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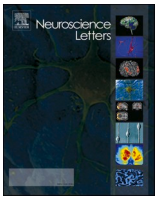

Splenium tract projections of the corpus callosum to the parietal cortex classifies Alzheimer's disease and mild cognitive impairment

Jean-Francois Delvenne *, Brian Scally, Melanie Rose Burke

School of Psychology, University of Leeds, United Kingdom

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ABSTRACT

The corpus callosum (CC) is the largest bundle of white matter tracts in the brain connecting the left and right cerebral hemispheres. The posterior region of the CC, known as the splenium, seems to be relatively preserved throughout the lifespan and is regularly examined for indications of various pathologies, including Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI). However, the splenium has rarely been investigated in terms of its distinct inter-hemispheric tract bundles that project to bilateral occipital, parietal and temporal areas of the cortex. The aim of the present study was to determine if any of these sub-splenium tract bundles are specifically affected by individuals with AD and MCI compared to normal controls. Diffusion Tensor Imaging was used to directly examine the integrity of these distinct tract bundles and their diffusion metrics were compared between groups of MCI, AD, and control individuals. Results revealed that differences between MCI, AD, and controls were particularly evident at parietal tracts of the CC splenium and were consistent with an interpretation of compromised white matter integrity. Combined parietal tract diffusivity and density information strongly discriminated between AD patients and controls with an accuracy (AUC) of 97.19%. Combined parietal tract diffusivity parameters correctly classified MCI subjects against controls with an accuracy of 74.97%. These findings demonstrated the potential of examining the CC splenium in terms of its distinct inter-hemispheric tract bundles for the diagnosis of AD and MCI.

1. Introduction

For years, research has considered how the white matter pathways of the brain are affected by Alzheimer's Disease (AD). Previously described as a disease of the grey matter localised in the hippocampus [1], it is now widely accepted that AD is associated with significant atrophy to white matter tissues of the brain [2–4]. Many studies have demonstrated that parameters extracted from white mater tracts in diffusion tensor imaging (DTI) scans yield highly accurate metrics for classifying groups of AD patients against groups of healthy controls [5–7]. DTI is a noninvasive, quantitative MRI technique that measures the rate and direction of movement of water molecules within tissues. Various parameters can be extracted from DTI: (1) *Mean Diffusivity* (MD), which describes the overall diffusivity in the tissue; (2) *Radial Diffusivity* (RD), which measures diffusion along the axis perpendicular to fire tracts; (3) *Axial Diffusivity* (DA), which quantifies diffusion along the axis parallel to fibre tracts; (4) *Fractional Anisotropy* (FA), which describes the general degree of anisotropy, or directionality dependence, within a voxel. Higher values of MD and RD reflect lower white matter integrity, whereas higher values of DA and FA could indicate greater white matter integrity [8]. Oishi and colleagues [5] found that fractional anisotropy (FA) of the fornix, the large bundle of white matter that is found below the corpus callosum (CC), was 81% accurate in classifying individuals with AD. Fieremans and colleagues [6] found high accuracy for radial diffusivity (RD) for all the main regions (genu, body, and splenium) of the corpus callosum (CC) in classifying AD patients against controls.

Whether changes in microstructural white matter integrity are evident during preclinical and prodromal stages of AD is of particular interest for detecting and classifying individuals in the early stages of the disease. Indeed, early identification and intervention is thought to have significant impact on disease progression [9]. The transitional stage between healthy ageing and dementia, such as AD, is known as Mild Cognitive Impairment (MCI). Early and accurate identification of MCI individuals might prevent further cognitive decline, including

Abbreviations: CC, Corpus Callosum; AD, Alzheimer's Disease; MCI, Mild Cognitive Impairment; AUC, Area under the curve; DTI, Diffusion Tensor Imaging; MD, Mean Diffusivity; RD, Radial Diffusivity; DA, Axial Diffusivity; FA, Fractional Anisotropy; ROI, Region of interest; FDR, False Discovery Rate.

