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Cognitive, Structural, and Microstructural Changes In Presymptomatic C9orf72 Carriers

Junhao Wen

Supervised by Olivier Colliot, Stanley
Durrleman and Anne Bertrand

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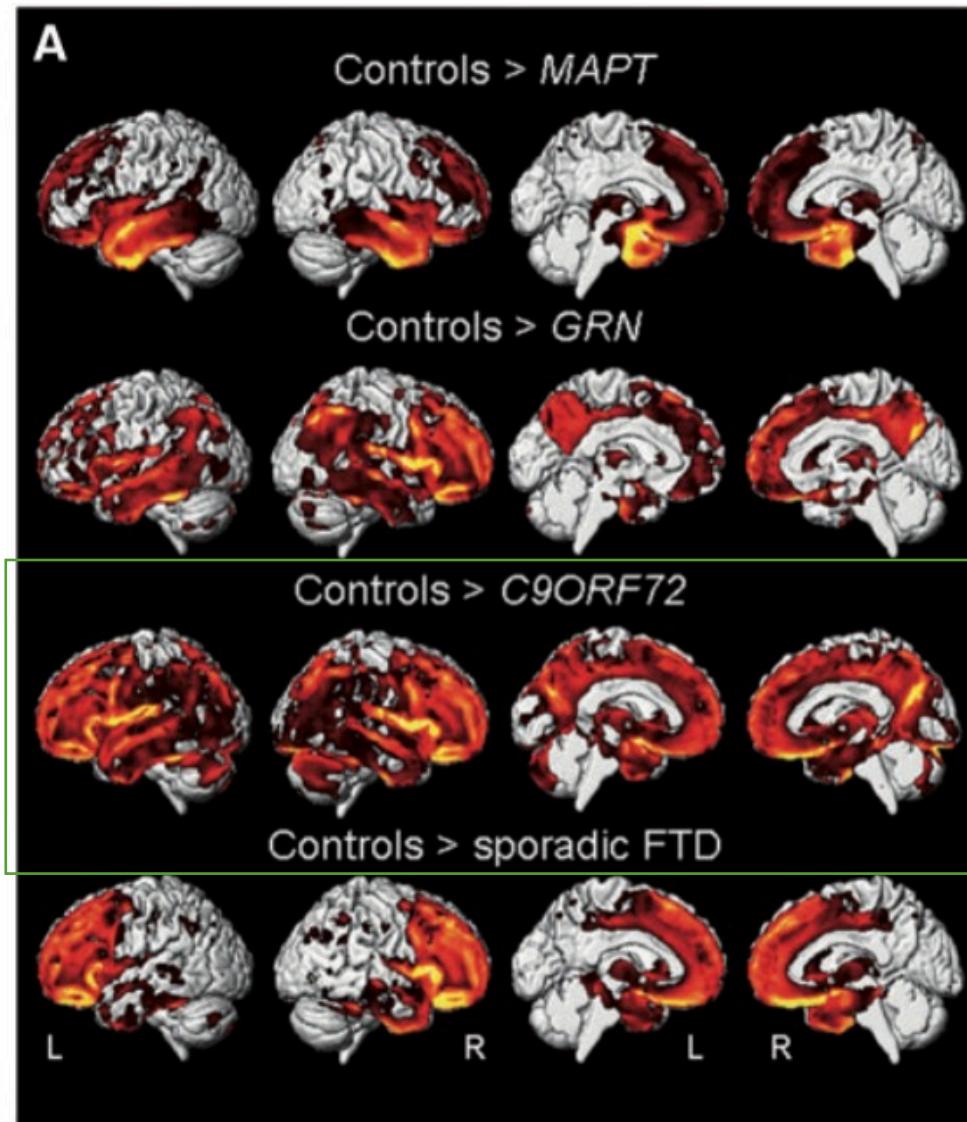
Frontotemporal lobar degeneration (FTLD)

Second cause for degenerative dementia in rather young people (< 60 years old):

- Affect the anterior regions (frontal & temporal lobe) of the brain
- Histologically heterogeneous
- Strong genetic component
- heterogeneous atrophy in mutations

C9orf72 (C9) mutation characteristics:

- Mutation identified in 2011 (*DeJesus-Hernandez et al., 2011*)
- Most frequent mutation for both FTLD and Amyotrophic Lateral Sclerosis (ALS)
- Histological abnormalities with TDP43 & depeptides



Whitwell et al., 2012

Group differences between presymptomatic (C9+) and control (C9-) subjects.

