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# **NODDI Highlights Promising New Markers In Presymptomatic C9orf72 Carriers**

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## Introduction

*C9orf72* repeat expansions are the most common genetic cause of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). (Majounie et al., 2012). Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that can detect microstructural changes in vivo by measuring water diffusion (Alexander et al. 2007). However, DTI has several limitations (Pierpaoli et al., 1996), that could be overcome using more advanced model, such as neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012). Neurite density index (NDI) and orientation dispersion index (ODI) from NODDI aim to quantify the density and dispersion of neurites. Besides, free water fraction (FISO) also captures the volume of free water in tissues at the microstructural level. In the present work, we studied a cohort of subjects at risk for carrying *c9orf72* mutation. NODDI metrics were compared to T1 and standard DTI metrics to detect group differences between presymptomatic subjects (c9+) and control subjects (c9-) during presymptomatic stage.

## Methods

Multi-shell diffusion-weighted images (DWI) were acquired on 38 c9+ and 29 c9- (the study group differs from Bertrand et al., 2017, by 11 subjects). 13 non diffusion-weighted volumes ( $b_0$ ) and three shells DWI with b-values of 300, 600 and 2200  $s/mm^2$  were acquired. Each subject also underwent a single-shell DWI sequence (used to fit DTI model) with b-values of 1000  $s/mm^2$ , and a 3D T1-weighted sequence. Multi-shell DWI data were corrected for susceptibility-induced distortions, eddy current-induced distortions and head motion. NODDI was then fitted generating NDI, ODI and FISO maps. NDI and ODI maps were nonlinearly registered onto John Hopkins University atlas template to calculate the mean values of NDI and ODI within white matter (WM) regions of interest (ROI). T1-weighted images were segmented using FreeSurfer and FISO maps were rigidly transformed onto FreeSurfer conformed space, in order to extract volumetry and FISO values within cortical and subcortical ROI. Additionally, the single-shell DWI was processed with the same approach as in Bertrand et al to obtain the mean values of FA, MD, RD and AD maps within WM ROI. Statistical analyses were performed using a general linear model, including age, sex and group as fixed effects and family kinship as random effect. Statistical significance was set at  $P < 0.05$  and correction for multiple comparisons was performed using Benjamini-Hochberg method. Additionally, effect size for the factor "group" was also reported for each metric using Cohen's  $f^2$ .

The image processing pipelines are publicly available in Clinica platform (<http://clinica.run>).

## Results

For WM analysis displayed in Fig 1, 10 tracts showed significant WM abnormalities in c9+ subjects with NDI, while only 5 tracts with DTI metrics. 7 of the 11 significant tracts detected by either NDI or DTI had higher effect size with NDI than with DTI metrics.

For cortex analysis shown in Fig 2, FISO detected significant free water alteration within 13 ROIs in c9+, while significant atrophy was detected within 11 ROIs in c9+. The difference of effect size was moderate between FISO and volumetry.

For subcortical analysis, volumetry identified significant atrophy in right thalamus, while FISO failed to reveal any free water alteration.

