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## RESEARCH ARTICLE

# Structural and functional connectivity in tau mutation carriers: from presymptomatic to symptomatic frontotemporal dementia

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**Abstract**

**INTRODUCTION:** Microtubule-associated protein tau (*MAPT*) mutations cause frontotemporal dementia (FTD), characterised by behavioural, language, and motor impairments due to brain connectivity disruptions. We investigated structural and functional connectivity in 86 mutation carriers and 272 controls to map connectivity changes at different disease stages.

**METHODS:** The CDR Dementia Staging Instrument plus National Alzheimer's Coordinating Center (NACC) Behaviour and Language domains (CDR plus NACC FTLD)

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stratified carriers into three groups: asymptomatic, prodromal, and symptomatic. We extracted measures of cortical thickness, white matter integrity, and functional connectivity, which were compared between each carrier group and controls using linear mixed models.

**RESULTS:** Early isolated functional disruptions in salience/visual networks were present in asymptomatic carriers, along with anterior cingulate gray matter reductions. In prodromal carriers, functional changes extended to other networks, with additional structural damage in temporal poles/cingulate.

**DISCUSSION:** This study shows that functional networks likely drive lifelong compensation for a genetically determined disease, manifesting clinically when structural damage reaches a critical threshold. This supports connectivity measures as potential biomarkers for *MAPT*-related neurodegeneration.

#### KEYWORDS

functional connectivity, genetic frontotemporal dementia, graph analysis, gray matter, macroscale organization, *MAPT*, mutation, neurodegeneration, tau, tau pathology, white matter

#### Highlights

- Our findings reveal the progressive and staged nature of structural and functional connectivity alterations in *MAPT* mutation carriers, with distinct patterns at each disease stage.
- In asymptomatic carriers, we identified early functional connectivity alterations in salience and visual networks, despite preserved white matter and only subtle gray matter atrophy. These appear to represent both response to pathology and possible compensatory mechanisms.
- In prodromal carriers, functional connectivity alterations were accompanied by structural damage, including cortical atrophy and white matter tract disruptions, in regions directly connected to early-affected networks.
- The sequential progression, from functional connectivity changes to structural degeneration, aligns with the hypothesis that tau propagates along axonal connections, disrupting neural network integrity before measurable atrophy occurs.
- We propose a theoretical data-driven model of biomarker evolution in *MAPT* mutation carriers, highlighting functional disruptions as early indicators and structural damage as a later-stage hallmark.
- These connectivity biomarkers have the potential to inform therapeutic strategies and clinical trial design.

## 1 | BACKGROUND

Many mutations in the microtubule-associated protein tau (*MAPT*) gene are pathogenic and known to lead to frontotemporal dementia (FTD), neurodegenerative conditions primarily affecting behaviour, language, and/or motor function.<sup>1,2</sup> *MAPT* mutation carriers often develop the behavioural variant of FTD (bvFTD), characterised by behavioural and personality deterioration, but also other clinical manifestations such as corticobasal syndrome (CBS), progressive supranu-

clear palsy (PSP), or an Alzheimer's-like syndrome.<sup>2</sup> Subjects with *MAPT* mutations typically exhibit an earlier age of symptom onset compared to carriers of other gene mutations like expansions in C9 open reading-frame 72 (*C9orf72*) or progranulin (*GRN*), sometimes as early as in the second decade of life.<sup>3-5</sup>

Neurodegenerative syndromes like FTD are thought to reflect the disruption of large-scale neuronal networks, with both structural and functional connectivity changes reported in patients.<sup>6-17</sup> Research suggests that the progression of these diseases may arise from the

propagation of pathological processes along anatomical and functional brain connectivity pathways.<sup>18-21</sup> A key challenge in the field is understanding how tau pathology spreads from its initial site of aggregation. Some studies propose that tau aggregates propagate to neighbouring brain regions,<sup>22</sup> while others suggest that tau spreads along synaptically connected networks.<sup>23</sup>

Although several studies have explored connectivity changes in *MAPT* mutation carriers, research is often limited by small sample sizes, and few studies have examined both structural and functional connectivity simultaneously. This gap hinders a comprehensive understanding of these two types of connectivity and their changes at different disease stages. Some evidence suggests that in *MAPT* mutation carriers, functional connectivity changes in frontotemporal circuits may precede structural atrophy.<sup>9,24</sup> Metabolism studies also highlight altered connectivity before detectable structural neurodegeneration occurs.<sup>25-27</sup> These early functional changes have also been reported to show patterns of change opposite to those seen in patients, possibly reflecting synaptic dysfunction related to tau pathology or compensatory mechanisms, suggesting potential as biomarkers for disease progression.<sup>26,28</sup>

The primary aim of this study was to identify which connectivity pathways become altered and when during the disease course in *MAPT* mutation carriers, shedding light on the molecular processes underlying neurodegeneration. Structural connectivity was assessed via cortical thickness and white matter (WM) tract integrity, while functional connectivity was examined through graph theory measures (local and global) and macroscale gradients of functional networks. Furthermore, we stratified *MAPT* mutation carriers into three groups, accounting not only for asymptomatic versus symptomatic status but also for the "grey zone" representing the transitional phase between these stages, defined here as "prodromal." Consistent with the existing literature, we hypothesised that changes in functional networks would be detectable from the earliest presymptomatic stages, whereas structural alterations would be more closely linked to symptom onset. Understanding these changes may enhance our knowledge of FTD pathology progression and contribute to the identification of biomarkers for early diagnosis, accurate staging, and effective disease monitoring.

## 2 | METHODS

### 2.1 | Participants

We included controls ( $n = 272$ ) and *MAPT* mutation carriers ( $n = 86$ ) from the sixth data freeze in the GENFI study. These participants completed a baseline visit between January 2012 and January 2021 across 24 centers in the United Kingdom, Canada, Italy, the Netherlands, Sweden, Portugal, Germany, France, Spain, and Belgium. The study was approved by each local ethics committees, written informed consent was obtained from all participants, and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Participants were screened and genotyped at their local sites. *MAPT* mutations included mutations in intron 10 (IVS10+14, IVS10+15A > C,

### RESEARCH IN CONTEXT

- 1. Systematic review:** This study builds on a growing body of literature investigating the neural correlates of tau-related neurodegeneration, specifically in the context of *MAPT* mutations associated with FTD. Neurodegeneration such as that involved in *MAPT*-related FTD involves the disruption of large-scale neuronal networks, with the propagation of pathological processes occurring along anatomical and functional brain connectivity pathways. A review of prior work informed the selection of advanced structural and functional imaging approaches and guided the definition of a well-characterised cohort of *MAPT* mutation carriers to better understand the mechanisms of pathology progression by identifying which connectivity pathways become altered and when during the disease course.
- 2. Interpretation:** Our findings demonstrate that functional network alterations emerge early in the disease process, preceding or co-occurring with structural damage in *MAPT*-associated FTD. These results support a model in which tau pathology disrupts large-scale brain networks early on, with subsequent structural degeneration reflecting a progression of these functional abnormalities. Additionally, the data suggest a dynamic interplay between pathological changes and potential compensatory mechanisms. Together, these insights highlight the importance of both functional and structural connectivity biomarkers in improving early diagnosis, disease staging, and therapeutic monitoring in tauopathies.
- 3. Future directions:** While clinical trials are under way for several forms of genetic FTD, *MAPT* mutation carriers remain underrepresented in therapeutic development efforts. Future research must prioritise the validation of robust and reliable biomarkers specifically tailored to this population. Longitudinal studies with larger cohorts are needed to confirm the temporal sequence of network changes and to assess their predictive value for clinical progression. Additionally, future trials will benefit from identifying biomarkers that are not only sensitive to disease onset and progression but also responsive to therapeutic intervention, thereby accelerating the path toward targeted treatment strategies for tauopathies.

