

Background

Frontotemporal dementia (FTD) is characterized by abnormal white matter (WM) integrity measured with conventional diffusion tensor imaging techniques. We aim to investigate the microstructural WM changes across disease stages of genetic FTD using the novel neurite orientation dispersion and density imaging (NODDI).

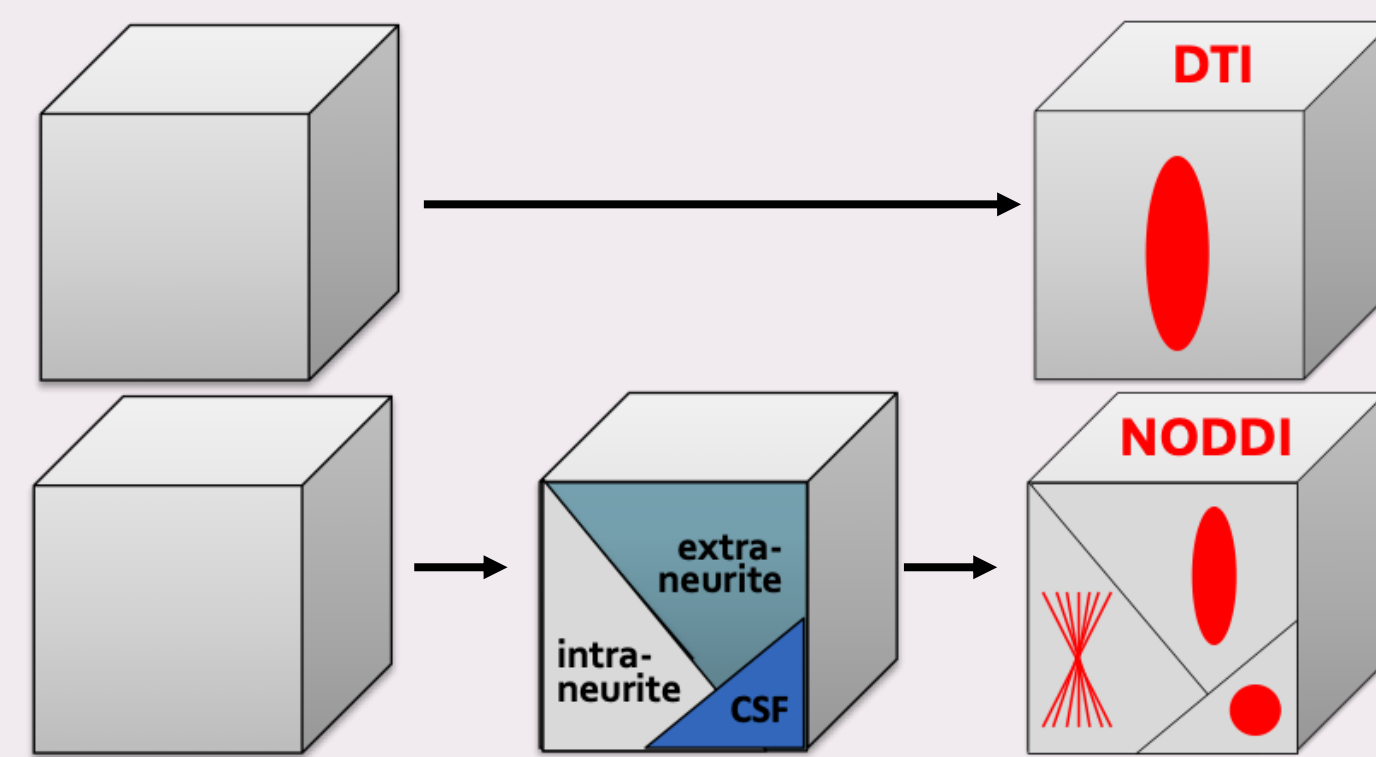


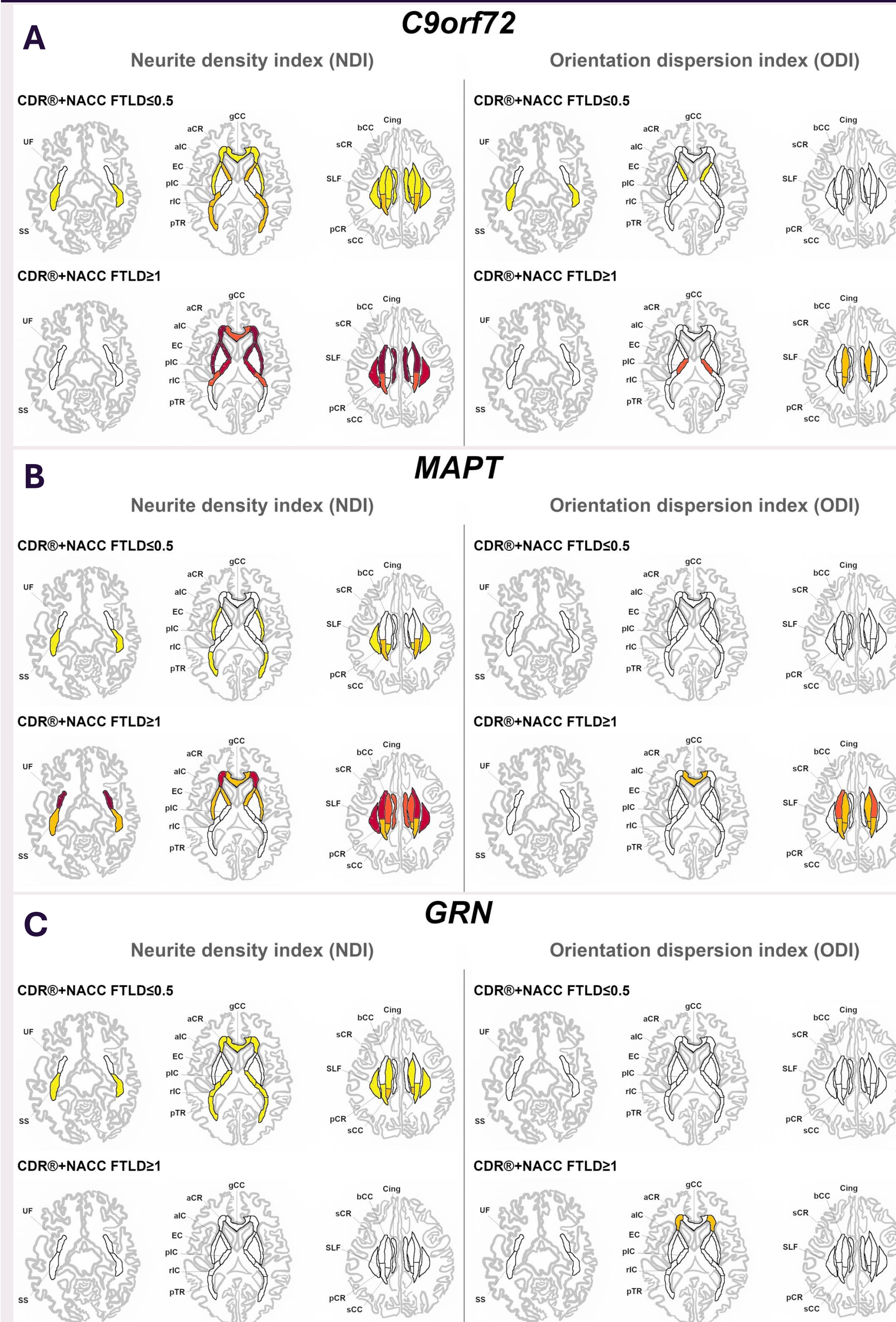
Figure 1. Example in a voxel of models of diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) for diffusion weighted MRI. Adapted from Slattery *et al.*, Neurobiology of Aging 2017.

Methods

Neurite density index (NDI) and orientation dispersion index (ODI) were extracted from NODDI sequences acquired on a 3T Siemens Prisma scanner at University College London, UK. 98 mutation carriers (age mean-SD: 47-14 years; 50% males) were divided into presymptomatic (41 *C9orf72*, 17 *GRN*, 12 *MAPT*) and fully symptomatic (9 *C9orf72*, 8 *GRN*, 11 *MAPT*) groups based on their global CDR[®] plus NACC FTLD scores (≤ 0.5 vs ≥ 1) (**Table**). Images were processed and corrected for tissue-weighted means. W-scores for NDI and ODI were computed from a regression model on 84 non-carrier healthy individuals (age: 55-15 years; 54% males), adjusting for their age and sex.

	NC	<i>C9orf72</i>		<i>MAPT</i>		<i>GRN</i>	
CDR [®] +NACC-FTLD score	--	≤ 0.5	≥ 1	≤ 0.5	≥ 1	≤ 0.5	≥ 1
N	84	41	9	12	11	17	8
Age years	55 (15)	41 (10)	67 (7)	39 (10)	61 (8)	40 (10)	64 (6)
Male %	54%	39%	78%	42%	64%	47%	75%

Results