* Corresponding author at: School of Psychology, Faculty of Medicine and Health, University of Leeds, Leeds LS2 9JT, United Kingdom.
E-mail address: j.f.delvenne@leeds.ac.uk (J.-F. Delvenne).

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development of AD. The fundamental pathophysiology of MCI is typical of AD symptomology, and is classified via neuropsychological assessment as an isolated and unambiguous memory deficit, but with preserved abilities of independent daily living [10]. Accuracy of white matter tract diffusion tensor parameters has also been assessed in MCI patients. For instance, Fieremans and colleagues [6] found that a decrease in the integrity of CC subdivisions was a highly accurate classifier of MCI patients against normal controls, reporting 91% for RD of the genu tracts (i.e., the anterior part of the CC), 88% for the midbody (i.e., the middle part of the CC), and 87% of the splenium (i.e., the posterior part of the CC). Furthermore, van Bruggen and colleagues [11] reported high accuracy values for classifying MCI patients who converted to AD against MCI patients that did not convert, using FA of the CC (94%), fornix (71%), left cingulum (94%) and right cingulum (85%).

Other studies that have not reported classification statistics have found significant differences between normal controls and MCI/AD patients in mean diffusion tensor parameters extracted from the splenium, indicating a reduction of white matter integrity with disease [12,13]. Acosta-Cabronero and colleagues [14] demonstrated that the level of splenium integrity was correlated with scores on the Addenbrooke's Cognitive Examination, a widely used test of cognitive deficit in AD. Furthermore, the splenium seems to be less affected in old age than other sections of the CC, in particular the anterior sections [15,16]. If the splenium is specifically affected by AD, and relatively unaffected by healthy ageing, diffusion tensor parameters of the splenium may be a particularly informative disease marker.

The 'splenium' label is commonly applied to the posterior quarter of the midsagittal CC. However, the white matter fibres that pass through this region are diverse and project bilaterally to distinct brain regions: the occipital, temporal and parietal lobes [17]. Although previous studies have found that the splenium appears to be relatively persevered in old age [18–20], we have recently shown that while splenium occipital tracts were preserved in older adults, temporal and parietal segments were particularly impaired [21]. Specifically, using DTI, we found that compared to young adults, older adults have significantly increased MD and RD (thus, lower white matter integrity) in temporal and parietal tracts of the splenium, while diffusivity of occipital segments was equivalent between the groups. Given this novel discovery of altered specific splenium tracts in healthy older adults, the present study aimed to address whether the distinct tract bundles that traverse the CC splenium were particularly compromised in MCI and AD compared to healthy older controls. By considering the splenium bundles in isolation, classification accuracy may be improved and we may gain novel insight into the white matter pathways that are targeted by AD.

Here, we implemented DTI tractography to reconstruct the splenium tract bundles in DTI scans submitted to the National Alzheimer's Coordinating Center database (USA) [22,23]. We compared a group of 20 MCI patients and a group of 20 AD patients to 20 healthy controls to determine if the distinct splenium tract bundles were differentially affected by AD neuropathology.

2. Method

2.1. Participants

Data for the present study were obtained from the National Alzheimer's Coordinating Center (NACC) repository [22,23], funded by the National Institute of Aging (USA). The NACC comprises of demographic, neurocognitive and clinical data, as well as genetic biomarker information and neuroimaging data from individuals seen at 34 Alzheimer's Disease Research Centers (ADRCs) in the United States. Scans that were performed within +/- 1 year of an individual's visit to an ADRC were requested. ADRC clinical judgements of cognitive status (item NACCUDSD) and underlying aetiology (item NACCALZP) were used to identify cognitively normal, MCI and AD individuals. Control individuals were identified as having no cognitive symptoms (NACCUDSD = 1) and no suspected underlying aetiology of AD (NACCALZP = 8). MCI patients were identified as having a clinically judged cognitive status consistent with MCI (NACCUDSD = 3) and a suspected primary aetiology of AD (NACCALZP = 1). AD patients were identified as having a clinically judged cognitive status consistent with AD (NACCUDSD = 4) and a suspected primary aetiology of AD (NACCALZP = 1). This yielded a total of 403 individuals. MRI parameters for images submitted to the NACC database vary by ADRC, and some acquisition information, such as echo time and repetition time, were unavailable. Therefore, only participants with consistent and complete DTI scanning parameters were selected to eliminate any between-site effects. On that basis, twenty MCI individuals were identified and selected. Equivalent numbers of control individuals and AD patients were then selected to match the age and gender distribution of the MCI group. All participants were free from neurological disease (e.g., stroke, Parkinson, etc.) and psychiatric conditions (e.g., depression, schizophrenia, etc.). The demographic characteristics of the final sample are outlined in Appendix 1.