IVS10+16, IVS10+16C > T, IVS10+3G > A, IVS10+16) as well as exonic missense mutations (G272V, L266V, L315R, P301L, P397S, Q351R, R406W, S320F, S356T). GENFI has strict eligibility criteria that includes only the inclusion of participants with confirmed pathogenic mutations. The distribution of mutations across our *MAPT* carrier groups is detailed in Table S1. All participants underwent a standard-

**TABLE 1** Demographic and neuropsychological details of sample studied, with values presented as mean ± standard deviation, unless otherwise noted.

Demographic data	MAPT carriers						Controls
	0 = asymptomatic		0.5 = prodromal		1 to 3 = symptomatic		
FTLD-CDR global score							
N	47		16		23		272
Sex ratio F:M	28:19		09:07		08:15		163:118
Age (years)	39.7 ± 11.0	0.003	42.2 ± 11.5	n.s.	56.4 ± 10.0	0.0001	45.8 ± 13.0
Education (years)	14.6 ± 3.3	n.s.	14.3 ± 2.4	n.s.	14.1 ± 3.4	n.s.	14.5 ± 3.4
MMSE	28.3 ± 6.1	n.s.	26.7 ± 7.4	n.s.	23.0 ± 7.1	<0.0001	28.9 ± 4.1
<i>Neuropsychological data</i>							
Benson figure recall	12.5 ± 3.9	n.s.	12.3 ± 5.0	n.s.	6.1 ± 4.8	<0.0001	12.9 ± 3.5
Camel and cactus	28.0 ± 8.2	n.s.	29.7 ± 2.6	n.s.	25.1 ± 3.9	<0.0001	29.3 ± 5.8
Trail Making Test A time	23.1 ± 10.3	n.s.	23.4 ± 5.4	n.s.	41.2 ± 17.1	<0.0001	26.6 ± 12.8
Trail Making Test B time	53.8 ± 23.4	0.03	59.1 ± 23.5	n.s.	133.1 ± 71.8	<0.0001	62.2 ± 33.6
Boston Naming Test	27.4 ± 4.5	n.s.	27.1 ± 3.2	n.s.	16.6 ± 6.9	<0.0001	27.4 ± 4.2
FCSRT immediate free	27.7 ± 12.1	n.s.	30.3 ± 10.6	n.s.	11.1 ± 8.2	<0.0001	30.3 ± 8.6
FCSRT immediate total	40.2 ± 15.7	n.s.	43.1 ± 8.3	n.s.	25.7 ± 10.8	<0.0001	43.8 ± 9.0
FCSRT delayed free	10.5 ± 4.9	n.s.	10.8 ± 4.8	n.s.	4.1 ± 3.9	0.0001	11.7 ± 3.4
FCSRT delayed total	13.4 ± 5.4	n.s.	14.5 ± 3.2	n.s.	9.3 ± 4.1	<0.0001	15.0 ± 3.1
Stroop ink time	47.0 ± 20.2	n.s.	46.0 ± 9.8	n.s.	85.0 ± 35.8	0.001	50.4 ± 15.8
Verbal fluency animals	23.3 ± 7.4	n.s.	23.4 ± 5.8	n.s.	13.4 ± 6.2	<0.0001	23.7 ± 6.7
Verbal fluency F	13.8 ± 5.7	n.s.	14.8 ± 4.7	n.s.	9.0 ± 5.3	0.0002	13.4 ± 5.2
Verbal fluency A	12.4 ± 5.3	n.s.	12.7 ± 4.8	n.s.	7.1 ± 4.6	<0.0001	12.3 ± 4.9
Verbal fluency S	13.7 ± 5.8	n.s.	16.6 ± 6.0	0.04	9.4 ± 4.0	0.0002	13.6 ± 5.6
miniSEA	23.1 ± 8.1	n.s.	24.5 ± 2.9	n.s.	19.1 ± 7.0	0.01	25.1 ± 4.7

The column to the right of the values is the result of statistical comparisons with control group; the *p* value is reported if there was no significant difference; n.s. is reported.

Abbreviations: FCSRT, Free and Cued Selective Reminding Test; FTLD-CDR, Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Behaviour and Language domains; MAPT, microtubule-associated protein tau; n.s., non-significant.

ised clinical assessment as described previously,<sup>29</sup> including the CDR Dementia Staging Instrument plus National Alzheimer's Coordinating Center (NACC) Behaviour and Language domains (CDR plus NACC FTLD), hereafter referred to as FTLD-CDR,<sup>30</sup> a measure of disease severity from which a global score can be calculated. The global score was used in this work to stage mutation carriers, with those having a score of 0 being considered asymptomatic, 0.5 as prodromal, and 1, 2, or 3 as symptomatic. We compared demographic details and neuropsychological test scores across multiple cognitive domains between each carrier group and controls, using chi-squared tests for sex and Kruskal-Wallis followed by Mann-Whitney U tests for continuous variables. Our sample's characteristics are summarized in Table 1.

## 2.2 | Neuroimaging sequences

Analogous imaging sequences were acquired on 3T magnetic resonance imaging (MRI) scanners at each GENFI site accommodating different manufacturers. A summary of the different scanners used and the specific protocol parameters for each can be found in Table S2.

For anatomical images, T1-weighted scans were acquired using a magnetisation prepared rapid acquisition gradient echo pulse sequence (MPRAGE). T2\*-weighted echo-planar imaging (EPI) pulse sequences for resting-state functional MRI (fMRI) were acquired for functional imaging. Participants were asked to lie with their eyes closed, without falling asleep, during the resting-state acquisition run. Finally, diffusion-weighted scans were acquired using single-shell diffusion encoding with a b-value of 1000 s/mm<sup>2</sup> and 64 diffusion directions. Data were collected using single-shot spin-echo echo-planar imaging (SE-EPI) with interleaved acquisitions of five non-diffusion-weighted (b = 0) images.

## 2.3 | Gray matter analysis

### 2.3.1 | Preprocessing

T1 scans that passed visual quality inspection were processed using FreeSurfer version 7.1.1. This pipeline performs cortical surface extraction, segmentation of subcortical structures, cortical thickness esti-

mation, spatial normalisation onto the FreeSurfer surface template (FsAverage), and parcellation of cortical regions based on different atlases.<sup>31</sup> We ran the recon-all cross-sectional analysis using Clinica's t1-freesurfer pipeline.<sup>32</sup> FreeSurfer segmentation outputs were each visually inspected for serious errors. When serious errors occurred, or when FreeSurfer crashed without providing outputs and this was not fixed by repeated attempts, FreeSurfer analyses of those scans were omitted. No manual correction of FreeSurfer segmentations was performed.

### 2.3.2 | Cortical thickness extraction

Gray matter (GM) thickness values were generated using the recon-all cross-sectional approach, which generated values across 327,684 vertices of the cortex, with a full width at half maximum of 20. FreeSurfer is a surface-based analysis (SBA), meaning that for each vertex, cortical thickness is calculated as the mean distance between vertices of a corrected, triangulated, estimated GM/WM surface and GM/cerebrospinal fluid (CSF) (pial) surface.<sup>33</sup>

## 2.4 | WM connectivity analysis

### 2.4.1 | Preprocessing

Diffusion-weighted images (DWI) were preprocessed using an in-house pipeline that combines state-of-the-art tools (DWEZ).<sup>34</sup> The overall steps involved, first, concatenation and denoising of the DWI volumes, followed by removing Gibbs ringing artifacts using MRtrix3 tools. Then we performed motion correction with FSL's mcflirt, extracted a mean  $b = 0$  image, and stripped the skull from the T1 image using SynthStrip, a Python singularity wrapper. Next, using Synb0-DISCO, a deep-learning tool, we generated a synthetic undistorted  $b = 0$  volume, which was input into FSL topup for DWI distortion correction. Finally, a new mean  $b = 0$  was extracted from the undistorted DWI volumes from which SynthStrip created a new brain mask. Tissue response, fiber orientation distribution, and tissue segmentation on the aligned DWI to T1w scan, followed by anatomical constrained tractography (ACT), were performed using MRtrix3.

