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Original Article

Cortical microstructure in familial frontotemporal dementia associated with MAPT, GRN, and C9orf72 pathogenic variants: Looking beyond atrophy☆

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ABSTRACT

Background: This study aimed to evaluate cortical mean diffusivity (cMD) as a sensitive biomarker for early neurodegenerative changes in familial frontotemporal lobar degeneration (FTLD) associated with C9orf72, GRN, and MAPT mutations. We compared cMD with cortical thickness (cTH) in detecting subtle microstructural alterations and examined its association with clinical severity and neurofilament light chain (NFL) concentrations.
Methods: We analyzed data from 322 participants, including symptomatic carriers of C9orf72 ($n = 85$), GRN ($n = 56$), and MAPT ($n = 58$) mutations, along with 123 healthy controls. Cortical microstructure was assessed using both cTH and cMD. Clinical severity was evaluated with the CDR plus NACC FTLD scale, and plasma NFL was measured as a marker of neuroaxonal injury.
Results: C9orf72 carriers exhibited the most widespread cortical thinning and increased cMD, while GRN and MAPT carriers showed more regionally restricted alterations. Across all mutation groups, cMD demonstrated higher sensitivity than cTH in detecting early changes. Furthermore, cMD values were significantly correlated with CDR plus NACC FTLD scores and NFL concentrations, underscoring its relevance to disease progression.
Conclusion: Cortical mean diffusivity outperforms cortical thickness in detecting early microstructural changes in familial FTLD. Its strong association with both clinical severity and neurodegeneration biomarkers highlights its potential utility for early diagnosis, disease monitoring, and individualized therapeutic strategies in FTLD.

1. Introduction

Frontotemporal lobar degeneration (FTLD) encompasses a diverse group of neurodegenerative disorders characterised by progressive shrinking of the frontal and temporal regions of the brain, leading to difficulties in behaviour, cognition, and language. FTLD includes several clinical subtypes, each distinguished by unique clinical symptoms and underlying pathology [1,2]. Genetic factors significantly shape clinical presentation and disease progression [3]. Approximately 30 % of FTLD cases are familial, commonly caused by pathogenic mutations in C9orf72 (chromosome 9 open reading frame 72), MAPT (microtubule-associated protein tau), and GRN (progranulin) [4–6]. Key pathological features of FTLD include neuronal loss, abnormal protein accumulation, synaptic dysfunction, glial activation, and inflammation [7,8]. These factors collectively cause brain structure changes at both large-scale (macrostructural) and cellular-level (microstructural).

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Table 1
Demographic and clinical data for participants.

Parameter	C9orf72	GRN	MAPT	C9 vs. GRN (*P* value)	C9 vs. MAPT (*P* value)	GRN vs. MAPT (*P* value)
N Age, years	85 48.5 (13.9)	56 55.2 (14.6)	58 42.9 (13.1)	0.03	>0.05	< 0.001
Male, no. (%)	39(45.9 %)	27 (48.2 %)	27 (46.6 %)	0.92	1.00	1.00
Education, years	15.6 (2.30)	15.5 (2.76)	15.6 (2.62)	0.99	1.00	1.00
MoCA	25.7 (11.4)	22.8 (8.16)	25.2 (5.48)	0.10	0.98	0.29
FTLD-CDR	2.79 (4.82)	3.31 (5.34)	2.00 (3.58)	0.84	0.58	0.22
NFL	18.8 (24.4)	26.0 (29.0)	9.89 (7.67)	0.10	0.03	<0.001
Healthy controls						
N	88	58	59			
Age, years	48.4 (13.4)	54.2 (13.0)	43.0 (12.9)			
Male, no. (%)	38(43.2 %)	33 (56.9 %)	27 (45.8 %)			

Abbreviations: C9orf72: C9orf72 gene mutation; GRN: Granulin gene mutation; MAPT: Microtubule-associated protein tau gene mutation; MoCA: Montreal Cognitive Assessment; FTLD-CDR: Clinical Dementia Rating for Frontotemporal Lobar Degeneration; NFL: Neurofilament light chain; N: Number of participants; M: Male; F: Female.

Although macrostructural changes such as cortical atrophy are well documented, microstructural changes, particularly in genetically defined FTLD, remain poorly understood. Clarifying these microstructural features is crucial, as it may facilitate earlier diagnosis and guide targeted treatments for FTLD.

Macrostructural changes like cortical thinning and atrophy are typically assessed with structural MRI. Neuroimaging studies of FTLD reveal distinct patterns of cortical thinning among clinical subtypes [9,10]. In contrast, cortical mean diffusivity (cMD), a microstructural imaging measure obtained from diffusion-weighted imaging, evaluates the diffusion of water molecules in cortical tissue, reflecting neuronal integrity, glial activation, and cellular membrane disruption [11]. Elevated cMD values suggest microstructural disruption and may appear before visible cortical atrophy. Studies in Alzheimer's disease and the amyotrophic lateral sclerosis–FTLD spectrum suggest cMD is a sensitive early marker of neurodegeneration [12–15]. Despite initial evidence supporting the advantages of cMD in various FTLD subtypes—such as behavioural variant frontotemporal dementia (bvFTD), non-fluent variant primary progressive aphasia (nfvPPA), and semantic variant primary progressive aphasia (svPPA) [16,17]—the specific microstructural alterations across genetic subtypes of FTLD remain unclear.

Although preliminary research indicates that cMD changes are broader and more sensitive than cortical thinning for identifying early alterations, few studies have directly compared cortical microstructure across MAPT, GRN, and C9orf72 mutation carriers. Thus, the extent and specificity of these microstructural alterations in different genetic variants remain uncertain. Addressing this critical gap in knowledge may significantly enhance early diagnosis, enable precise disease classification, and inform genotype-specific treatment strategies.