2.2. DTI acquisition and pre-processing

Descriptions of the scan parameters are as follows: 40 directions for b-values of 1000 s/mm^2, 8 scans at b = 0, voxel size = 1 × 1 × 2.5 mm^3, FOV = 255 mm^2, 52 axial slices, matrix size = 255 × 255. Corrections for DWI signal drift, subject motion and eddy current induced distortions, as well as brain extraction, were made using the ExploreDTI software [24].

2.3. DTI tractography

The tractography protocol was identical to the one used in Delvenne and colleagues [21]. Regions of interest (ROIs) were drawn onto the DTI scans of each participant to isolate the occipital, temporal and parietal tract bundles that pass through the splenium. Diffusion tensor parameters FA, DA, MD and RD were extracted from each bundle for each participant and used as dependent variables in the analysis. As well as an analysis of the full unsegmented tract bundles, we also conducted an analysis of the bundles segmented at +/- 6 mm (three 2 mm slices) around the midsagittal slice. This was done to minimise potential confounding effects of tract length or density [25]. The same DTI scalars were extracted for segmented tract bundles.

2.4. Statistical analysis

We aimed to test for group differences in the splenium tract in FA, DA, MD and RD. Since quantitative streamline measures have been shown to covary with DTI scalars [25], we first examined group differences in approximate tract density. Tract density is defined as the cumulative density of the voxels that a given reconstructed tract passes through. We first tested for group differences in the approximate tract density of each tract bundle using one-way ANCOVA models, with Group as the independent variable, and gender as a covariate, at each ROI (i.e., occipital, temporal, and parietal tract bundles of the splenium). We included tract density as a covariate in addition to gender in the following analyses. ANCOVA models with a between-subjects factor Group were used to test for group differences in FA/DA/MD/RD at each ROI. In the interest of preserving statistical power, and because we were particularly interested in differences between Control-MCI and Control-AD groups, we ran separate models to compare these groups directly. False discovery rate (FDR) adjustments for multiple comparisons were implemented across the models for each combination of ROI, DTI metric and Group. The same analysis protocol was conducted for both the full tract and segmented tract analysis. For display purposes, MD and RD values were scaled by a factor of 1000, and DA values by a factor of 100. Tracts that significantly differentiated between AD/MCI and control older adults were submitted to receiver operator characteristic (ROC) analysis, to determine the classification accuracy of the DTI measures.

Classification accuracy is given using the *area under the curve* (AUC) measure expressed in a percentage. Sensitivity and specificity values for the optimum threshold are also presented, which describe the ability to correctly detect disease states and non-disease states, respectively.

3. Results

3.1. Full tract analysis

The results are shown in Fig. 1A and Table 1A. There were no significant differences in tract density between controls and MCI individuals. AD patients had significantly reduced tract density compared to controls in the occipital and parietal tract bundles. As one control participant, one MCI patient and five AD patients were missing parietal tracts, they were removed from the following analysis of the diffusion tensor metrics.

When group differences in FA/DA/MD/RD at each ROI (i.e., occipital, temporal, and parietal tract bundles of the CC splenium), no significant differences in full tract diffusion tensor metrics between controls and MCI patients that withstood the FDR correction were found. However, significant differences in parietal tract MD and RD were apparent between controls and AD patients (Fig. 1B, Table 1B), showing higher MD and RD values in AD patients.