Brain atrophy:

- Diffused cortical atrophy is detected in frontal, temporal and parietal lobes.
- Thalamic atrophy appears as a reliable effect of C9 mutation.

White matter integrity loss (DTI):

- Frontal-temporal related tracts showed alteration in microstructure.

Limitations:

- Relatively small data sample for C9+ (< 20).
- DTI results are not specific enough and CSF contamination.

Prevdemals Study



Dataset:

- Prevdemals is a multicentric French cohort of patients with genetic FTLD&ALS due to C9 mutation, and of first-degree relatives (C9+ & C9-) at risk for C9 mutation.
- Anatomical MRI, **single-shell** and **multishell** diffusion MRI were included .

Characteristics	Mean (SD)		
	C9+	C9-	P value
N	39	41	--
Age	45.2 (13.9)	39.8 (11.1)	.08
Female, No. (%)	24 (62)	22 (59)	.78

Table 1: Study group characteristics for *anatomical MRI*

Characteristics	Mean (SD)		
	C9+	C9-	P value
N	29	38	--
Age	44.8 (13.5)	40.7 (11.5)	.18
Female, No. (%)	17 (59)	19 (50)	.65

Table 2: Study group characteristics for *diffusion MRI*

Objectives

By means of multimodal MRI and a big cohort, we aim to:

- Detect cognitive changes in C9+;
- Find brain atrophy pattern in C9+ from anatomical MRI;
- Evaluate white matter integrity loss using diffusion MRI;
- Evaluate the added value of **NODDI** using multishell dMRI compared to **DTI** and **anatomical MRI**.
 - NODDI metrics [neurite density index (**NDI**) and orientation dispersion index (**ODI**)] vs DTI metrics [fractional anisotropy (**FA**), mean diffusivity (**MD**), radial diffusivity (**RD**) and axial diffusivity (**AD**)]
 - NODDI metric [(free water fraction (**FWF**))] vs anatomical metric (**volumetry**)

Image Processing & Statistics

Image processing was performed on Clinica software.

- Anatomical MRI: *clinica run t1_freesurfer_cross_sectional**
- Single-shell & multishell diffusion MRI: *clinica run dwi-**



ROI-based generalized linear model:

For this mixed effect linear model, Volume is the j -th measure of i -th subject, the covariates will be *sex*, *age*, and *group*, *family_kinship* is the random effect.

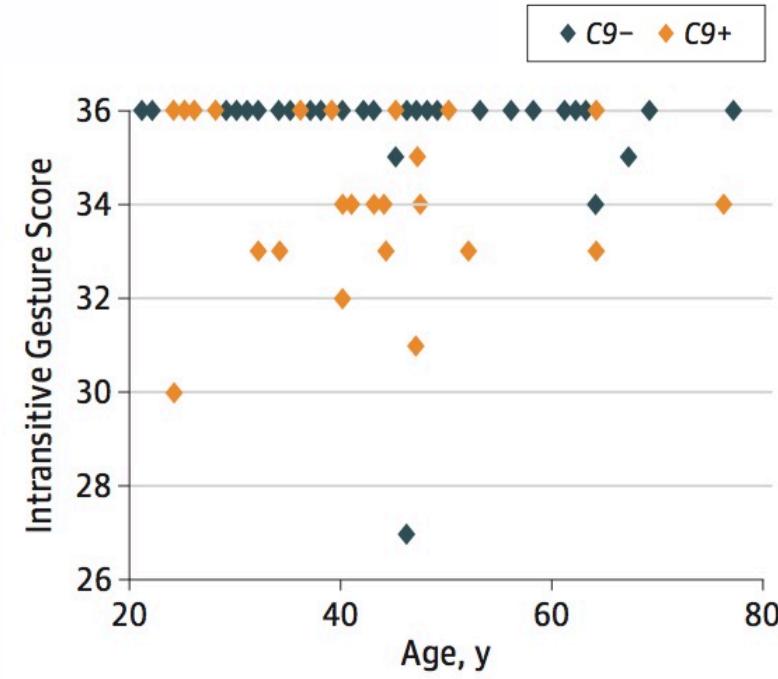
$$Y_{ik}^{(j)} = \mu + \beta \times \text{gender}_i + \lambda \times \text{age}_i + \eta \times \text{group}_i + U_k + \epsilon_{ik}^{(j)}$$