Further details regarding this pipeline can be found in the openly available repository: <https://github.com/Vince-LD/DWEZ>.

### 2.4.2 | Segmentation and data extraction

To extract WM bundles, we used TractSeg, a Python-implemented tool.<sup>35</sup> This applies a novel convolutional neural network-based approach that directly segments WM tracts using a fiber orientation distribution function. As opposed to atlas-based methods, this pipeline does not assume a common anatomy between subjects and therefore relies on each individual's anatomical structure. For every subject, we obtained segmentation of 21 WM tracts of interest based on previous evidence: bilateral uncinate, bilateral inferior longitudi-

nal fascicle, bilateral cingulum, bilateral arcuate fascicle, and bilateral superior longitudinal fascicle divided into three bundles and the corpus callosum divided into seven sections (rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium). Figure 1 is a schematic representation of each tract segmented. Moreover, each tract obtained was divided into 100 segments. Thus, for each position along all tracts, we extracted measures of WM integrity, including fractional anisotropy (FA), as well as mean diffusivity, radial diffusivity (RD), and axial diffusivity.

Further details regarding the TractSeg toolbox can be found in Wasserthal et al.<sup>35</sup> or in the openly available repository: <https://github.com/MIC-DKFZ/TractSeg>. Out of the total sample, 46 controls, 17 asymptomatic, three prodromal, and five symptomatic MAPT carriers were not included in the WM analyses because they did not have a diffusion scan or the data extraction process failed.

## 2.5 | Functional connectivity analysis

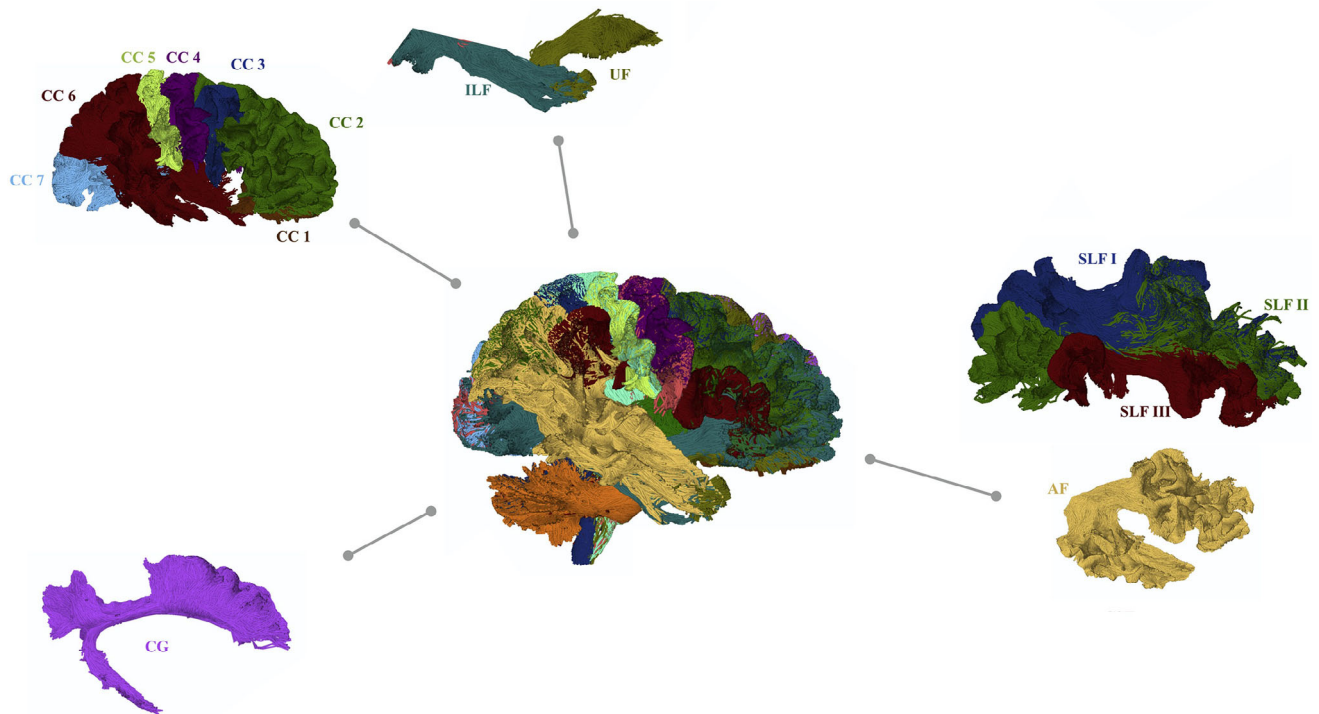
### 2.5.1 | Preprocessing

T1 scans and fMRI resting-state time series for all participants were preprocessed using fMRIPrep 21.0.1 27, an automated Nipype-based preprocessing pipeline for fMRI data implemented in Python, which uses tools from software packages including FSL, ANTs, FreeSurfer, and AFNI.<sup>36</sup> Briefly, the pipeline included bias field correction, skull stripping, brain tissue segmentation, slice time correction, correction for head motion parameters, co-registration to corresponding structural image, and non-linear spatial normalisation to MNI space. Further details on anatomical and functional data preprocessing can be found in [Supplementary Methods](#).

To remove physiological and other sources of noise from the fMRI time series, fMRI confounds generated with fMRIPrep were loaded using the Python package load\_confound (version 0.6.4). Six motion parameters, signals estimated from CSF and WM, their derivatives, quadratic terms, and squares of derivatives were regressed out from functional data separately for each run. The rs-fMRI data from each subject was smoothed with a full width at half maximum 6 mm Gaussian kernel and temporally bandpass filtered in the 0.01 to 0.1 Hz frequency range. Resting-state time series with a mean framewise head displacement of more than 0.5 were excluded, as was done in previous work with similar patient populations.

### 2.5.2 | Parcellating and data extraction

Resting-state time series were spatially parcellated according to the Schaefer atlas (400 parcels across seven functional networks).<sup>37</sup> The Schaefer atlas was chosen for its basis in resting-state functional networks. Using the Nilearn connectome Python package, after standardising the time series, we computed each subject's correlation matrix applying the Ledoit-Wolf estimator to adjust for the small number of volumes used and ensure matrix stability for downstream analyses. We then used the bct package implemented in Python to



**FIGURE 1** Tracts segmented and extracted using the automated TractSeg tool. For tracts existing in the left and right hemispheres, only the right one is shown. Adjusted from Wasserthal et al.<sup>35</sup> AF, arcuate fascicle; CC, corpus callosum (rostrum [CC 1], genu [CC 2], rostral body [CC 3], anterior midbody [CC 4], posterior midbody [CC 5], isthmus [CC 6], splenium [CC 7]); CG, cingulum; ILF, inferior longitudinal fascicle; SLF, superior longitudinal fascicle (I, II, III); UF, uncinata fascicle.

apply a proportional threshold, retaining only the top 17% of strongest connections (by absolute value) in each functional connectivity matrix. The thresholded matrices were then binarised, creating binary masks of the strongest connections. These binary masks were used to filter each corresponding correlation matrix, isolating only the strongest connections for further analysis.