3.2. Segmented tract analysis

The analysis of the segmented tract bundles (i.e., segmented at +/- 6 mm around the midsagittal slice) revealed no differences in tract density between controls and MCI. However, AD patients had significantly reduced tract density compared to controls in the occipital and parietal tract segments (Fig. 1C, Table 1C).

When group differences in FA/DA/MD/RD at each ROI (i.e., occipital, temporal, and parietal tract bundles of the CC splenium) were tested, MCI patients had significantly increased MD and RD in parietal tract segments as compared to controls. Effects of AD were widespread. At occipital segments, AD patients had significantly higher FA and higher DA than controls. In parietal segments, AD patients had higher MD, RD and DA than controls. In temporal segments, AD patients had higher FA and DA, but lower RD than controls (Fig. 1D, Table 1D).

The multivariate accuracy of segmented parietal MD and RD from the splenium for classifying MCI patients against controls was tested. ROC analysis yielded an AUC of 74.97% (sensitivity = 63.15%, specificity = 73.68%). For AD patients, classification accuracy of segmented parietal MD, RD, DA and tract density was tested, yielding an AUC of 97.19% (sensitivity = 93.33%, specificity = 94.74%).

4. Discussion

In the present study we used DTI tractography to examine differences in the occipital, parietal and temporal tract bundles of the CC splenium between cognitively normal older adults and adults with MCI or AD. We found significant differences in occipital and parietal tract density between AD and control individuals in both the full and segmented tract bundles, where AD patients had significantly lower density. In contrast, no modulations of tract density were seen in MCI patients when compared to controls.

With regard to diffusivity, the full tract analysis revealed no difference between MCI patients and controls. However, AD patients had higher MD and RD values in parietal tracts as compared to controls, suggesting lower white matter integrity [8]. The analysis of segmented tract bundles yielded differences in AD patients at all tract segments: higher FA values at occipital and temporal tracts, higher DA values at occipital, parietal and temporal tracts, higher MD and RD values at parietal tracts, and lower RD values at temporal tracts. Differences in MCI patients were exclusively evident at parietal tracts with higher MD and RD values. Combined parietal tract information (MD, RD, DA and tract density) strongly discriminated between AD patients and controls with an accuracy of 97.19%. Combined parietal MD and RD parameters correctly classified MCI subjects against controls with an accuracy of 74.97%.

For the most part, the differences observed in MCI and AD patients were consistent with an interpretation of compromised white matter integrity. Increases in MD and RD have been linked to demyelination of white matter tracts in histological studies [26], while increases in DA have been shown to be linked to axonal damage [27]. Both types of atrophy have been demonstrated to occur in Alzheimer's disease [28], consistent with the effects observed in the AD patients of present study. Strong effects were particularly evident in the parietal tracts of AD patients, yielding a high classification accuracy of 97.19%, with equivalently high sensitivity and specificity statistics. To our knowledge, this is the first study to demonstrate that posterior parietal commissural tracts of the CC splenium are a strong classifier of AD. Commissural parietal tract information could be included as features in predictive algorithms to classify AD in future initiatives. The majority of MCI patients were also correctly categorized using parietal tract information (specifically the parameters MD and RD) with a lower accuracy of 74.97%, suggesting that a sizeable portion of patients are exhibiting this marker at early prodromal stages of the disease. Future longitudinal research on MCI is needed to examine whether this could constitute a predictive marker for AD. Our previous study [21] has shown that normal ageing is associated with reductions in commissural parietal tract integrity of the CC splenium. Altered commissural parietal tract integrity is therefore not specific to AD, and the deterioration of integrity in AD likely reflects an acceleration of the deterioration observed in normal ageing.

