age are shown in Figures 1. In the left panel, we illustrated the predicted cognition z-score trajectories by FA-Genu and PIB values maintaining education/occupation as constant. We found that the participants with low FA-Genu and high PIB declined fastest among the groups.

3.2. FA-HCB for prediction of longitudinal cognitive decline

The results of the linear mixed effect models of FA-HCB, which were conducted as part of our sensitivity analyses, are presented in Table 3. In all three models of FA-HCB, education/occupation was an important component as in the FA-Genu models. Older age significantly predicted faster rate of annual cognitive decline in models with FA-HCB alone and model 2 (FA-HCB+ with PIB). FA-HCB had significant interactions with sex and PIB in model 2. FA-HCB predicted cognitive decline (interaction with time) only in models 1 and 2. In the third model (FA-HCB, PIB and cortical thickness), only PIB and cortical thickness but not FA-HCB significantly predicted the longitudinal rate of cognitive decline. However there were significant interactions of FA-HCB with PIB and FA-HCB with baseline age in model 3. The predicted cognition z-score trajectories by the FA-HCB and PiB levels maintaining education/occupation as constant are illustrated in Figure 2. We found that although the participants with low FA-HCB and high PIB declined fastest among the groups, the FA-HCB interacts with PIB. The Comparison of these results with FA-Genu suggests that FA-Genu is a better DTI marker than FA-HCB which may be in the pathway of the AD biomarker cascade.

3.2. DTI association with WMH

The linear mixed model results with both DTI marker and WMH after adjusting for age, time from baseline, and education/occupation score results in a simplified model as shown in Table 4 because WMH drops out due to non-significant effect. Therefore only the DTI marker, FA-Genu (p=0.01) but not WMH, significantly predicted longitudinal cognition.

4. DISCUSSION

The present study aimed to examine the utility of DTI imaging for predicting cognitive decline in MCI individuals over 60 years of age in conjunction with brain amyloidosis and neurodegeneration. The major findings of this population based study are as follows:(1) FA-Genu was significantly associated with cognitive rate of decline in MCI individuals even after adjusting for information provided by amyloid deposition and neurodegeneration; (2) FA-HCB was not significantly associated with cognitive rate of decline after adjusting for amyloid deposition and neurodegeneration; and (3) only FA-Genu and not WMH was associated with cognitive decline when the model contained both WMH and FA-Genu.

DTI is a promising biomarker for studying the integrity of WM in MCI. Here, we found a significant association between WM structural integrity, measured by FA-Genu, and cognitive decline among MCI participants. Importantly, this association was independent of PIB and cortical thickness, supporting its utility as a biomarker in MCI.

The well-defined mechanism of cognitive impairment is that of cortical disconnection (Catani and ffytche, 2005; Lamar et al., 2008) which has been suggested to be influenced by CVD (Croall et al., 2017; Tu et al., 2017; Tuladhar et al., 2015). The CC is the largest WM tract in the brain and plays a crucial role in interhemispheric communication. The loss of these connections can disrupt connectivity of several cortical regions and recognized in age related cognitive declines (O'Sullivan et al., 2001). These WM changes can therefore be the underlying cause of widespread cognitive impairment in CVD characterized by predominant dysfunction in attention, psychomotor speed, and executive function.

Several lines of evidence indicate the relationship between frontal lobe damage and vascular disease (Knopman et al., 2015; Tullberg et al., 2004) suggesting that the genu of the CC is the most susceptible region to vascular disease effects. Further, FA-Genu was found to capture early changes due to systemic vascular health which lends itself as a useful CVD biomarker in MCI (Vemuri et al., 2018). As reported in prior studies (Croall et al., 2017; Vemuri et al., 2018), FA is a sensitive marker of CVD. We did not investigate MD here because it measures overall water diffusion and may be less specific to subtle microstructure WM abnormalities due to CSF contamination (CSFC). The contribution of partial volume effect due to CSFC has been found more problematic in brain structures with close proximity of ventricles such as the fornix and the genu of CC (Concha et al., 2005; Jones and Cercignani, 2010). Additionally, a greater CSFC for the diffusivity measurements than FA was demonstrated previously in the fornix of the older adults (Metzler-Baddeley et al., 2012) and genu of CC in the MCI subjects (Berlot et al., 2014).