For each parcel of the Schaefer atlas from the binarised and filtered matrices, we extracted four graph theory metrics: two relating to the extent of connections of the parcel and two relating to graph organisational principles. First, degree and strength quantify the number and strength of connections a node (parcel in this case) has. Second, eigenvector centrality considers the centrality and number of connections of a node, while the clustering coefficient corresponds to how much of the network clusters together. These four graph metrics enabled us to assess both local and global properties, offering deeper insights into the structural and functional changes with the different resting-state networks.

Moreover, we extracted macroscale connectivity gradients by applying generalised Canonical Correlation Analysis (gCCA) to all our subjects' time series using the Python-implemented package *mvlearn* (<https://mvlearn.github.io/references/embed.html#generalized-canonical-correlation-analysis-gcca>), as was done in previous work.<sup>17,38</sup> This decomposes the functional connectome into primary components, referred to as gradients, with each gradient explaining different levels of variance in connectivity. These gradients discriminate across levels of the cortical hierarchy (i.e., sensory processing

vs higher-order cognition), whereas region-specific values along the gradient, referred to as embedding values, reflect the similarity in connectivity along the sensory-transmodal axis. Further details on the connectome gradient mapping specific pipeline can be found in [Supplementary Methods](#).

### 2.5.3 | Statistical analyses

We compared cortical thickness values between each *MAPT* carrier group and controls using separate general linear models per cortical vertex. These models were adjusted for participants' age, sex, education, total intracranial volume, and site of data acquisition. Pointwise false positives were controlled for with false discovery rate to account for the 327,684 vertices, and cluster-level multiple comparisons were controlled for with random-field theory, applying a vertex-wise cluster threshold of 0.01. Moreover, as the same control group was used in the three models, we corrected the *p* value threshold using Bonferroni ( $0.05/3 = p < 0.016$ ). We thus identified regions that showed significant reductions of GM thickness in each group compared to controls. We calculated effect sizes for each region using Cohen's *d*.

WM tract integrity metrics, graph metrics, and connectivity gradient embedding values were compared between each *MAPT* carrier group and controls using linear mixed-effects models. In each model, the metrics were the dependent variables, while network/tract, group, age, and sex were the fixed effects. Site of acquisition, subject, and

parcel/position were included as random effects. We investigated the Network/Tract  $\times$  Group interaction effect to determine which networks or tracts showed significant differences in each group compared to controls.  $P$  values were corrected for multiple comparisons using Benjamini and Hochberg for both the number of contrasts and number of networks/tracts.

Statistical analyses were performed using R version 4.3.3.

## 3 | RESULTS

### 3.1 | Participant groups

Carriers in the asymptomatic group were significantly younger than controls ( $p = 0.003$ ), while carriers in the symptomatic group were significantly older than controls ( $p = 0.0001$ ). There were no significant differences between any carrier group and controls for years in education or sex distribution ( $p > 0.05$ ). Symptomatic patients scored significantly worse compared to controls on tests spanning visual and verbal memory, processing speed, naming, semantic associations, verbal fluency, executive function, and social cognition. Asymptomatic and prodromal groups showed no significant neuropsychological test score differences compared to controls, apart from better performances in asymptomatic carriers for the Trail Making Test B time ( $p = 0.03$ ) and in prodromal carriers for verbal fluency letter S ( $p = 0.04$ ). Group averages, standard deviations, and  $p$  values compared to controls are in Table 1.

### 3.2 | Cortical thickness

In asymptomatic carriers, cortical thickness showed sparse areas of thinning in the left anterior cingulate gyrus, with low effect size. In carriers in the prodromal phase, cortical thinning was apparent in the left cingulate and left temporal pole, with medium effect size. Finally, in symptomatic carriers, cortical thinning affected bilateral temporal lobes, both lateral and mesial, left cingulate, as well as bilateral frontal lobes, with high effect sizes. Figure 2 illustrates these results on the cortical surface, and details of the statistical results are reported in Table S3.

### 3.3 | WM connectivity

No WM tracts showed alterations (in any metric) compared to controls in asymptomatic *MAPT* carriers. However, in prodromal carriers, reduced FA was identified in the rostrum of the corpus callosum, bilateral uncinate fasciculus, and left cingulum compared to controls, as well as increased RD in the left uncinate. In symptomatic *MAPT* carriers, reduced integrity as measured across several metrics was found in the anterior (rostrum, genu, rostral body, anterior midbody) and splenium of the corpus callosum, as well as bilateral uncinate fasciculus, bilateral inferior longitudinal fasciculus, and left cingulum. Figure 3 shows a summary of the results (panel A) as well as the average FA and RD val-

ues for each group along the tracts that showed early changes (panel B). The results of the model are presented in Table S4.

## 3.4 | Functional connectivity

Asymptomatic *MAPT* carriers showed significant differences in eigenvector, degree, and strength, which decreased in the salience ( $p < 0.02$ ) and increased in the visual ( $p < 0.0002$ ) network compared to controls. In prodromal carriers, this pattern was maintained (apart from visual network strength, which did not show significant differences), with further decreases within the salience network. Prodromal carriers also showed the addition of eigenvector reductions in frontoparietal ( $p = 0.001$ ) and increases in sensorimotor ( $p = 0.002$ ) networks, as well as increases in default-mode degree ( $p < 0.0001$ ). There were no significant differences in clustering coefficient for any network in asymptomatic and prodromal carriers ( $p > 0.05$ ). In the symptomatic group, several networks showed reductions across different graph metrics. Figure 4 shows a summary of the results (panel A) as well as the mean values of each metric for each group within the visual and salience networks (panel B). The results of the model are presented in Table S5.

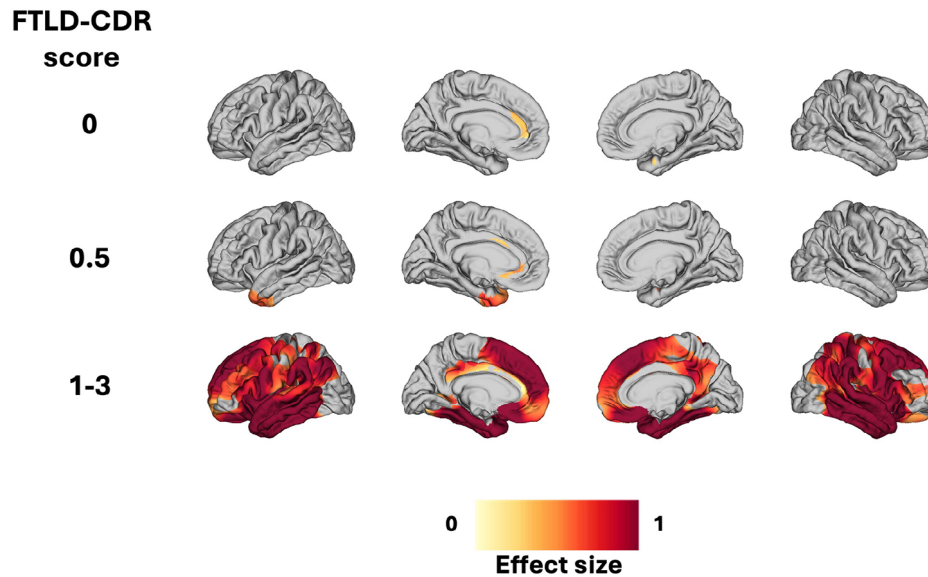
The principal gradient anchored sensorimotor areas at its positive extreme and default mode at its negative extreme, with a gradual transition from sensory to transmodal association networks similar to what was reported in previous work. Along the secondary gradient, the visual network occupied the negative extreme, while areas from the salience populated the positive end of this gradient. Figure 5 illustrates these gradients. These same gradients were reported previously using the same method and a similar population of patients with FTD.<sup>17</sup> Brain regions with the highest or lowest embedding values are at the extremes of the axis, contributing most to the latent component and having the most differentiated functional connectivity. Regions with similar embedding values have similar connectivity patterns, and those near the center (embedding value around 0) contribute less to the latent component.