To overcome these diagnostic and therapeutic challenges, combining imaging biomarkers such as cMD with clinical scales and biological markers may be essential. The Frontotemporal Lobar Degeneration Clinical Dementia Rating (FTLD-CDR) scale offers a structured approach to evaluate cognitive and behavioural impairments, supporting clinical assessment, monitoring disease progression, and treatment evaluation. Plasma neurofilament light chain (NFL), an established biomarker, is increasingly used for early detection and ongoing monitoring of neurodegeneration, especially in FTLD [18]. Elevated plasma NFL typically reflects neuronal injury, particularly during early disease stages [19]. Combining NFL measurements with imaging biomarkers can enhance clinical stratification and enable personalised therapeutic approaches [20].

In this multicentre study, we investigated cortical thickness and cortical mean diffusivity (cMD) in genetic subtypes of FTLD associated with MAPT, GRN, and C9orf72 mutations. We tested whether cMD would be more sensitive than cortical thickness for detecting early cortical changes specific to each genetic subtype. Additionally, we explored the relationship between these imaging measures, clinical severity (as measured by FTLD-CDR), and plasma NFL concentrations. We hypothesised that cMD would better reflect genotype-specific cortical degeneration, correlating more accurately with clinical and biological markers of disease severity. These findings may provide a robust basis for improved early diagnosis, enhanced clinical decision-making, and personalised interventions in familial FTLD.

2. Methods

2.1. Study participants

Participants were recruited from the ALLFTD consortium, a multicenter, observational study designed to enhance clinical understanding and therapeutic strategies for FTLD [21]. A total of 322 participants were included, consisting of individuals with pathogenic mutations in C9orf72 (*N* = 85), GRN (*N* = 56), or MAPT (*N* = 58), as well as non-carrier family members (*N* = 123). The FTLD patients were diagnosed based on consensus clinical criteria and confirmed by genetic testing [22]. Healthy controls, matched by age and sex, had no neurological or psychiatric disorders and were free of the pathogenic mutations.

2.2. Genetic testing

All participants were subjected to genetic testing to ascertain the presence or absence of specific mutations linked to FTLD. Comprehensive methodologies and outcomes of the genetic testing are documented in a separate publication (Ramos et al., this issue). Although clinical genetic testing is available to all participants, most asymptomatic individuals have chosen not to partake in it. Nevertheless, all participants are involved in research-based genetic testing, with the results remaining confidential from clinicians and undisclosed to the participants. Consequently, the mutation status for each participant is determined exclusively through research testing [23].

2.3. Neuroimaging data acquisition

All MRI images were obtained using 3T scanners equipped with an 8-channel phased-array head coil. The acquisition of high-resolution T1-weighted images was performed using a 3D magnetization-prepared rapid gradient echo sequence, with the following settings: TR = 2300 ms, TE = 3 ms, TI = 900 ms, an 8° flip angle, and voxel dimensions of 1.2 × 1 × 1 mm. In the axial plane, diffusion tensor imaging (DTI) was executed using a single-shot echo-planar imaging sequence, featuring a TR of 10,200 ms, an in-plane matrix of 128 × 128. Each DTI acquisition included 41 diffusion-weighted directions and 5 non-diffusion-weighted (b0) volumes. Slice thickness was 2.7 mm, yielding isotropic 2.7-mm resolution.

FreeSurfer (version 6.0.0) was used to process structural T1-weighted MRI data to assess cortical thickness, which is the distance from the gray/white matter boundary to the pial surface [24,25]. Subsequently, the cortical thickness (cTH) maps were transformed into the fsaverage space of FreeSurfer and smoothed using a Gaussian kernel