Multiple studies have documented CC atrophy in clinically diagnosed MCI and AD dementia (Elahi et al., 2015; L. Wang et al., 2009), and some have reported predominant atrophy in the anterior part (Thomann et al., 2006; Zhu et al., 2012). However, the CC changes in MCI across studies have not been consistent (Thomann et al., 2006; H. Wang and Su, 2006). A previous Rotterdam Study in MCI patients with CVD found microstructural damage in the genu, internal and external capsule, and periventricular WM, but in those without CVD, deterioration was found along the hippocampal tract (Papma et al., 2014) suggesting that the anterior changes may be more specific to CVD. A consistent DTI change in the genu was also demonstrated in patients with subcortical vascular dementia (Chen et al., 2009) further supporting our use of FA-Genu.

One would argue against using a specific tract instead of global DTI measures. For example, data from the participants of Atherosclerosis Risk in Communities Study (ARIC) showed an association between overall DTI measures with cognitive decline, incident MCI, dementia and mortality longitudinally (Power et al., 2019). The same was true in a recent Harvard Aging Brain Study where a global FA measure significantly predicted longitudinal cognitive decline even after adjusting for amyloid level (Rabin et al., 2019). However we specifically chose FA-Genu because other limbic tracts such as hippocampal cingulum and fornix have been observed in preclinical AD (Chao et al., 2013; Gold et al., 2014; Jacobs et al., 2018; Rieckmann et al., 2016), suggesting its relationship with amyloid pathology. The sensitivity analyses we conducted in Table 3 support associations between HCB and AD pathophysiology. With amyloidosis and neurodegeneration in the model (model 3), we did not find any significant interaction between FA-HCB and time. The observed interaction between FA-HCB and PiB suggests that CGH may be a part of the AD pathway (Jacobs et al., 2018). More importantly, measuring FA-Genu we are able to capture the independent effect of vascular disease. We also performed sensitivity analyses using cognitive subdomains which indicated variability in associations across the domains as expected due to the heterogeneity seen in etiology of MCI (supplementary table).

Evaluating conventional CVD measures like WMH is important to determine the utility of DTI over traditional measures. Although the modifiable cardiovascular risk factors such as hypertension, diabetes and BMI are identified in association with WM integrity declines (Wassenaar et al., 2019), measurement of WMH provides the extent of CVD damage. While WMH alone was predictive of cognitive decline, we found that WMH was not predictive of cognitive decline in the combined linear mixed model with FA-Genu in the model. These findings support the independent utility of FA-Genu for predicting cognitive performance in MCI patients aged 60 years and older as it may be able to capture more subtle microstructural damage.

The present study has some strengths and limitations. A major strength is the availability of amyloid PET, MRI, and longitudinal cognitive outcomes in a population based sample. There are several limitations. We relied on simple and robust measures (genu FA and global cognitive- z score) to study the relationship between DTI metrics and longitudinal cognitive decline after accounting for AD biomarkers. The small sample size to detect subtle effects such as those with WMH may limit the findings of the study. Highly educated individuals in the cohort may have an influence on the generalizability of this study. There is some regional variability in the etiology of WMH as shown recently (Al-Janabi et al., 2018; Graff-Radford et al., 2019; Weaver et al., 2019) but we only considered global WMH in this work and not regional WMH because global WMH is the typically used CVD measure in most aging and dementia studies. Additionally, newer biophysical modelling methods that may allow for robust metrics such as NODDI (Neurite Orientation Dispersion and Density Imaging) and Free Water Elimination (FWE) may be helpful in providing better metrics of WM integrity and will be part of future investigations. In contrast to DTI, these techniques could reliably account for the partial volume effects by CSFC and therefore provide better sensitivity even in the asymptomatic/preclinical stages.