Principal and secondary gradients revealed some significant differences within middle networks of the gradients in asymptomatic and prodromal groups compared to controls, but not within extreme-end networks. Both the principal and secondary gradients showed widespread differences in various networks in symptomatic *MAPT* carriers. Figure 6 presents the embedding values on the cortical surface for each *MAPT* group for each gradient. The results of the model are presented in Table S6.

## 4 | DISCUSSION

### 4.1 | Damage across different disease stages

Aligning with previous research, we found minimal GM reductions at early stages, limited to the left anterior cingulate cortex in asymptomatic carriers and left temporal pole in prodromal carriers.<sup>25,29,39–43</sup> Additionally, asymptomatic carriers showed no evidence of compro-



**FIGURE 2** Cortical thickness effect sizes (Cohen's  $d$ ) for each microtubule-associated protein tau carrier group compared to controls. FTLD-CDR score, A. Clinical Dementia Rating plus National Alzheimer's Coordinating Center Behavioural and Language domains global score.

mised diffusion in WM tracts, even when using our along-the-tract approach, which allows for the detection of localised changes within specific segments of the tracts. These results show that sparse GM atrophy precedes WM damage in the early disease stages.

Prodromal carriers showed reduced FA in the anterior corpus callosum (rostrum), bilateral uncinate fascicles, and left cingulum, alongside increased radial diffusivity in the left uncinate fascicle. These tracts are located near atrophic regions in the temporal lobes and anterior cingulate, highlighting the synergy between GM and WM changes. Notably, uncinate fascicles have been implicated in studies on presymptomatic *MAPT* carriers.<sup>39,44,45</sup> These structural changes occur in regions and tracts related to early cognitive symptoms in *MAPT* carriers: anomia, semantic and episodic memory impairments.<sup>46-49</sup> Our results show WM integrity becomes affected only in prodromal carriers, when subtle clinical changes may be present but insufficient for a diagnosis.<sup>44,45,50,51</sup> A recent study found WM changes in asymptomatic carriers; however, these results were based on a small sample and were uncorrected for multiple comparisons.<sup>52</sup> Moreover, although some previous work suggested that mean diffusivity was sensitive to early changes in *MAPT* mutation carriers,<sup>51</sup> our findings align with research highlighting the greater sensitivity of FA for detecting such early alterations.<sup>52</sup>

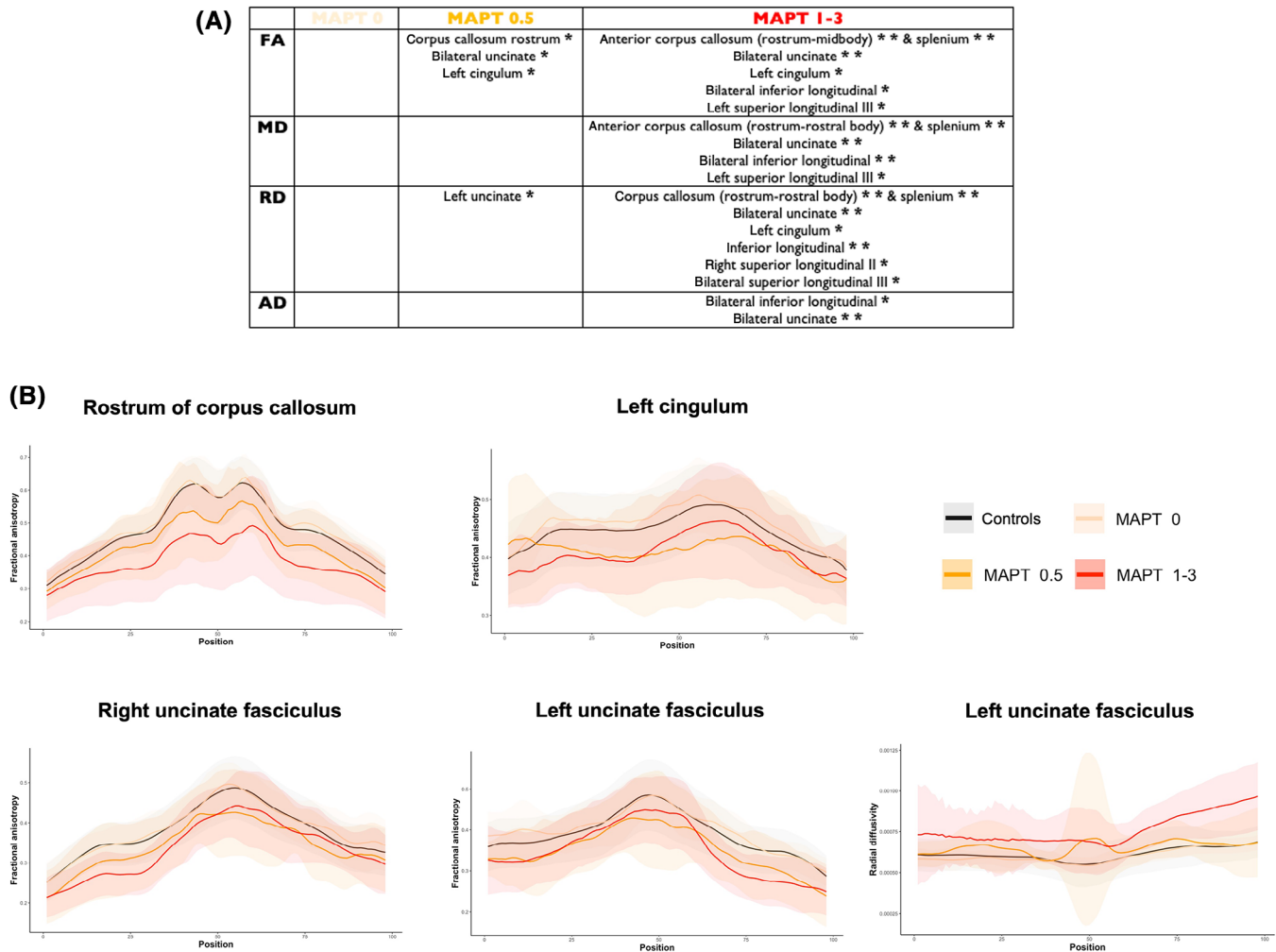
Our results in prodromal carriers support the hypothesis that tau pathology may progress via WM tracts,<sup>53</sup> where tau pathology propagates in a "prion-like" manner along connected networks.<sup>18,54</sup> *Post mortem* studies in *MAPT* mutation carriers<sup>55</sup> and animal models expressing mutant tau<sup>56</sup> confirm early WM degeneration as a key pathological feature. Interestingly, radial diffusivity changes in the left uncinate fascicle were notable in prodromal carriers in our study and showed significant increases in more tracts compared to axial or mean diffusivity in symptomatic carriers, possibly suggesting that myelin is particularly vulnerable to tau pathology. These findings align

with studies showing early WM alterations, progressing to disorganised myelinated fiber arrangements with enlarged interaxonal spaces in later stages.<sup>57,58</sup> Our results suggest myelin disruption as a critical element in the progression to bvFTD in *MAPT* mutation carriers.