Corrected P value and Effect size (cohen's f²) of each ROI were reported.

Cognitive changes

Cognitive analyses:

- C9+ has significantly lower scores for the subscores of intransitive gestures test compared to C9-
(Significance remained in participants younger than 40 years old).

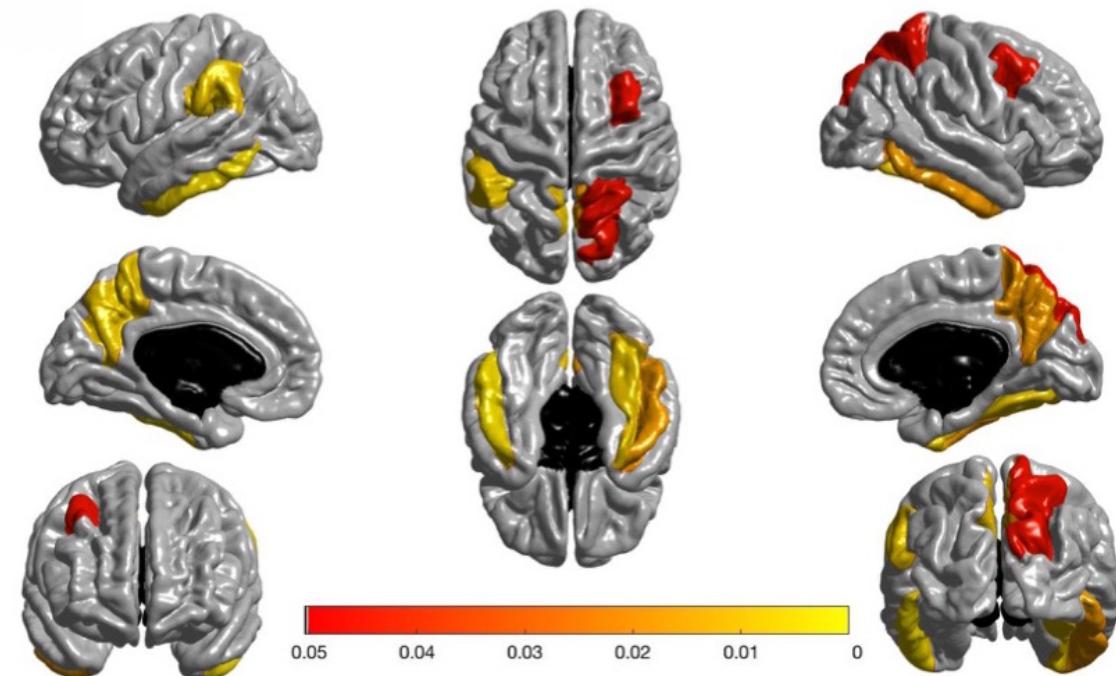


Bertrand and Wen., 2018

Anatomical MRI Analyses

Cortical analyses:

- Diffused atrophy in C9+ group, with a sparing of parietal cortex, frontal cortex, and inferior temporal cortex (*Significance remained in participants younger than 40 years old*).