5. CONCLUSIONS:

Our findings illustrate the complex interplay between brain structure, brain function, and cognitive decline in MCI. Greater DTI measures (indicator of brain reserve or structure) predicted slower decline over time. Accounting for brain structure (neurodegeneration and WM integrity) and amyloid strengthen our findings. DTI has significant utility for prediction of cognitive decline in MCI from population-based sample and will provide complementary information to AD biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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3. The data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

4. ***Standard protocol approvals, registrations, and patient consents***: The study was approved by the Mayo Clinic and Olmsted Medical Center institutional review board and written informed consent was obtained from all participants.

5. All authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data.

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Highlights:

- DTI changes in the genu of the corpus callosum predicts cognitive decline in MCI.
- Poor white matter health provided prognostic information beyond Alzheimer's disease biomarkers.
- DTI measure in the genu provided greater prognostic information than the WMH.

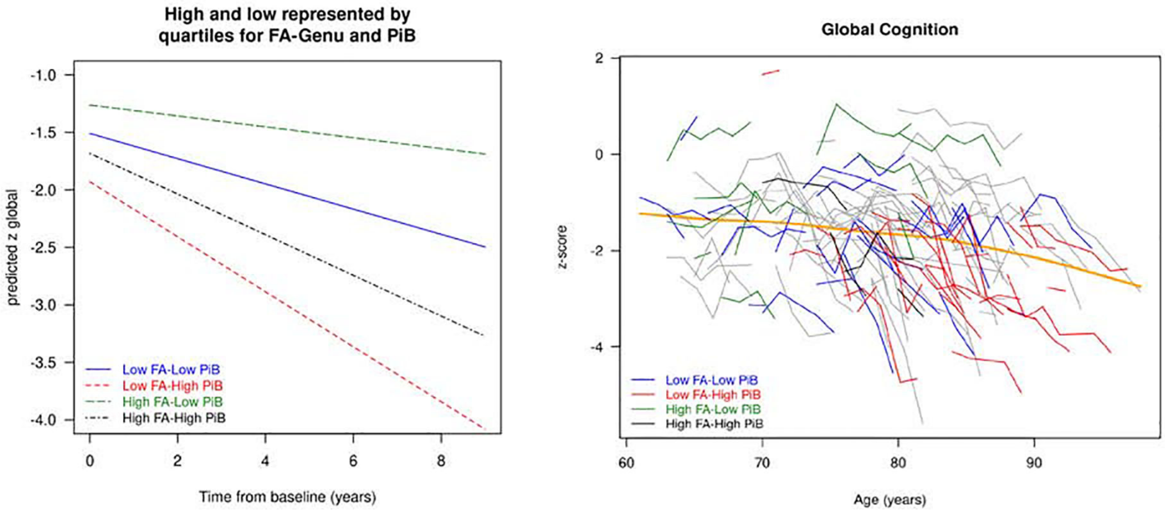

Figure 1:

(Left) The predicted global cognitive trajectories for a 78 year old participant by time from baseline for a given FA-Genu and amyloid level. In the graph, low and high were defined by 25th and 75th percentiles. (Right) Spaghetti plot of global cognition as a function of age.