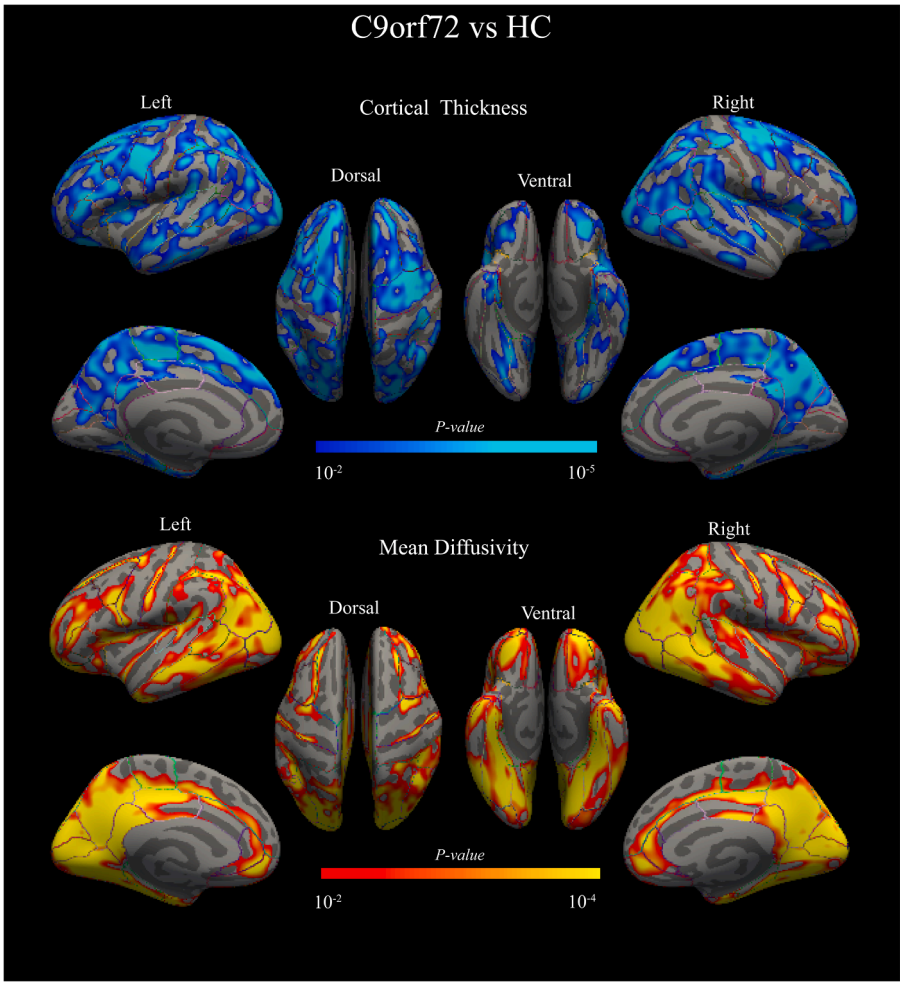

Fig. 1. Comparison of Cortical Thickness and Cortical Mean Diffusivity between C9orf72 Genotype FTLD Patients and Cognitively Healthy Controls. Upper Panel: C9orf72 genotype FTLD patients show significant cortical thinning compared to matched healthy controls (HC). The blue regions indicate areas of thinner cortex in the C9orf72 group. Cortical thickness analysis was adjusted for age, sex, and center, with significance set at $P < 0.01$. Lower Panel: C9orf72 genotype FTLD patients exhibit significantly higher cMD compared to matched HC. The red-yellow regions represent areas of increased cMD in the C9orf72 group. The cMD analysis was adjusted for age and sex, with significance set at $P < 0.01$.

with a full-width at half-maximum (FWHM) of 10 mm. DWI data were preprocessed with FSL software (version 6.0.4), including eddy current correction, motion correction, and bias field correction. cMD was calculated using surface-based methods in FreeSurfer, with partial volume effects corrected. The cMD maps were smoothed with a 10-mm FWHM Gaussian kernel after being projected onto the fsaverage surface.

2.4. Clinical assessments

Disease severity was evaluated using the Frontotemporal Lobar Degeneration Clinical Dementia Rating (CDR® plus NACC FTLD) scale, which provides a standardized measure of cognitive and behavioral impairments [26].

2.5. Plasma neurofilament light chain (NFL)

NFL levels were quantified as a biomarker of neuronal injury. Plasma samples were collected in ethylene diamine tetra-acetic acid (EDTA) tubes, centrifuged at 1500 g for 15 min at 4 °C, aliquoted, and stored at −80 °C. NFL concentrations were measured using the Quanterix NF-Light assay, a single-molecule array (Simoa) digital immunoassay, following the manufacturer's protocol. Samples were tested in duplicate on a Quanterix HD-X Analyzer, with quality control measures conducted during each run to ensure consistency and reliability.

2.6. Statistical analysis

Using R software version 4.0.5, statistical analyses were performed. Differences in cortical thickness and cMD between genetic groups (MAPT, GRN, C9orf72) and healthy controls were assessed using general linear models (GLMs). To account for batch effects and adjust for covariates, including age and sex, we applied neuroCombat for harmonization of imaging data across different MRI sites [27]. Correlation analyses examined the relationships between imaging metrics cTH and cMD), CDR® plus NACC FTLD scores, and plasma NFL concentrations. Statistical significance was determined through Monte Carlo simulations (10,000 permutations) with family-wise error correction, using a significance threshold of $P < 0.01$. Following the participant recruitment and data acquisition outlined above, the study methodology is summarized in the flowchart (Graphic Abstract).

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of all participants are detailed in Table 1. Statistical analysis revealed no significant differences in age or sex distribution between each subtype of frontotemporal lobar degeneration (FTLD) and their respective control groups.

