White matter hyperintensities correlate with neuropsychiatric manifestations of Alzheimer's disease and frontotemporal lobar degeneration

Annual Scientific Meeting – Canadian Geriatric Society

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Presenter Disclosure

Philippe Desmarais, MD, FRCPC, MHSc (c)

- **Relationships with financial sponsors:** *none*

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Mitigating Potential Bias

Philippe Desmarais, MD, FRCPC, MHSc (c)

- The sponsors of the study had no role in the study design, data collection, data analysis, or data interpretation.

Background

Alzheimer's disease (AD)

- Most prevalent neurocognitive disorder with advancing age
- Neuropsychiatric manifestations are frequent and distressing

Frontotemporal lobar degeneration (FTLD)

- Multiple neurodegenerative pathologies with overlapping clinical features
- Various cognitive, neuropsychiatric, and motor manifestations
- Clinical phenotypes:
  - *Behavioural variant frontotemporal dementia (bvFTD);*
  - *Primary Progressive Aphasia (PPA);*
  - *Corticobasal syndrome (CBS);*
  - *Progressive supranuclear palsy (PSP).*

Background

Gray matter atrophy and clinical manifestations

- Mesial temporal atrophy ➔ episodic memory and learning deficits[1]
- Orbitofrontal atrophy ➔ disinhibition, impulsivity[2]

White matter changes

- White matter hyperintensities (WMHs) were associated in AD with[3]:
  - ➔ *executive dysfunction*
  - ➔ *mental processing speed impairment*
  - ➔ *memory deficits*

[1] Bruen *et al.*, *Brain*, 2008; [2] Zamboni *et al.*, *Neurology*, 2008;
[3] Ramirez *et al.*, *Alzheimer's Research & Therapy*, 2014

Objective

To better understand the relationships between regional white matter hyperintensities and neuropsychiatric symptoms in patients with sporadic Alzheimer's disease and frontotemporal dementia and related disorders.

Methods

Study Design

Cohort series from the Sunnybrook Dementia Study

- Ongoing longitudinal study of subjects with/without cognitive impairment
- Subjects undergo extensive assessments:
  - Neuropsychological batteries: MMSE, MoCA, DRS, and various other tests;
  - Neuropsychiatric batteries: NPI, BEHAVE-AD;
  - Genetic testing: APOEε genotype, others;
  - Brain imaging: standardized MR and SPECT imaging.

Case Selection

Retrospective selection and analysis of autopsy-confirmed cases of:

- Alzheimer's Disease (AD);
- Frontotemporal dementia (FTD) due to:
  - Tau proteinopathy (i.e. Pick's disease);
  - TDP-43 proteinopathy;
- Progressive supranuclear palsy (PSP);
- Corticobasal degeneration (CBD).

As well as healthy controls (HC) for comparison purposes.

Methods

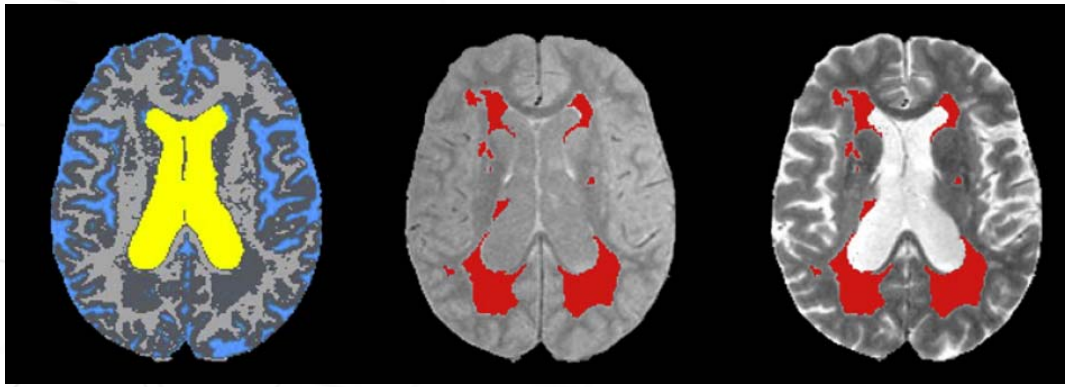
Data Collection

- Demographic data: sex, age, education level
- Comorbidities: vascular risk factors and cardiovascular events
- Disease: age at onset, age at assessment, pathology findings
- Baseline neuropsychological & neuropsychiatric results:
  - Neuropsychiatric inventory (NPI): total score, caregiver score, and 12 subscale items
- Baseline brain imaging volumetrics obtained on a 1.5 Tesla GE Signa system:
  - T1-, T2-, and PD-weighted axial cuts;
  - 3 mm slice thickness.