In the segmented analysis, AD patients had higher occipital and temporal FA and lower temporal RD than controls, which are consistent with an interpretation of higher integrity in the AD group. The FA metric can be difficult to interpret because FA is mathematically constructed from a combination of the other diffusion parameters [29]. Increased FA may reflect compromised RD or increased DA [30], which applies here to the increased FA and reduced DA of temporal commissural tracts in the AD group. It seems unlikely that AD patients are experiencing significantly improved temporal tract axonal integrity compared to healthy counterparts. However, to our knowledge this is the first study that has considered temporal commissural tracts of the CC splenium in isolation. Replication of this finding is necessary to draw conclusions from this seemingly incompatible finding.

The present study benefitted from samples of MCI and AD patients recruited in a clinical setting, in which expert clinical judgements about symptom aetiology were available to categorise individuals into the respective study groups. Additionally, the groups were carefully matched to avoid confounding effects of age and sex. The DTI tractography method itself is associated with various limitations. Anisotropy cannot be correctly estimated at voxels where independent DTI tracts diverge [31]. However, commissural tracts of the midsagittal CC are unidirectional and uninfluenced by crossing fibres [32], and therefore our analysis of the segmented tract bundles will have avoided any influence of crossing tracts. Diffusion tensor parameters may also be influenced by factors such as streamline count [25] and the diameter and packing density of the anatomical fibres [33]. In the present study we attempted to control for group differences in streamline count (tract density) in our statistical analysis. Quantification of axon diameter and packing density were not accessible using the DTI method. Although it is unknown if AD modulates these features, the group differences in diffusion tensor scalars observed in this study may reflect underlying group differences in fibre diameter or packing density. To preserve statistical power, we did not examine group differences in the left and right hemisphere projections of the CC tract bundles. Fibres of the CC are naturally asymmetrical, although this may be influenced by factors like sex, handedness and individual differences [17,34,35]. Given that asymmetric neurodegeneration in AD has been observed [36], left or right tract segments could potentially be differentially affected by