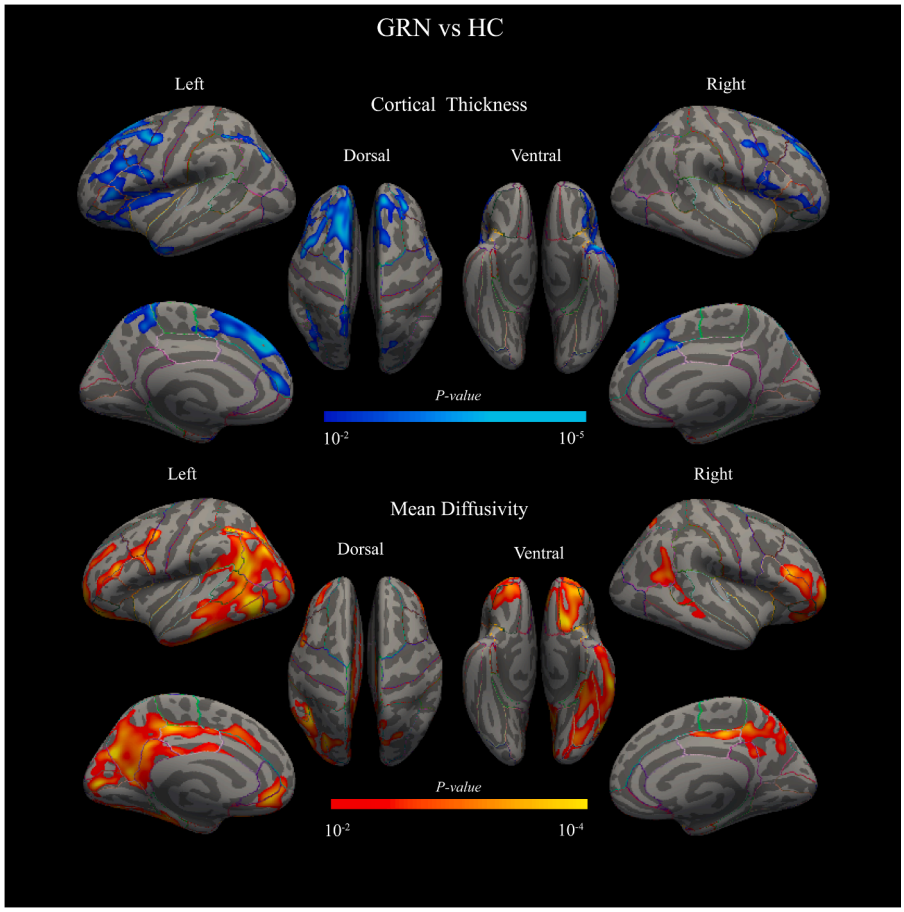

Fig. 2. Comparison of Cortical Thickness and Cortical Mean Diffusivity between GRN Genotype FTLD Patients and Cognitively Healthy Controls. Upper Panel: GRN genotype FTLD patients exhibit significant cortical thinning compared to matched healthy controls (HC). The blue regions represent areas of thinner cortex in the GRN group. Cortical thickness analysis was adjusted for age, sex, and center, with significance set at $P < 0.01$. Lower Panel: GRN genotype FTLD patients show significantly elevated cMD compared to matched HC. The red-yellow regions indicate areas of higher cMD in the GRN group. The cMD analysis was adjusted for age and sex, with significance set at $P < 0.01$.

However, significant age differences were observed among the three FTLD subtypes, with the GRN subtype being older than the C9orf72 and MAPT subtypes. Significant differences in CDR® plus NACC FTLD scores were observed across the FTLD subtypes, with the GRN group showing higher impairment scores compared to the C9orf72 and MAPT subtypes. For NFL levels, the GRN group exhibited significantly higher values, indicating greater neuronal damage compared to the C9orf72 and MAPT subtypes, with healthy controls showing lower NFL levels in comparison.

3.2. Comparison of cTH and cMD across FTLD subtypes

We first compared cTH and cMD between C9orf72 genotype FTLD patients and cognitively healthy controls without the pathogenic gene. As shown in Fig. 1, the C9orf72 group exhibited cortical thinning in multiple regions, including the bilateral superior frontal gyrus, head of the middle frontal gyrus, posterior inferior frontal gyrus, superior and inferior parietal gyri, posterior cingulate gyrus, middle and inferior temporal gyri, lateral occipital lobe, entorhinal cortex, and parahippocampal gyrus. This thinning was relatively symmetric across both hemispheres. The cMD map, however, revealed a broader involvement, spanning the entire frontal, temporal, parietal, and occipital cortices.

Next, we compared cTH and cMD between GRN genotype FTLD patients and healthy controls. As shown in Fig. 2, the GRN group exhibited cortical thinning in the left superior frontal gyrus, head of the middle frontal gyrus, triangular part of the inferior frontal gyrus, supramarginal gyrus, precentral gyrus, insula, superior parietal gyrus, and temporal pole. Notably, the left hemisphere showed more extensive involvement, with cMD changes extending into the temporal, parietal, and occipital cortices. On the right side, cortical thinning was observed in the superior frontal gyrus, head of the middle frontal gyrus, precentral gyrus, and insula. The cMD map on the right side covered a larger area, including the middle frontal gyrus, orbital inferior frontal gyrus, precuneus, and posterior cingulate gyrus. In the GRN group, both cTH and cMD showed more extensive involvement on the left side than on the right.

Finally, we compared cTH and cMD between MAPT genotype FTLD patients and healthy controls. As shown in Fig. 3, the MAPT group demonstrated cortical thinning in the left superior frontal gyrus, middle frontal gyrus, insula, middle temporal gyrus, inferior temporal gyrus, parahippocampal gyrus, and entorhinal cortex. The cMD map on the left side was more extensive, encompassing the frontal and temporal lobes as well as the occipital lobe. On the right side, cortical thinning was observed in the head of the middle frontal gyrus, precentral gyrus, temporal lobes, parahippocampal gyrus, and entorhinal cortex, with the cMD map extending to the occipital lobe and inferior parietal gyrus. The MAPT group showed more extensive cortical regions affected by cMD than cTH on both sides.