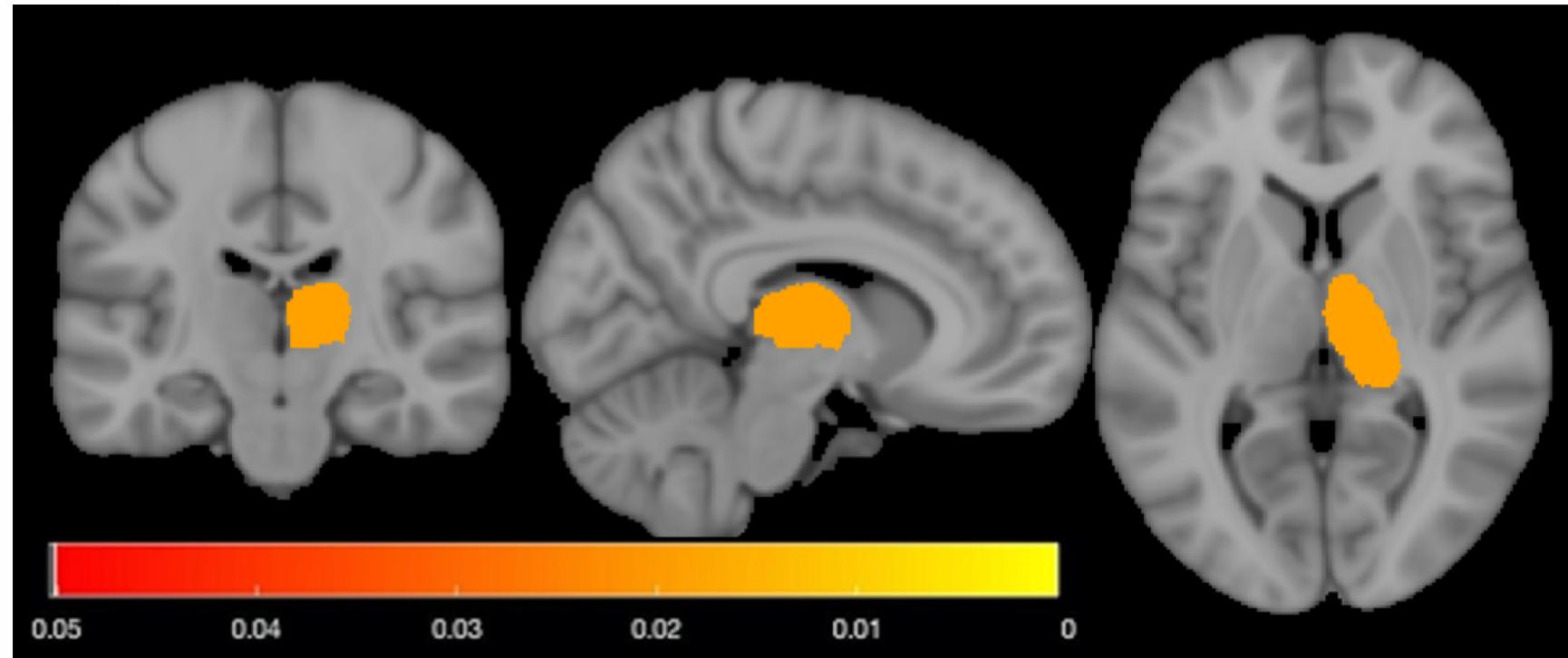


Bertrand and Wen., 2018

Anatomical MRI Analyses

Subcortical analyses:

- C9+ showed subcortical atrophy in right thalamus (*Significance remained in participants younger than 40 years old*).