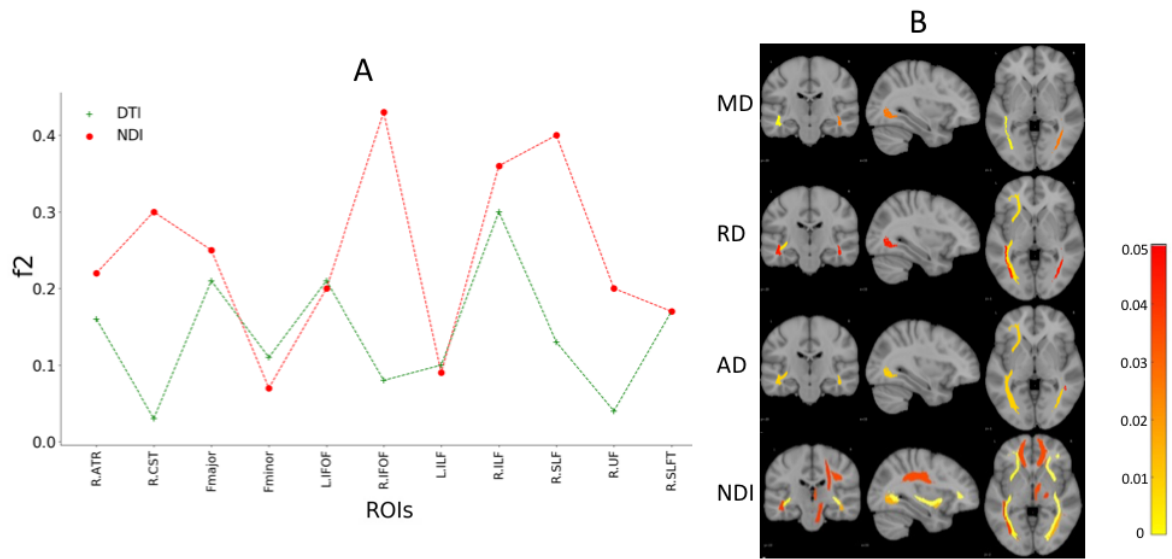
## Conclusions

We demonstrate that NDI offers higher sensitivity than DTI metrics to detect white matter alteration in presymptomatic carriers of *c9orf72* mutation. FISO was comparably sensitive, as compared to volumetry, for the detection of cortical changes. However, FISO failed to detect any free water alteration in subcortical structures. Overall, NODDI may provide more sensitive biomarkers than DTI for the detection of white matter integrity disruption during the presymptomatic stage of neurodegenerative diseases. This could have implications for the monitoring of disease trajectory and therapeutic interventions in presymptomatic subjects.

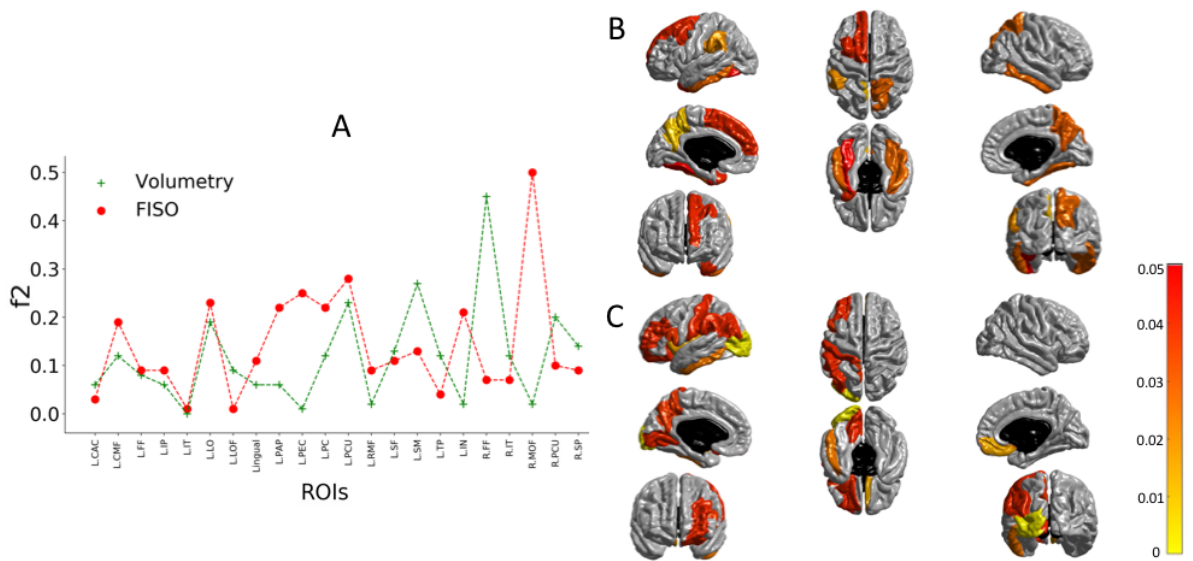
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## Figures



**Fig 1.** A) Effect size corresponding to the effect of *C9orf72* mutation on DTI and NDI. B) Corrected P value corresponding to the effect of *C9orf72* mutation on DTI and NODDI metrics. No significance was detected for FA and ODI.



**Fig 2.** A) Effect size corresponding to the effect of *C9orf72* mutation on Volumetry and FISO. B) Corrected P value corresponding to the effect of *C9orf72* mutation on Volumetry within cortical ROI. C) Corrected P value corresponding to the effect of *C9orf72* mutation on FISO within cortical ROI.