3.3. Correlations between cTH, cMD, and CDR® plus NACC FTLD scores

We next assessed the correlation between cTH and cMD with disease

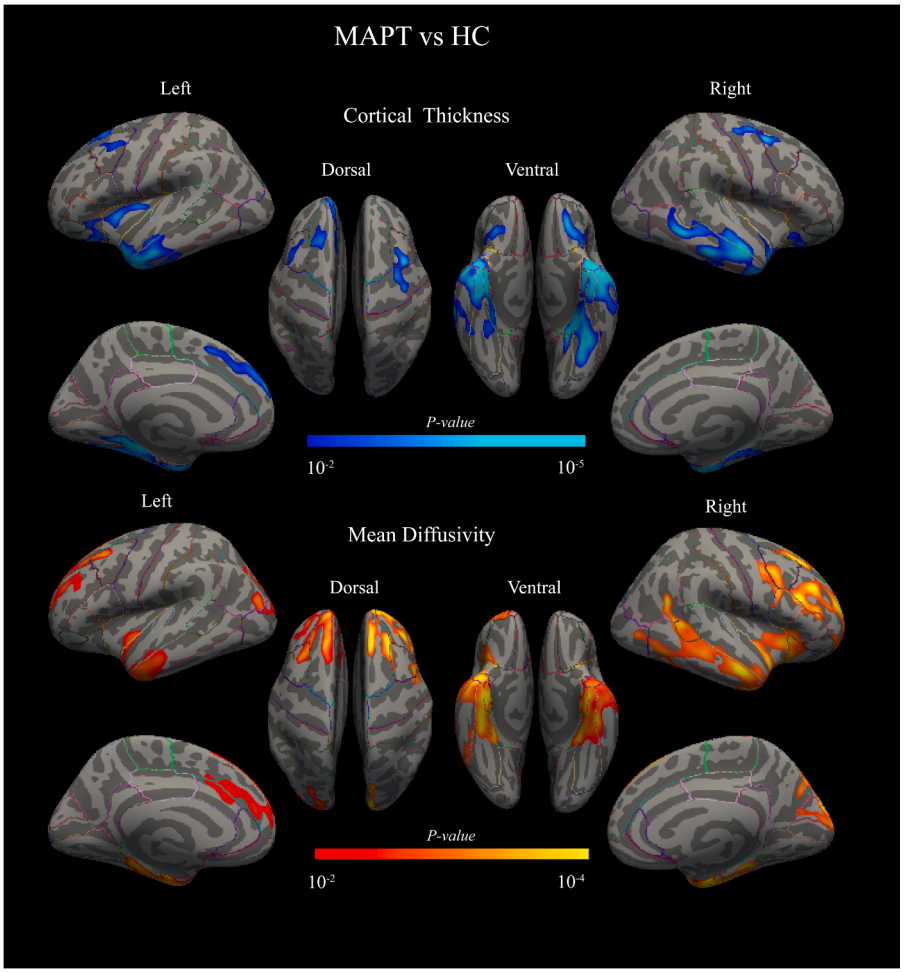

Fig. 3. Comparison of Cortical Thickness and Cortical Mean Diffusivity between MAPT Genotype FTLD Patients and Cognitively Healthy Controls. Upper Panel: MAPT genotype FTLD patients show significant cortical thinning compared to matched healthy controls (HC). The blue regions represent areas of thinner cortex in the MAPT group. Cortical thickness analysis was adjusted for age, sex, and center, with significance set at $P < 0.01$. Lower Panel: MAPT genotype FTLD patients exhibit significantly elevated cMD compared to matched HC. The red-yellow regions indicate areas of higher cMD in the MAPT group. The cMD analysis was adjusted for age and sex, with significance set at $P < 0.01$.

severity, as measured by the CDR® plus NACC FTLD scores. In patients with the three genetic subtypes of FTLD, we found that CDR® plus NACC FTLD scores were negatively correlated with cTH in the frontal, temporal, insular, supramarginal, parietal, and occipital cortices across both hemispheres. Additionally, the correlation between cMD and CDR® plus NACC FTLD scores was more extensive, involving broader positive correlation regions across both hemispheres (Fig. 4).

3.4. Correlation between cTH, cMD, and NFL levels

We next examined the correlation between cTH, cMD, and NFL levels. In the C9orf72 group, NFL levels were negatively correlated with cTH in the frontal, temporal, supramarginal gyrus, and precuneus regions. The correlation between NFL levels and cMD extended beyond these areas, reaching the occipital cortex (Fig. 5, upper panel). In the GRN group, NFL levels were negatively correlated with cTH in the frontal, temporal, and supramarginal gyrus regions. Additionally, NFL levels were positively correlated with cMD in the frontal and temporal cortices, with the correlation extending to the left occipital lobe. Extensive negative correlations between cTH and NFL levels were observed across both hemispheres. In the MAPT group, NFL levels were negatively correlated with cTH in the frontal and temporal cortices. Furthermore, the positive correlation between NFL levels and cMD in the frontal and temporal regions extended to the occipital and parietal lobes. These findings indicate a large positive correlation between cMD and NFL levels in the MAPT group.

4. Discussion

This study provides valuable insights into cortical microstructural changes in familial FTLD across distinct genetic subtypes, specifically C9orf72, GRN, and MAPT mutations. Our findings demonstrate that C9orf72 genotype patients exhibit the most extensive cortical involvement, affecting multiple regions, including the frontal, temporal, parietal, and occipital lobes. This is consistent with prior studies suggesting that C9orf72 mutations are associated with widespread cortical degeneration. In contrast, patients with GRN and MAPT mutations showed more localized cortical thinning, indicating that the extent of cortical involvement may vary depending on the underlying genetic mutation. Additionally, we found that cMD changes extended over a broader area compared to cortical thickness cTH, further emphasizing the potential of cMD as a sensitive biomarker for early microstructural alterations in FTLD. These results underscore the importance of incorporating cMD into clinical assessments, as it may offer more comprehensive insights into disease progression and prove advantageous over traditional structural measures like cTH in detecting early neurodegenerative changes.