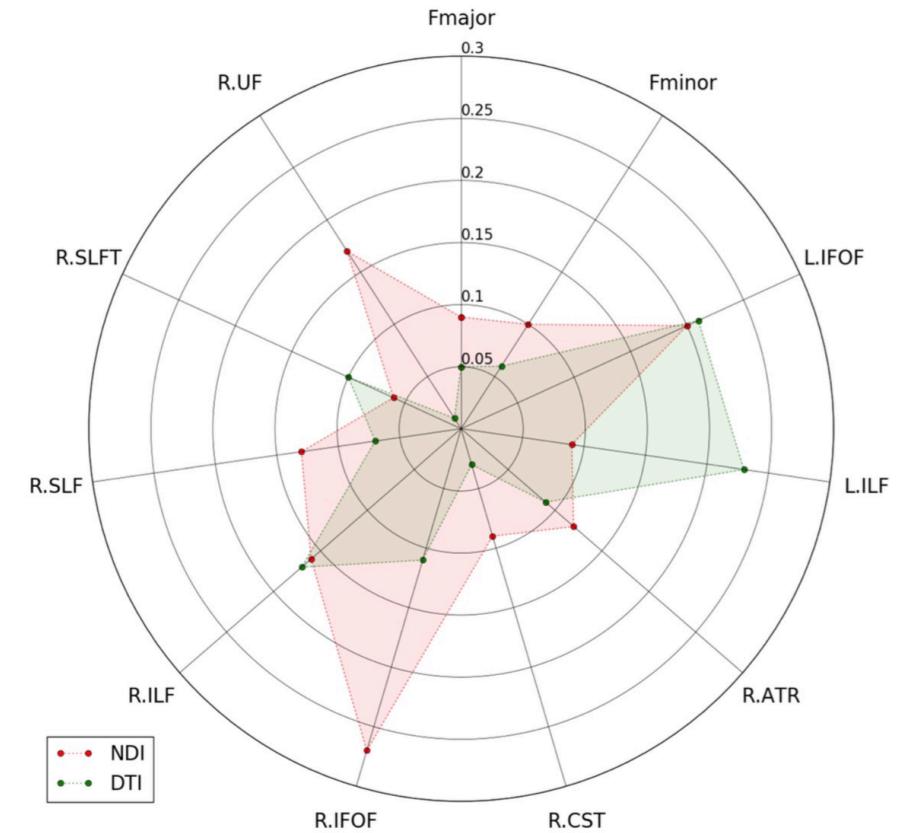
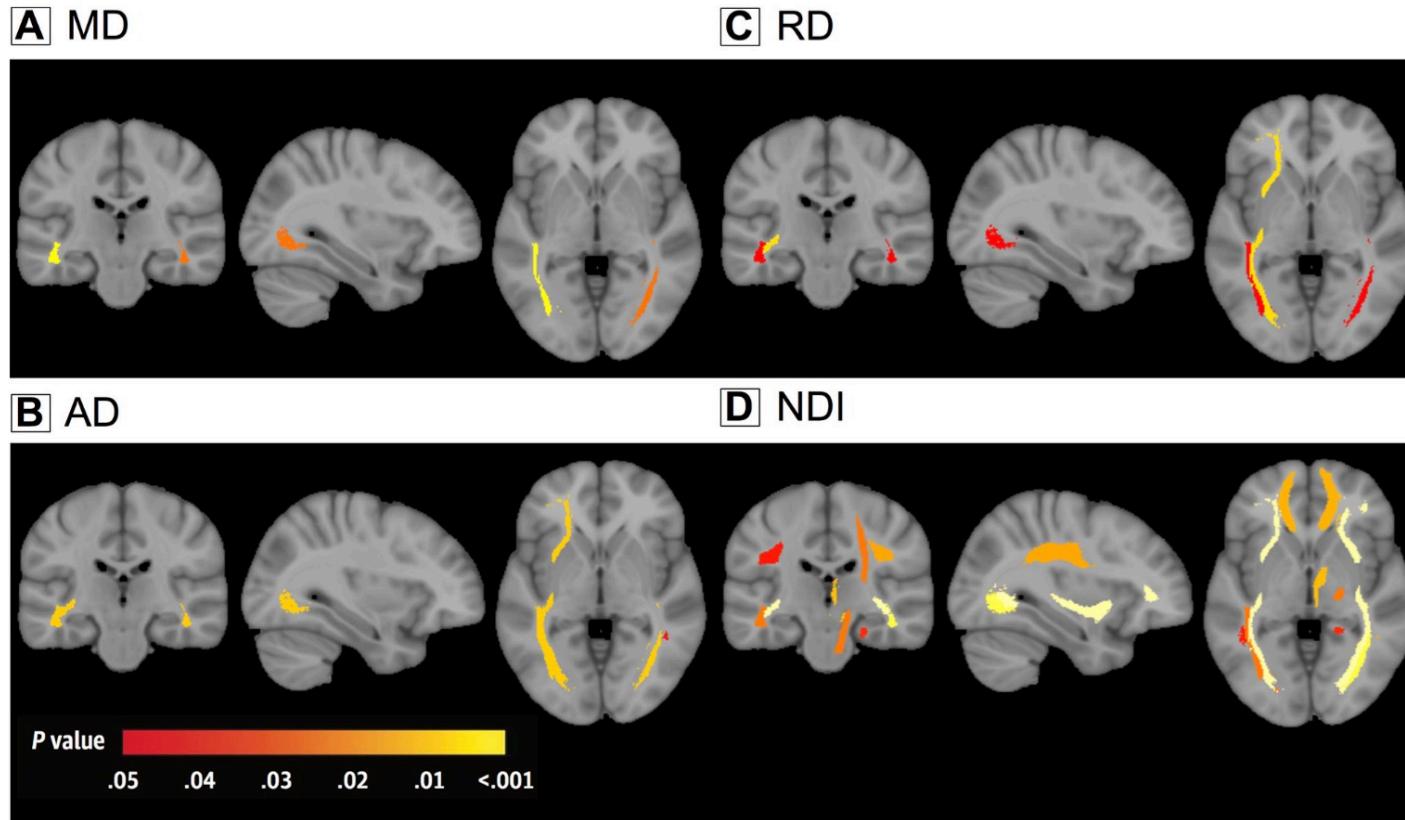