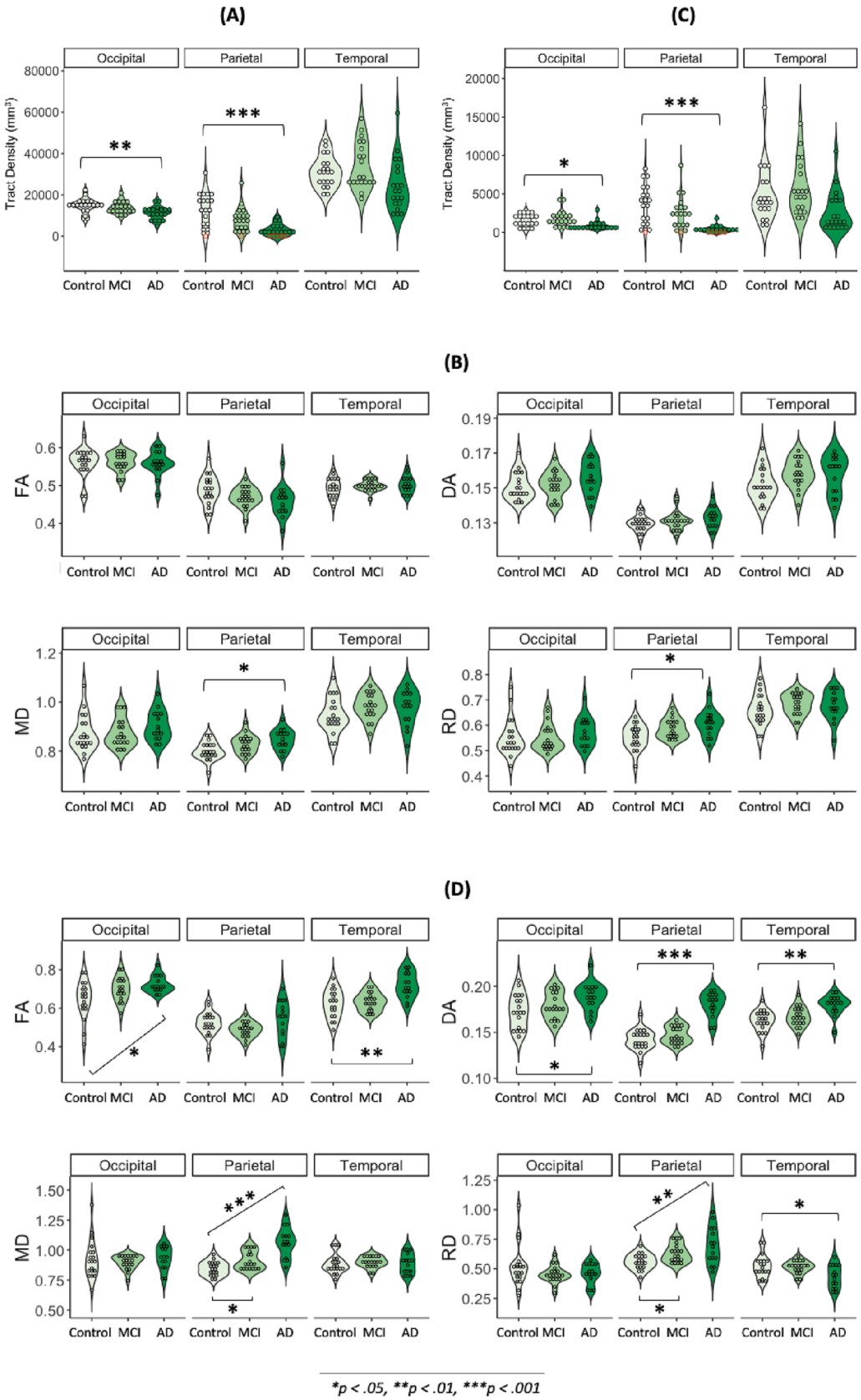

Fig. 1. **(A)** Violin plots illustrating the distribution of approximate tract density in Control, MCI and AD individuals across full occipital, parietal and temporal splenium bundles. **(B)** Violin plots illustrating the distribution of FA, DA, MD and RD values across full occipital, parietal and occipital splenium bundles. **(C)** Violin plots illustrating the distribution of approximate tract density across segmented occipital, parietal and temporal splenium bundles. **(D)** Violin plots illustrating group distributions in diffusion tensor metrics across occipital, parietal and occipital splenium segments. Circles represent individual data points. Red circles (n = 7) represent a value of zero, indicating the absence of tracts from DTI tractography.

Table 1
Group comparisons of **(A)** full bundle tract densit, **(B)** full bundle diffusion tensor metrics, **(C)** segmented bundle tract density, and **(D)** segmented bundle diffusion tensor metrics.