In addition to the observed cortical thinning, our study highlights the

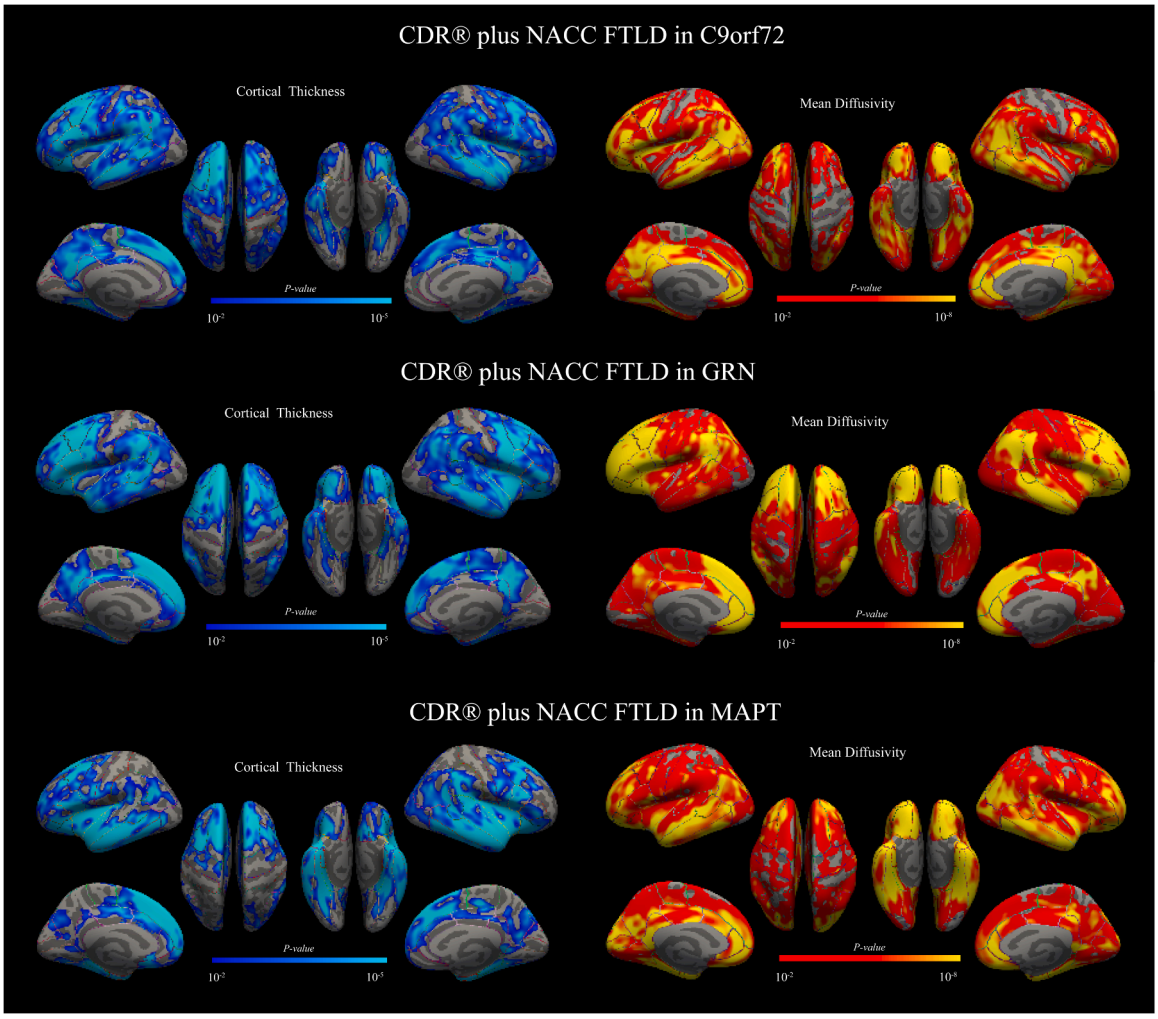

Fig. 4. Correlation between Cortical Thickness, Cortical Mean Diffusivity, and CDR® plus NACC FTLD Scores. Left Panel: Correlation between cortical thickness and CDR® plus NACC FTLD scores in the C9orf72 group (top), GRN group (middle), and MAPT group (bottom). Right Panel: Correlation between cortical mean diffusivity (cMD) and CDR® plus NACC FTLD scores in the C9orf72 group (top), GRN group (middle), and MAPT group (bottom). In all three groups, cortical thinning (blue) was associated with higher CDR® plus NACC FTLD scores, while larger areas of increased cMD (red-yellow) were observed with higher CDR® plus NACC FTLD scores. All analysis was adjusted for age, sex, and center, with significance set at $P < 0.01$.

significance of cMD as an early biomarker of neurodegeneration in familial FTLD. While traditional structural measures like cTH provide valuable insights into disease progression, cMD offers a more sensitive detection of microstructural changes that precede visible atrophy. This aligns with findings from studies in AD and amyotrophic lateral sclerosis (ALS)-FTLD, where cMD has been shown to reflect early neuronal disruption, even in the absence of detectable cortical thinning [28–30]. Importantly, our study extends this knowledge by providing direct comparisons across different FTLD genetic subtypes—C9orf72, GRN, and MAPT—demonstrating the unique microstructural patterns associated with each mutation. These findings are consistent with the notion that cMD is a more comprehensive measure for early neurodegenerative changes than cTH alone. Specifically, the C9orf72 group exhibited widespread cortical involvement, with cMD changes extending beyond areas of cortical thinning. In contrast, the GRN and MAPT groups exhibited more localized alterations in cortical structure, suggesting that genetic mutations differentially impact brain regions and pathways. Notably, cMD changes in the MAPT group were more extensive than those observed with cTH, supporting the hypothesis that cMD may be a more sensitive marker for the early stages of cortical degeneration. This distinction is crucial for identifying individuals at higher risk of disease progression before substantial cortical atrophy occurs, offering potential for earlier intervention.