Bertrand and Wen., 2018

Diffusion MRI Analyses

WM analyses:

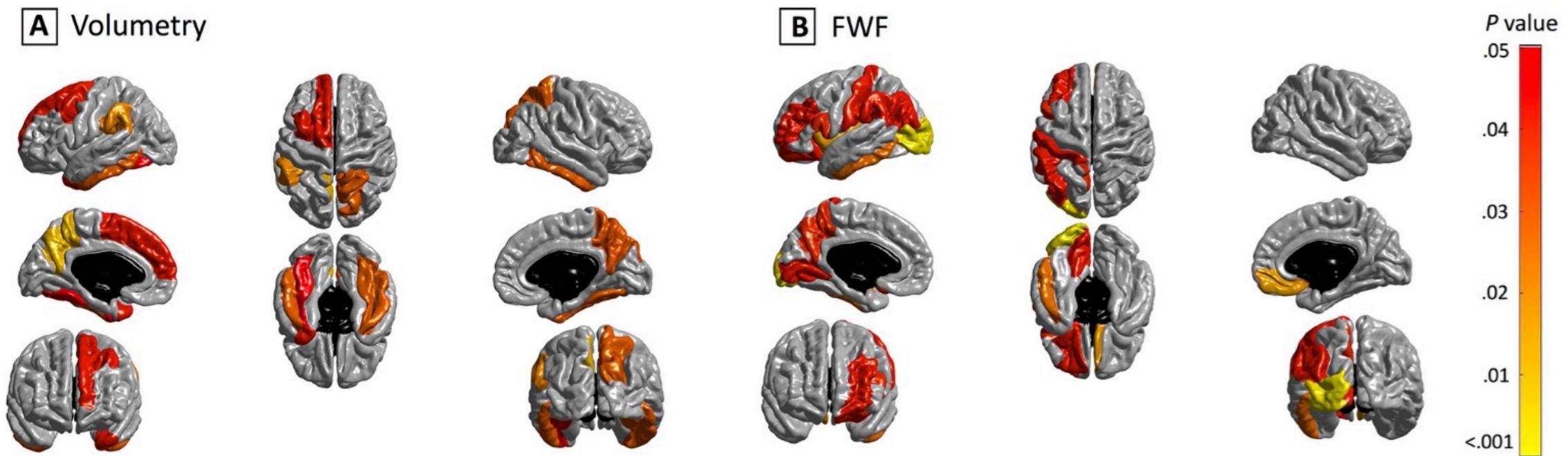
- C9+ demonstrated white matter abnormalities in 10 tracts with NDI and only 5 tracts with DTI metrics.
- Effect size was significantly higher for the NDI than for DTI metrics in two tracts.