Contrasting with the onset of structural connectivity changes in the prodromal stage, functional connectivity alterations were evident in asymptomatic carriers ( $n = 47$ ), with graph metrics found to be decreased in the salience but increased in the visual network. Functional connectivity changes in *MAPT* carriers, particularly in the salience network and anterior cingulate cortex, have been reported before.<sup>28,39,59</sup> PET studies further highlight early functional alterations in the anterior cingulate and insula regions,<sup>25-27</sup> which are found *post mortem* to be most affected by tau aggregation in *MAPT*-associated FTD.<sup>60</sup> Moreover, these regions align with clinical symptoms of bvFTD, involving executive dysfunction, apathy, and social cognition deficits. As graph metric alterations correlate with synaptic density, early functional connectivity changes likely reflect synaptic disruptions.<sup>61</sup> Synaptic loss accounts for functional connectivity reductions not explained by atrophy, suggesting these changes may precede myelin and axonal damage as well as GM atrophy. Together, these findings point toward a progression from early synaptic dysfunction to structural degeneration in *MAPT*-related neurodegeneration, though this warrants validation in a longitudinal sample.

## 4.2 | Neural compensation

Our study is the first to identify functional connectivity changes in visual network in presymptomatic *MAPT* carriers, despite the preserved structural integrity of the occipital lobe even in later disease stages. This may reflect connectome diaschisis, where a "lesion" induces distal connectivity changes, either increased or decreased.<sup>62</sup>



**FIGURE 3** A. Summary of tracts showing significantly different diffusion metrics in each microtubule associated protein tau (*MAPT*) carrier group compared to controls, \* $p < 0.05$ , \*\* $p < 0.005$ . FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity. B. Adjusted mean fractional anisotropy and radial diffusivity values from mixed model for each group, with shaded standard deviation, along tracts showing significant early changes in *MAPT* prodromal carriers compared to controls.

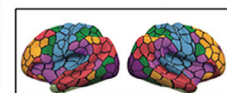
Consistent with this concept, visual network exhibited connectivity changes opposite to those observed in salience network, which aligns with expected pathology-driven alterations. In the same vein, enhanced metabolic activity in asymptomatic *MAPT* carriers, which diminishes in symptomatic stages, has been reported.<sup>26</sup> Similar visual network alterations have been observed in patients with sporadic bvFTD and primary progressive aphasia using functional connectome gradient mapping.<sup>17</sup> Such changes may arise from overexcitation due to reduced inhibitory control from affected networks, such as the salience network.<sup>11,13,63-65</sup> Alternatively, they may reflect compensatory mechanisms in response to pathology.<sup>17</sup> Despite early functional disruptions, *MAPT* carriers remained clinically asymptomatic, as highlighted by finding no differences between their cognitive test scores and those of controls (or, if so, better performances), supporting the concepts of neurodevelopmental resilience in genetic FTD<sup>66</sup> and compensatory hyperconnectivity preserving cognitive function in early disease stages.<sup>28</sup> These findings suggest that pathology-induced disruptions in certain networks may drive increased visual

network connectivity, highlighting the interplay between resilience and vulnerability in early *MAPT*-related neurodegeneration.

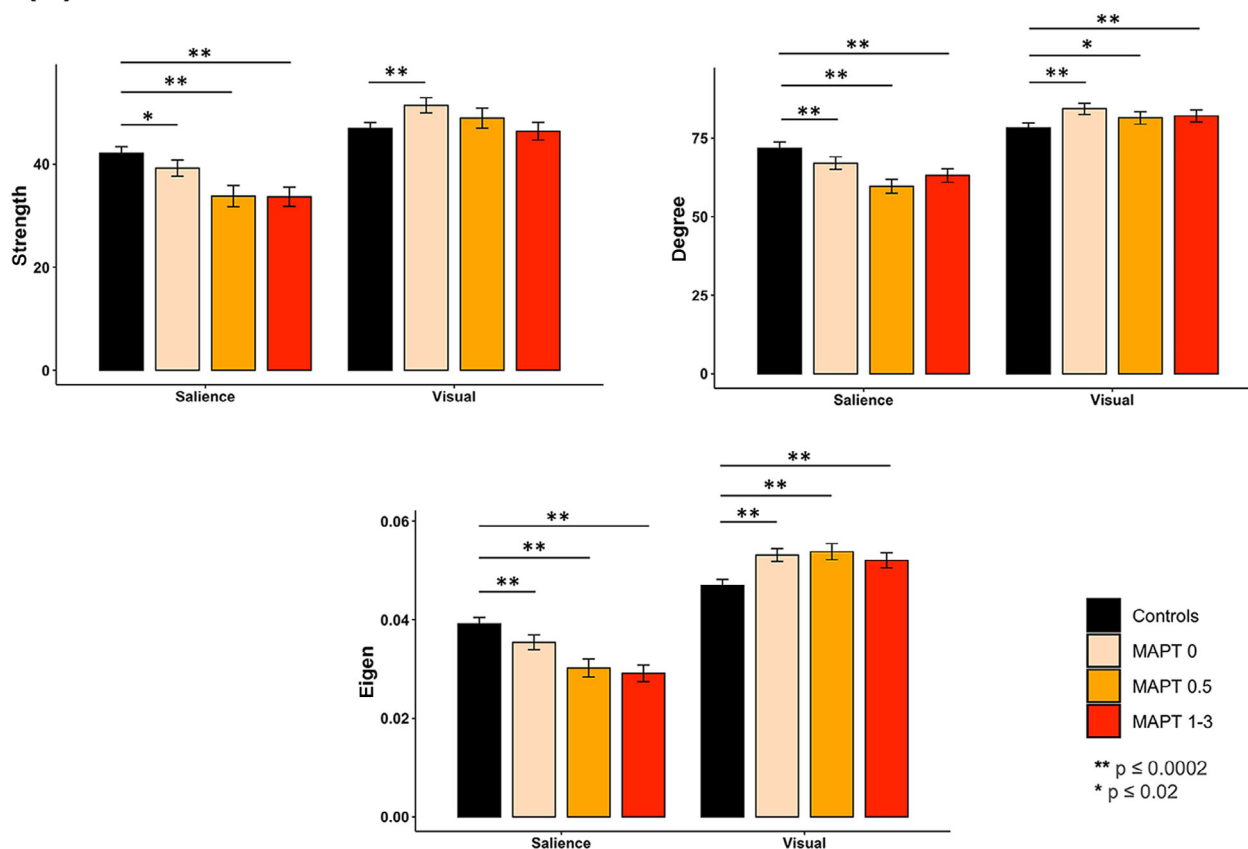
The extent to which *MAPT* mutations cause neurodevelopmental differences in human carriers remains unclear. However, it is well established that tau expression changes dynamically during neurodevelopment, with isoform expression varying across neurodevelopmental and neurodegenerative stages.<sup>67</sup> Decades ago, it was suggested that abnormal tau phosphorylation in neurodegenerative diseases, such as Alzheimer's, may result from the reactivation of pathways involved in tau phosphorylation during brain development.<sup>68</sup> The functional connectivity differences observed in our study may reflect altered "wiring" of the brain in *MAPT* mutation carriers from development, potentially representing compensatory mechanisms that delay pathological tau aggregation during early neurodevelopment.<sup>66</sup> Studying carriers at a young age could help distinguish between changes stemming from neurodevelopmental processes and those related to early neurodegeneration, providing crucial insights for developing intervention strategies for *MAPT* mutation carriers.