Overall, the most abnormal values ($<2.5^{\text{th}}$ percentile of controls) were found in NDI for symptomatic *C9orf72* (antero-superior corona radiata, cingulum, anterior internal and external capsule, **Figure 2A**) and *MAPT* (uncinate fasciculus, **Figure 2B**).

Moreover, symptomatic *C9orf72* showed abnormal NDI values ($<5^{\text{th}}$ percentile) in the posterior internal capsule and superior longitudinal fasciculus, while symptomatic *MAPT* showed similar NDI values in the antero-superior corona radiata and superior longitudinal fasciculus.

The most abnormal values for ODI were found in the posterior internal capsule and superior coronal radiata in symptomatic *C9orf72* and *MAPT* respectively ($<10^{\text{th}}$ percentile).

Presymptotically, abnormal values for NDI ($<25^{\text{th}}$ percentile) were found in several tracts, particularly in the internal capsule, posterior corona radiata, posterior thalamic radiation in *C9orf72*, splenium of corpus callosus in *GRN* (**Figure 2C**), and posterior corona radiata in *MAPT*.

For ODI, only presymptomatic *C9orf72* showed significantly negative w-scores in the sagittal stratum and anterior internal capsule ($>25^{\text{th}}$ percentile).

Figure 2: White matter involvement in presymptomatic (top row) and symptomatic (bottom row) *C9orf72*, *MAPT* and *GRN* mutation carriers. Colours indicate the percentiles corresponding to the mean w-scores when significantly lower than non-carriers.



Conclusion

Reduced axonal density measured with NDI appears the main cause of WM changes in genetic FTD, which was measurable before symptom onset.