Diffusion MRI Analyses

Cortical GM analyses:

- FWF was increased in 13 regions in C9+, whereas 11 regions displayed volumetric atrophy.

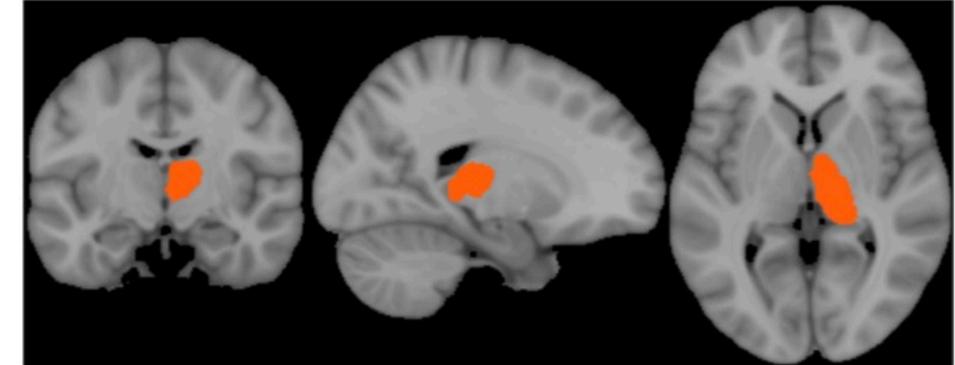


Diffusion MRI Analyses

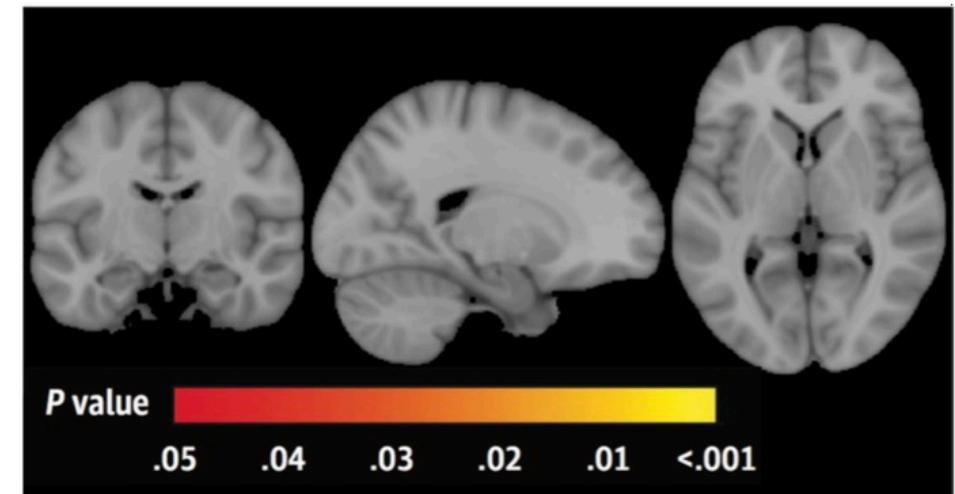
Subcortical GM analyses:

- C9+ showed subcortical atrophy of the right thalamus.

A Volumetry



B FWF



Discussion

Discussion:

- Cognitive, structural, and microstructural alterations are detectable in young C9 individuals.
- NODDI provides higher sensitivity and greater tissue specificity compared with conventional DTI for identifying white matter abnormalities in the presymptomatic C9 carriers.
- Distinct degenerative processes (ie., brain atrophy and free water expanding) could occur in cortical and subcortical structures at the same time during the presymptomatic stage.

Conclusion:

- Our work contributes a better understanding of the preclinical phase of C9 disease and encourages the use of a multishell DWI sequence and NODDI in clinical studies.



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BRAIN DATA SCIENCE



Thank you for your attention !