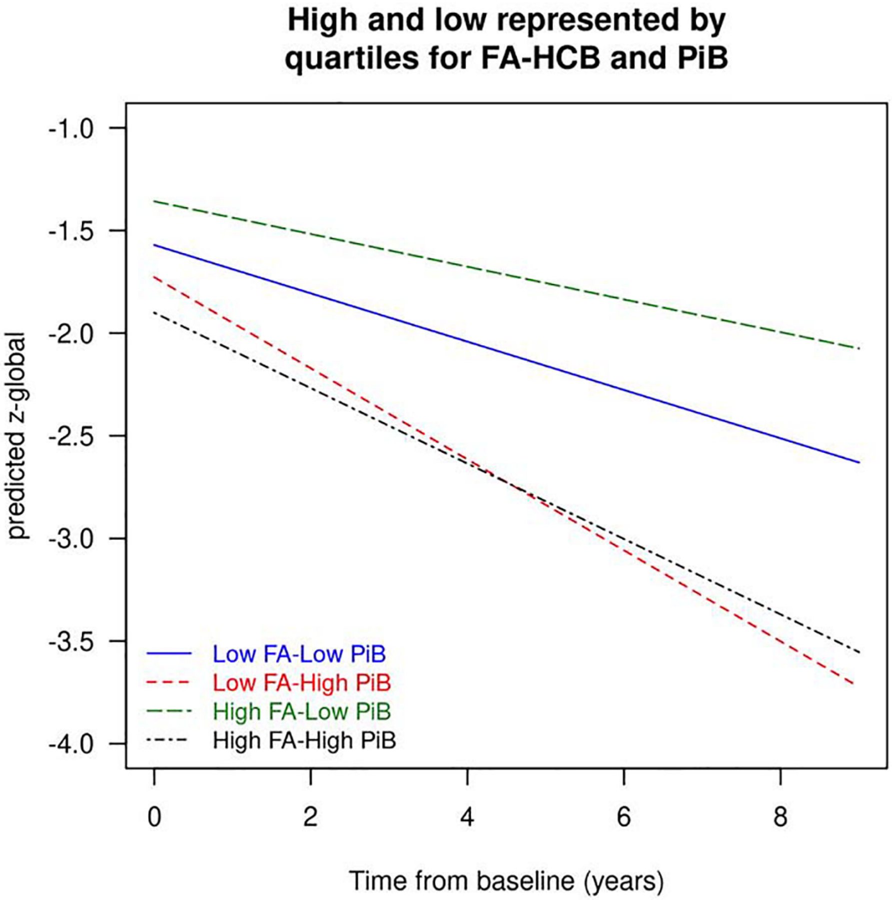

Figure 2:

The predicted global cognitive trajectories for a 78 year old participant by time from baseline for a given FA-HCB and amyloid level. In the graph, low and high were defined by 25th and 75th percentiles.

Table 1.

Characteristics table of MCI subjects with the mean (SD) listed for the continuous variables and count (%) for the categorical variables.

Characteristic	All Subjects n = 132
Demographics	
Age, yrs	77.3 (7.4)
Males, no. (%)	78 (59%)
APOE, no. (%)	51 (39%)
Intellectual Enrichment	
Education/Occupation	11.7 (2.7)
Education, yrs	13.8 (2.9)
Cognitive Measures	
MMSE	25.8 (1.8)
Global z-score	−1.58 (0.97)
Memory z-score	−1.56 (1.06)
Language z-score	− 1.29 (1.20)
Attention z-score	−1.40 (1.44)
Visualspatial z-score	−0.79 (1.06)
PiB, Neurodegeneration, and Follow-up	
PIB SUVr	1.83 (0.55)
PIB+, no. (%)	73 (55%)
Neurodegeneration, mm	2.73 (0.21)
Neurodegeneration+, no. (%)	93 (72%)
Follow-up, yrs	4.05 (2.16)
Dementia Progression, no. (%)	19 (14%)
Vascular Markers	
Cardio Metabolic Condition	2.71 (1.47)
FA-Genu	0.57 (0.06)
FA-HCB	0.45 (0.04)
WMH/Total Intracranial Volume	0.014 (0.011)

Table 2:

Mixed models evaluating the utility of the Genu FA (FA-Genu) in predicting cognitive performance