Furthermore, cMD has shown promise as a sensitive biomarker for detecting microstructural changes associated with neurodegeneration in various neurodegenerative diseases. Specifically, in behavioral variant frontotemporal dementia (bvFTD), cMD has proven effective in identifying early microstructural alterations [17]. Studies have also demonstrated that cMD is more sensitive than cTH in detecting early cortical structural changes, as seen in Parkinson's disease [31] and other neurodegenerative diseases [12,32]. Unlike cortical thinning or gray matter atrophy, which can be difficult to detect in the early stages, cMD can identify microstructural changes such as neuronal loss, glial cell proliferation, and intercellular space alterations, providing valuable insights into the disease process before significant macroscopic changes occur [13,15]. However, research on cortical structure in FTLD patients with different genotypes remains limited. Our study, which directly compared cMD changes across C9orf72, GRN, and MAPT genotypes, reveals distinct patterns of microstructural involvement. C9orf72 mutations, the most common genetic cause of familial FTLD, are typically inherited in an autosomal dominant manner and often lead to severe clinical symptoms such as behavioral changes, language impairments, and motor dysfunction. These symptoms are associated with more widespread cortical involvement [33,34]. Consistent with this, our study further confirms that cMD changes in the C9orf72 group extend beyond regions of cortical thinning, affecting additional areas impacted

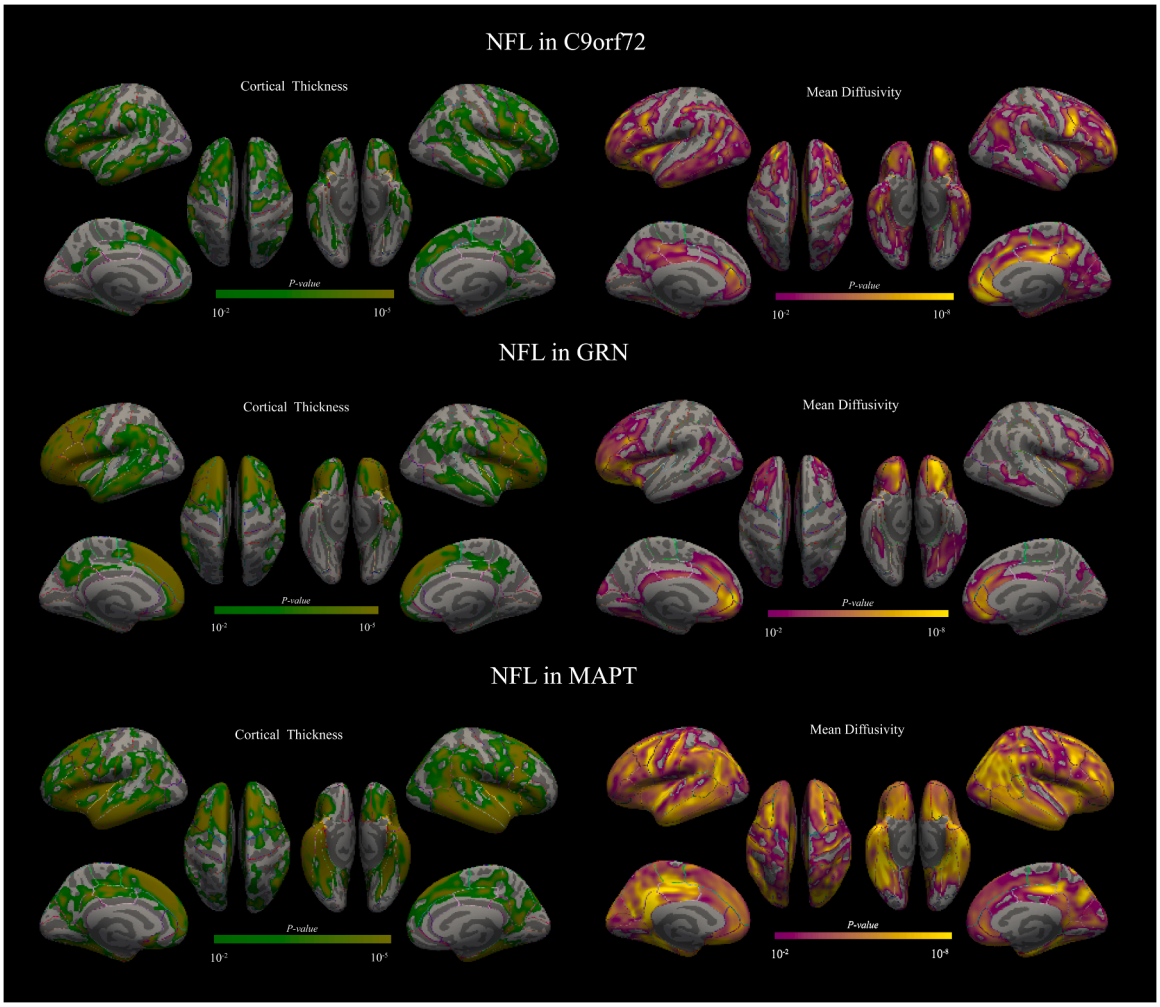

Fig. 5. Correlation between Cortical Thickness, Cortical Mean Diffusivity, and NFL Levels. Left Panel: Correlation between cortical thickness and neurofilament light chain (NFL) levels in the C9orf72 group (top), GRN group (middle), and MAPT group (bottom). Right Panel: Correlation between cortical mean diffusivity (cMD) and NFL levels in the C9orf72 group (top), GRN group (middle), and MAPT group (bottom). In all three groups, regions of cortical thinning (green) were associated with higher NFL levels, while areas of increased cMD (purple-yellow) were correlated with higher NFL levels. All analysis was adjusted for age, sex, and center, with significance set at $P < 0.01$.

by the disease. In contrast, GRN and MAPT groups exhibited more localized cortical damage. Notably, in all three genotypes, cMD changes were more extensive than cTH alterations, suggesting that cMD may be a more sensitive marker for detecting cortical damage across the genetic subtypes of FTLD.