(A)

	<b>MAPT 0</b>	<b>MAPT 0.5</b>	<b>MAPT 1-3</b>
<b>Strength</b>	Saliency ↓ Visual ↑	Saliency ↓	Saliency ↓ Sensorimotor ↓
<b>Degree</b>	Saliency ↓ Visual ↑	Default-mode ↑ Saliency ↓ Visual ↑	frontoparietal ↓ Default-mode ↓ Saliency ↓ Sensorimotor ↓ Visual ↓
<b>Eigenvector</b>	Saliency ↓ Visual ↑	Saliency ↓ Visual ↑ Frontoparietal ↓ Sensorimotor ↑	Saliency ↓ Visual ↓ Frontoparietal ↓ Sensorimotor ↓ Dorsal attentional ↓ Default-mode ↓
<b>Clustering</b>			Sensorimotor ↓ Saliency ↓



(B)

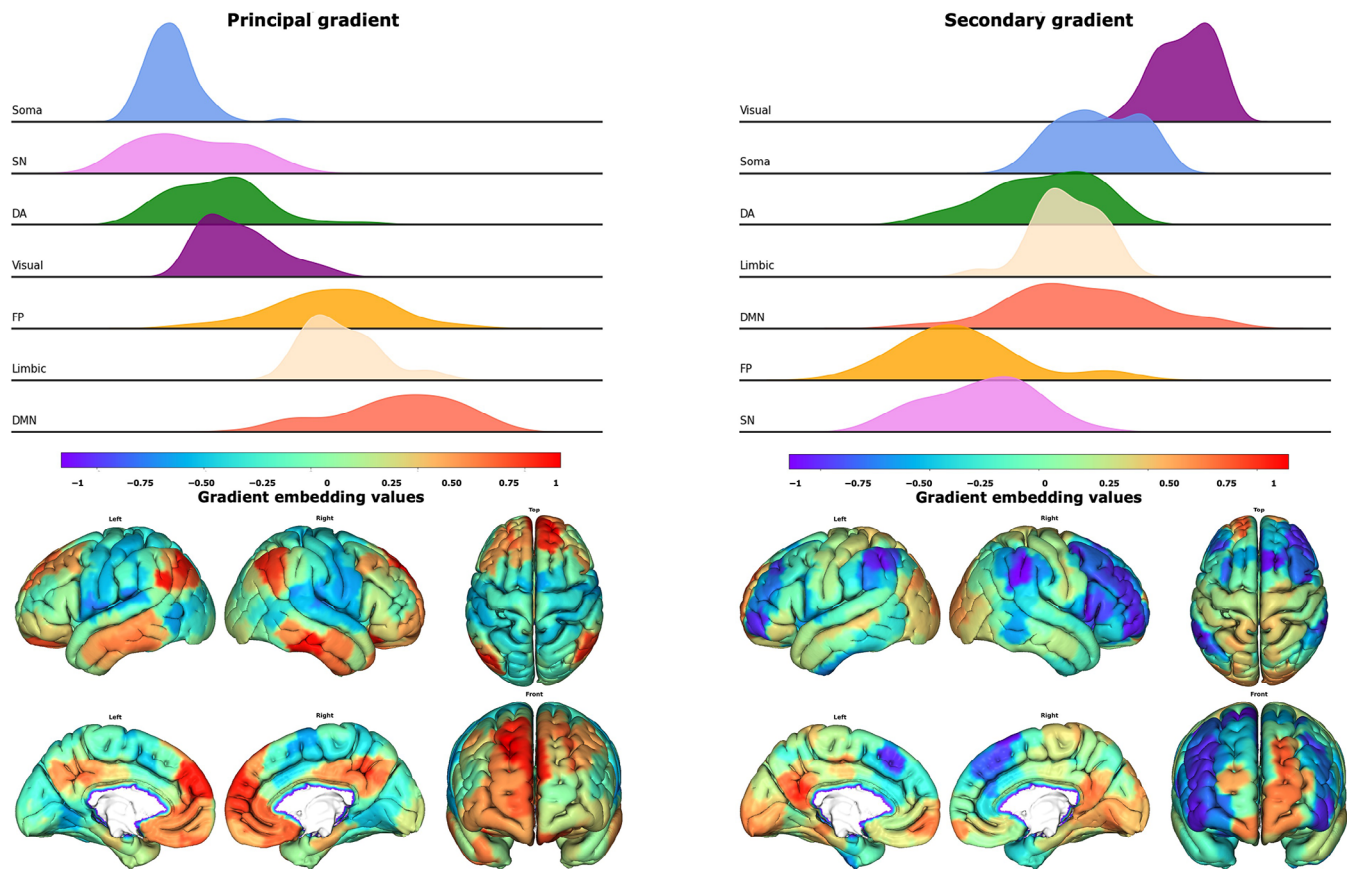


**FIGURE 4** A. Summary of networks showing significant different graph metrics in each microtubule associated protein tau (MAPT) carrier group compared to controls, with the direction of change depicted by an arrow. B. Adjusted means and standard errors from mixed model for each group and for different graph metrics within saliency and visual networks which showed early changes compared to controls.

### 4.3 | Complementary measures of functional connectivity

Our analysis showed focal functional connectivity changes from the asymptomatic stage, while global disruptions were only evident in symptomatic stages. Clustering and macroscale gradients remained

intact in asymptomatic and prodromal carriers. Specifically, no major differences were observed in the principal or secondary gradients, with preserved organisation of extreme-end networks (sensorimotor and default mode for the principal gradient, saliency and visual for the secondary gradient). This contrasts with findings in symptomatic FTD<sup>17</sup> and aligns with reports of within-network changes and intact



**FIGURE 5** Distribution of principal and secondary gradient embedding values for each network in controls and projected on cortical surface.

global organisation in presymptomatic carriers.<sup>69</sup> These results suggest global connectivity, crucial for cognitive resilience, is preserved at early stages, with structural and functional disruptions becoming widespread only at symptom onset.<sup>69,70</sup> Again, this aligns with our findings of preserved cognitive function in asymptomatic and prodromal *MAPT* mutation carrier groups.