Models	Variable	Coefficient (s.e.)	p-value
FA-Genu AIC 973.9088	Intercept	−2.118 (1.625)	0.19
	Time	−0.068 (0.267)	0.80
	Baseline age	−0.028 (0.013)	0.04
	Education/occupation	0.097 (0.032)	0.003
	FA-Genu	2.730 (1.726)	0.12
	FA-Genu × time	0.748 (0.289)	0.01
	Baseline age × time	−0.006 (0.002)	0.002
FA-Genu+ PIB AIC 940.3542	Intercept	−4.050 (1.003)	<0.001
	Time	−0.517 (0.152)	<0.001
	Education/occupation	0.077 (0.030)	0.011
	FA-Genu	3.607 (1.557)	0.022
	PiB	−0.803 (0.306)	0.01
	FA-Genu × time	0.904 (0.255)	<0.001
	PiB × time	−0.246 (0.049)	<0.001
FA-Genu+ PIB + Cortical thickness AIC 900.9365	Intercept	−5.543 (1.401)	<0.001
	Time	−1.193 (0.222)	<0.001
	Education/occupation	0.090 (0.029)	0.003
	FA-Genu	2.833 (1.605)	0.08
	PiB	−0.738 (0.315)	0.021
	Cortical thickness	0.650 (0.452)	0.15
	FA-Genu × time	0.528 (0.268)	0.049
	PiB × time	−0.164 (0.052)	0.002
	Cortical thickness × time	0.307 (0.076)	<0.001

Table 3:

Mixed models evaluating the utility of the hippocampal cingulum bundle FA (FA-HCB) in predicting cognitive performance

Models	Variable	Coefficient (s.e.)	p-value
FA-HCB AIC 968.5585	Intercept	8.694 (5.222)	0.10
	Time	0.008 (0.260	0.98
	Baseline age	−0.029 (0.013)	0.028
	Education/occupation	−0.844 (0.429)	0.051
	FA-HCB	−20.270 (11.221)	0.073
	FA-HCB × time	1.002 (0.413)	0.016
	FA-HCB × education/occupation	2.083 (0.946)	0.03
	Baseline age × time	−0.008 (0.002)	<0.001
FA-HCB + PIB AIC 949.1162	Intercept	−2.306 (2.795)	0.41
	Time	−0.046 (0.243)	0.85
	Baseline age	−0.021 (0.014)	0.12
	Male	−5.078 (2.156)	0.02
	Education/occupation	0.078 (0.031)	0.014
	FA-HCB	4.021 (5.477)	0.46
	PiB	6.545 (3.458)	0.061
	FA-HCB × time	0.823 (0.388)	0.034
	FA-HCB × male	11.395 (4.773)	0.019
	FA-HCB × PiB	−15.960 (7.759)	0.042
	PiB × time	−0.199 (0.056)	<0.001
	Baseline age × time	−0.005 (0.002)	0.026
FA-HCB+ PIB + Cortical thickness AIC 899.9934	Intercept	21.230 (11.670	0.07
	Time	−1.074 (0.215)	<0.001
	Baseline age	−0.412 (0.163)	0.013
	Education/occupation	0.089 (0.030)	0.003
	FA-HCB	−49.805 (25.514)	0.053
	PiB	9.937 (3.896)	0.012
	Cortical thickness	0.252 (0.476)	0.60
	FA-HCB × baseline age	0.868 (0.360)	0.017
	FA-HCB × PiB	−23.645 (8.760)	0.008
	PiB × time	−0.155 (0.054)	0.004
	Cortical thickness × time	0.371 (0.072)	<0.001
	FA-HCB × time	0.568 (0.383)	0.14

Table 4:

Mixed models evaluating the utility of the Genu FA (FA-Genu) in conjunction with WMH predicting cognitive performance

Model	Variable	Coefficient	S.E	P-value
FA-Genu + WMH AIC 995.102	Intercept	−2.462	1.694	0.147
	Time	−0.110	0.285	0.699
	Baseline age	−0.026	0.014	0.066
	Education/occupation	0.103	0.034	0.003
	FA-Genu	2.231	1.866	0.234
	WMH	−0.091	0.136	0.506
	FA-Genu × time	0.727	0.296	0.014
	Baseline age × time	−0.006	0.002	0.011
	WMH × time	−0.011	0.018	0.543
	Educ/occ × time	−0.005	0.005	0.372