Additionally, we observed a broad correlation between cMD and both CDR® plus NACC FTLD scores and NFL levels. Notably, compared to cTH, cMD exhibited a stronger correlation with CDR® plus NACC FTLD, further emphasizing its sensitivity and broad applicability as a biomarker. In the correlation analysis with CDR® plus NACC FTLD, we found that cMD showed a more extensive range of correlations across all three genetic subtypes, consistent with previous studies [16,17]. Similarly, in the correlation analysis with NFL levels, we observed the same results, except for the GRN group, which may be attributed to the limited sample size in our study. CDR® plus NACC FTLD is a standardized tool used to assess cognitive and behavioral impairments in FTLD patients, with widespread application in both clinical trials and diagnostic settings [26,35]. In our study, we observed a negative correlation between cTH and CDR® plus NACC FTLD scores in patients from all three genetic groups, indicating that cortical thickness progressively thins as the disease advances, with this change correlating with the worsening of cognitive and behavioral symptoms. However, the correlation between cMD and CDR® plus NACC FTLD was more widespread, with increases in cMD more consistently associated with higher CDR® plus NACC FTLD scores across different genetic subtypes.

Our study also provides important insights into the relationship between cMD and biomarkers of neuronal injury, particularly NFL, in familial FTLD. The positive correlation between cMD and NFL levels observed across C9orf72, GRN, and MAPT genotypes further supports cMD as a valuable microstructural marker for neurodegeneration. Elevated NFL levels, which reflect neuronal damage, were consistently associated with increased cMD in the cortical regions most affected by the disease, such as the frontal, temporal, and parietal cortices. This finding suggests that cMD may serve as an early, sensitive indicator of neuronal injury, providing complementary information to plasma biomarkers like NFL. Interestingly, the correlation between cMD and NFL was most pronounced in the C9orf72 and MAPT groups, while the GRN group exhibited a weaker correlation. This difference may reflect the distinct pathological mechanisms underlying each genetic subtype, as well as sample size limitations in the GRN group. Nonetheless, the consistent pattern observed in the C9orf72 and MAPT groups highlights the utility of cMD in monitoring disease progression and detecting early neurodegenerative changes [19,36]. The broad correlation between cMD and NFL levels across the three genotypes in our study emphasizes the potential of cMD as a non-invasive biomarker for monitoring the progression of familial FTLD. By incorporating both cMD and NFL,

clinicians may be able to improve the early diagnosis, monitoring, and clinical stratification of FTLD patients, particularly in the asymptomatic or pre-symptomatic stages, where traditional imaging techniques such as structural MRI may not yet show significant changes

Although our study highlights the sensitivity and potential application of cMD in FTLD genetic subtypes, there are several important limitations to consider. First, the sample size in this study is relatively small. While we compared patients from the C9orf72, GRN, and MAPT genotypes, the sample size for each genotype remains limited. Future studies should aim to expand the sample size for more robust validation. Second, this study is cross-sectional, which prevents us from establishing a causal relationship between changes in cMD and the development of clinical symptoms. Longitudinal studies are needed to examine how cMD dynamically changes as FTLD progresses and how these changes correlate with the onset and development of clinical symptoms. This is especially important for patients in the early stages, where symptoms have not yet manifested, and the predictive value of cMD changes requires further validation. Finally, cMD in our study was not corrected for free water components, which may affect mean diffusivity measurements. While this study focused exclusively on familial FTLD and utilized cMD as a biomarker for early neurodegenerative changes, we acknowledge that the extensive cortical involvement in C9orf72 patients may resemble patterns observed in AD, particularly with widespread cortical involvement. Although direct comparisons with sporadic or familial AD were beyond the scope of this study, future work incorporating AD cohorts—especially using cMD as a discriminative biomarker—may help clarify its differential diagnostic value. Additionally, we note that regions affected in C9orf72 carriers (such as the frontal and insular cortices) are generally distinct from the temporoparietal pattern typical of AD, which may aid in differentiation. Free water-corrected cMD may offer more accurate assessments for finer evaluations of neurodegenerative changes [37]. Free water-corrected MD may provide more accurate assessments for fine-tuned evaluations of neurodegenerative changes.

In conclusion, cMD is a sensitive biomarker for early microstructural changes in familial FTLD, particularly across C9orf72, GRN, and MAPT genotypes. Our study highlights the distinct microstructural patterns associated with each genetic subtype and demonstrates cMD's superiority over cTH in detecting early neurodegeneration. The correlation between cMD, CDR® plus NACC FTLD scores, and NFL levels underscores its potential for early diagnosis and disease monitoring. These findings support cMD as a valuable tool for advancing clinical practice and personalized therapeutic strategies in FTLD.

Ethical approval

The study was approved by the institutional review boards at each participating center. All participants provided written informed consent prior to enrollment, in accordance with the Declaration of Helsinki. Genetic testing, neuroimaging procedures, and clinical assessments were conducted in compliance with ethical guidelines, ensuring participant confidentiality and the protection of personal data.

CRediT authorship contribution statement

Lijuan Wang: Writing – review & editing, Writing – original draft, Investigation. **Si Cen:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Li Zhao:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology. **Junfeng Tang:** Software, Investigation. **Pengcheng Xu:** Writing – review & editing, Supervision. **Pusheng Quan:** Visualization, Supervision. **Wencai Ding:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100306.

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