#### 4.4 | Theoretical progression model

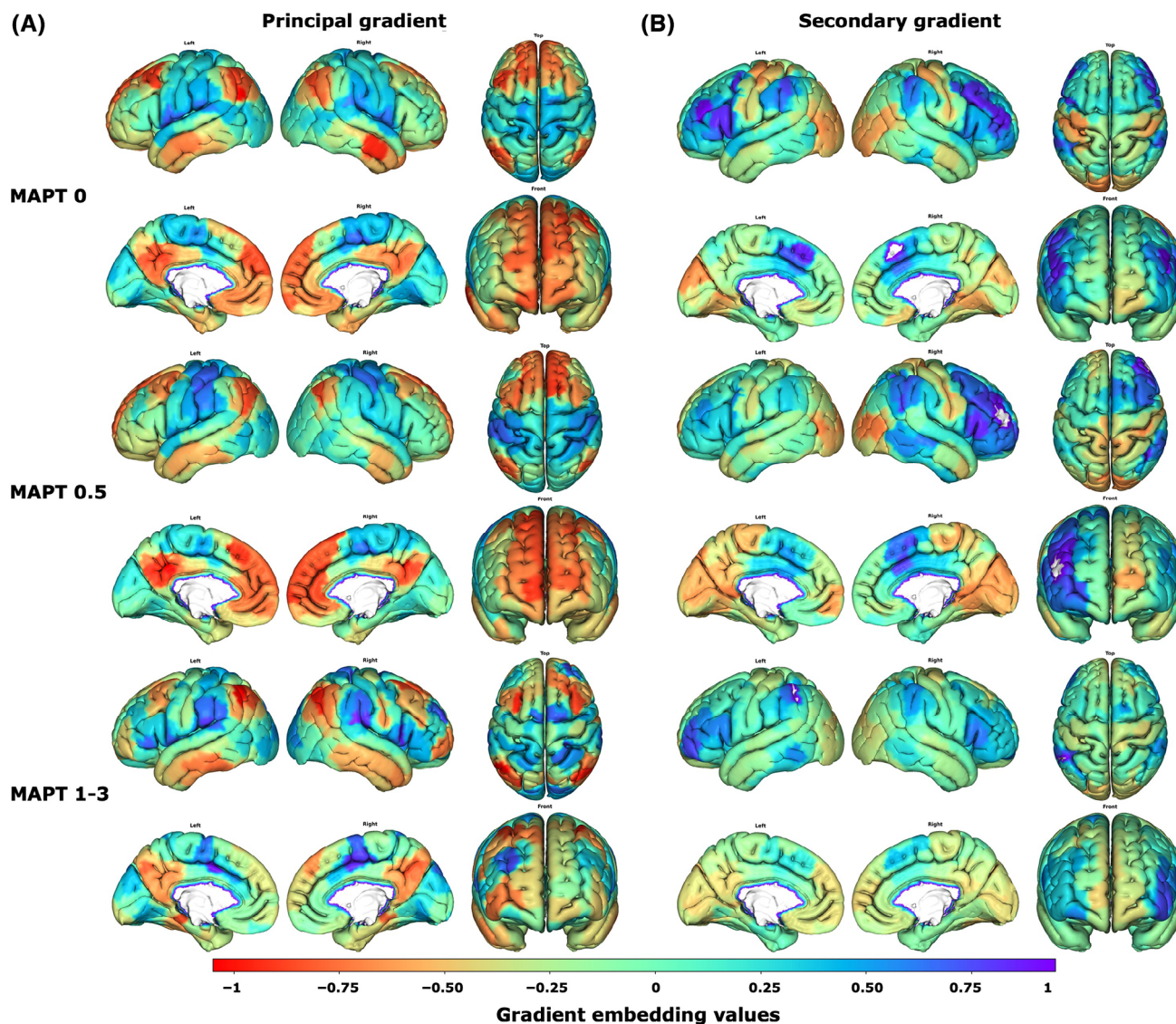
Our findings suggest a pathophysiological progression model for *MAPT* mutation carriers that begins with focal tau pathology targeting neurons within functional network hubs (anterior cingulate cortex). This leads to sparse early GM atrophy. Early functional connectivity network, related to the targeted neurons (salience network) but also those that are not (visual network), are either triggered by this pathology or serve a (compensatory) function different from that of controls, possibly since neurodevelopment stages. Network disruptions likely encourage the propagation of pathology via initially intact axonal pathways, causing demyelination and diffuse structural connectivity changes in regions connected to affected hubs. These stages align with the hypothesis of tau spreading along axonal connections,<sup>71</sup> causing functional network disruptions before widespread atrophy occurs. Very recent work in Alzheimer's disease suggests that pathological pro-

tein deposition of amyloid beta can induce hyperconnectivity between tau epicenters and posterior brain regions vulnerable to tau accumulation, with this increased connectivity mediating faster tau spreading.<sup>72</sup> This again highlights that hyperconnectivity precedes neocortical tau propagation while being instrumental in its progression.

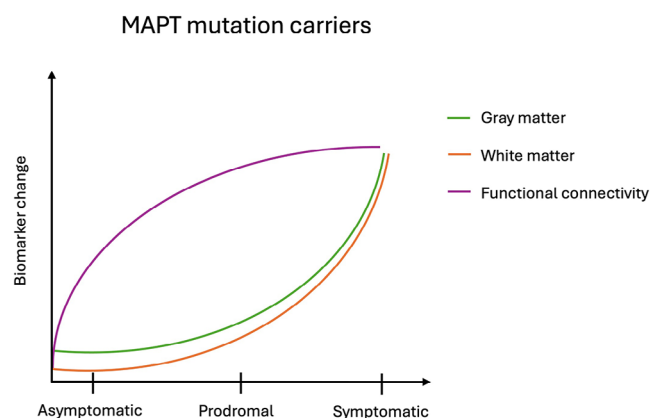
We propose a theoretical model of biomarker evolution in *MAPT* mutation carriers (Figure 7), where functional dysconnectivity emerges as an initial disease indicator, followed by structural degeneration as the disease advances. Structural connectivity disruptions become widespread in later stages, coinciding with global functional alterations. Our framework aligns with prior hypotheses,<sup>73</sup> incorporating multimodal data from the same cohort and offering robust evidence for the dynamic progression of *MAPT*-related neurodegeneration. Early focal functional changes, potentially reversible, may serve as biomarkers for monitoring treatment efficacy, while later structural alterations signify irreversible damage. Validating these biomarkers is crucial for enhancing patient stratification and evaluating disease-modifying therapies in clinical trials.

#### 4.5 | Strengths and limitations

Our study benefited from multimodal imaging to evaluate structural and functional connectivity in conjunction, a rarity in presymptomatic



**FIGURE 6** Principal and secondary gradient embedding values projected on cortical surface for each microtubule associated protein tau (MAPT) carrier group.



**FIGURE 7** Theoretical model of gray matter, white matter, and functional connectivity neuroimaging biomarker evolution in microtubule-associated protein tau-mutation carriers.

FTD research. Large sample sizes enabled precise subgrouping while avoiding underpowered groups, though the prodromal carrier group remained modest. Moreover, the large control group enabled a more accurate assessment of potential demographic influences, such as sex and age, which were unevenly distributed across the different carrier groups and were therefore included as covariates in our statistical models. Notably, we observed contrasting sex ratios: asymptomatic and prodromal carriers were predominantly female, whereas symptomatic carriers were more often male. This discrepancy was likely influenced by societal factors, as women are more frequently primary caregivers and tend to remain in this role for longer, a pattern that is well documented in dementia research.<sup>74</sup>

The study's quasi-longitudinal design provides valuable insights but cannot replace true longitudinal studies, which are essential to validate our results and refine our theoretical biomarker evolution model. Further, we did not analyse mutation-specific differences, which

are known to influence atrophy patterns.<sup>75</sup> Additionally, though both structural and functional neuroimaging modalities were included, tractography and connectomics are completely different methodologies with disparate underlying priors. Therefore, our findings cannot be directly compared. Employing multivariate multimodal methods would enhance the integration and interpretation of these findings.

## 5 | CONCLUSION

MRI biomarkers, being non-invasive, cost-effective, and suitable for longitudinal studies, hold promise for tracking or predicting disease progression and guiding therapeutic strategies. This study highlights functional connectivity changes as an early biomarker and structural changes as indicators of advanced stages. By interpreting these findings balancing pathology and compensation, we propose a model of biomarker evolution in *MAPT*-related neurodegeneration. Understanding these dynamics, whether specific to tau pathology or shared across proteinopathies, could aid in developing early interventions to preserve compensation and slow progression. In conclusion, our results highlight the relevance of investigating GM and WM structure alongside functional connectivity in genetic FTD, particularly in presymptomatic stages. Although not directly translatable to clinical use yet, these findings lay essential groundwork for future biomarker development and patient stratification.

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Local ethics committees approved the study at each site, and all participants provided written informed consent. The study was conducted according to the Declaration of Helsinki.

#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the [Supporting Information](#).

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## SUPPORTING INFORMATION

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