			Control vs. MCI				Control vs. AD			
	ROI	*Metric*	*F*	*p*	p_{FDR}	*np2*	*F*	*p*	p_{FDR}	*np2*
(A)	Occipital	Density	1.33	0.257	0.308	0.030	12.83	0.001	0.003	0.250
	Parietal	Density	3.91	0.055	0.083	0.090	22.95	0.000	0.000	0.380
	Temporal	Density	0.95	0.336	0.336	0.020	4.25	0.046	0.083	0.100
(B)	Occipital	FA	0.02	0.888	0.917	0.007	0.06	0.806	0.917	0.042
		MD	0.01	0.917	0.917	0.005	2.05	0.162	0.299	0.001
		DA	0.24	0.630	0.756	0.001	3.41	0.074	0.178	0.035
		RD	0.02	0.899	0.917	0.010	0.95	0.338	0.477	0.006
	Parietal	FA	4.03	0.052	0.157	0.022	5.78	0.022	0.117	0.003
		MD	5.53	0.024	0.117	0.116	12.36	0.001	0.033	0.180
		DA	1.44	0.237	0.405	0.092	4.31	0.046	0.157	0.231
		RD	6.04	0.019	0.117	0.083	10.34	0.003	0.036	0.078
	Temporal	FA	0.69	0.413	0.551	0.007	1.26	0.270	0.405	0.125
		MD	3.71	0.062	0.166	0.127	1.35	0.254	0.405	0.025
		DA	5.17	0.029	0.117	0.153	2.69	0.111	0.242	0.080
		RD	2.08	0.159	0.299	0.087	0.47	0.499	0.630	0.001
(C)	Occipital	Density	0.81	0.374	0.449	0.170	9.20	0.004	0.013	0.195
	Parietal	Density	2.18	0.148	0.222	0.832	28.39	0.000	0.000	0.428
	Temporal	Density	0.56	0.457	0.457	0.981	4.96	0.032	0.064	0.115
(D)	Occipital	FA	3.94	0.055	0.110	0.108	8.09	0.008	0.023	0.215
		MD	0.41	0.524	0.662	0.005	0.06	0.801	0.853	0.002
		DA	1.69	0.203	0.287	0.069	7.60	0.010	0.026	0.141
		RD	2.50	0.123	0.210	0.059	1.69	0.203	0.287	0.084
	Parietal	FA	4.49	0.041	0.090	0.079	0.71	0.406	0.541	0.047
		MD	8.77	0.005	0.019	0.163	45.23	0.000	0.000	0.407
		DA	2.52	0.121	0.210	0.060	79.63	0.000	0.000	0.591
		RD	9.53	0.004	0.016	0.168	11.45	0.002	0.009	0.115
	Temporal	FA	0.26	0.615	0.703	0.014	20.11	0.000	0.001	0.266
		MD	0.29	0.593	0.703	0.008	0.00	0.973	0.973	0.003
		DA	1.88	0.179	0.286	0.062	20.05	0.000	0.001	0.326
		RD	0.05	0.818	0.853	0.003	6.86	0.014	0.033	0.102

ageing and Alzheimer pathology. Future work could benefit from examining lateralisation effects in healthy older adults and individuals with AD symptoms.

To conclude, this study is the first to indicate that disruption of the parietal commissural tracts of the CC splenium is a highly predictive feature of AD, and moderately indicative of MCI. Further work is necessary to determine the functional specificity of interhemispheric parietal white matter tracts of the CC splenium, which according to the literature are a largely understudied pathway of the brain. Future investigations that classify AD patients from DTI scans would benefit from segmentation of CC tracts, with a focus on parietal interhemispheric tract parameters.

Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

We confirm the manuscript is original, not previously published, and not under concurrent consideration elsewhere. Participants were treated in accordance with the Declaration of Helsinki. We confirm that all authors have reviewed the contents of the manuscript, approved its contents, and validated the accuracy of the data.

CRediT authorship contribution statement

Jean-Francois Delvenne: Funding acquisition, Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Brian Scally:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft. **Melanie Rose Burke:** Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix 1. . Demographic characteristics of NACC sample

	Control ($n = 20$)	MCI ($n = 20$)	AD ($n = 20$)	p value
Age (years), mean (SD)	75.45 (3.80)	75.45 (3.91)	75.95 (3.72)	= 0.892
Education (years), mean (SD)	15.80 (3.24)	15.00 (3.08)	14.7 (2.70)	= 0.495
Gender, Female (n (%))	10 (50.0)	10 (50.0)	9 (45.0)	= 0.938
Race, White (n (%))	20 (100.0)	20 (100.0)	20 (100.0)	> 0.999
Handedness, Right-handed (n(%))	19 (95.0)	17 (85.0)	18 (90.0)	= 0.587
MMSE, mean (SD)	29.15 (0.99)	25.68 (2.75)	21.85 (3.70)	**< 0.001**
Global CDR® *				**< 0.001**
0.0 = no impairment (n (%))	17 (85.0)	0 (0.0)	0 (0.0)	
0.5 = questionable impairment (n (%))	3 (15.0)	20 (100.0)	9 (45.0)	
1.0 = mild impairment (n (%))	0 (0.0)	0 (0.0)	11 (55.0)	

* Clinical Dementia Rating. p value (obtained though one-way ANOVA tests) is highlighted in bold when it is below 0.05.

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