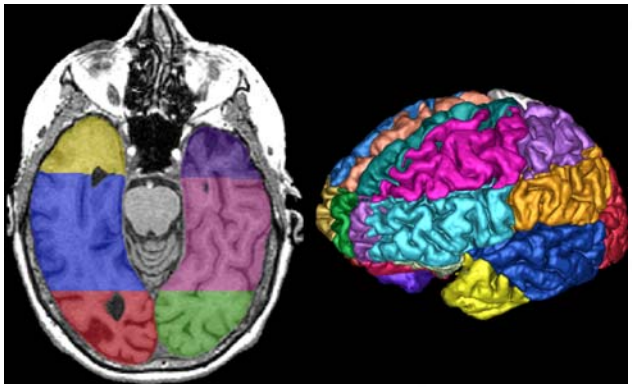
Methods

Imaging Analysis

- **MR imaging processing included:**
  - Segmentation and parcellation procedures[1];
  - Volumetrics for regional and whole-brain regions;
  - Values adjusted for total intracranial volume (TIV).



Segmentation and Lesion Explorer segmentation



SABRE Parcellation

[1] Ramirez et al., *NeuroImage*, 2011

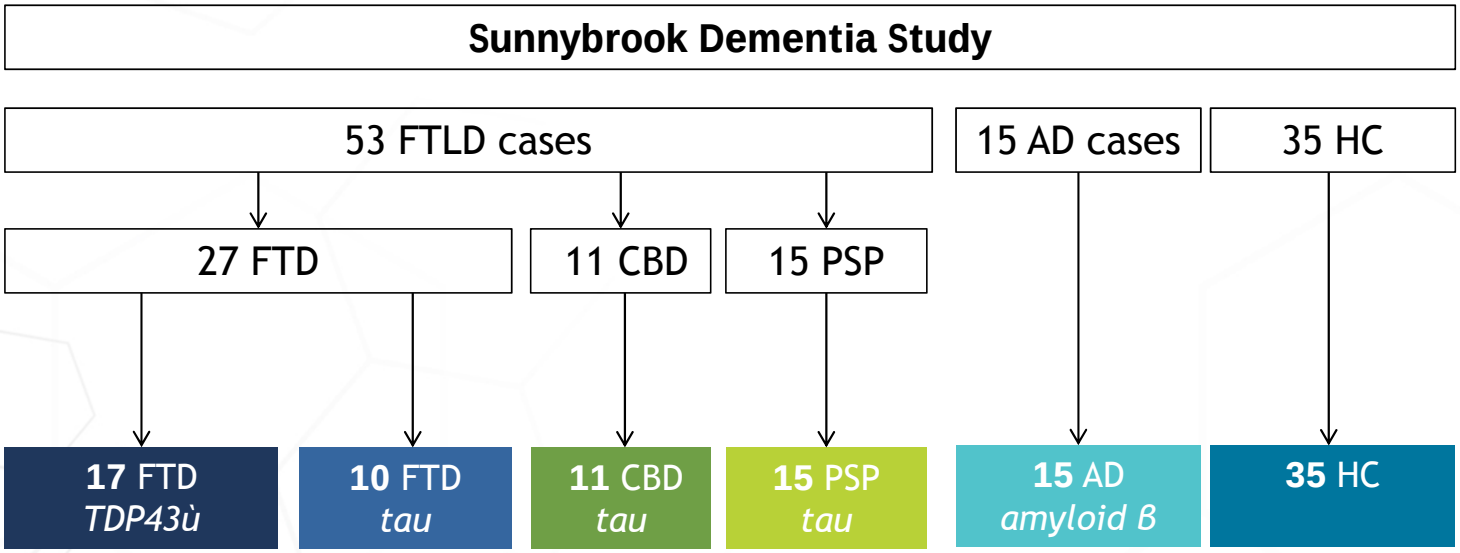
Methods

Data Analysis

- **Linear regressions:**
  - dependent variables = items of the NPI;
  - predictors = regional WMH volumes;
  - covariates = age, sex, educational level, and corresponding regional GM volumes
- Statistical analyses were performed with IBM® SPSS ® Statistics 24.0

Results

Identified Cases



Results

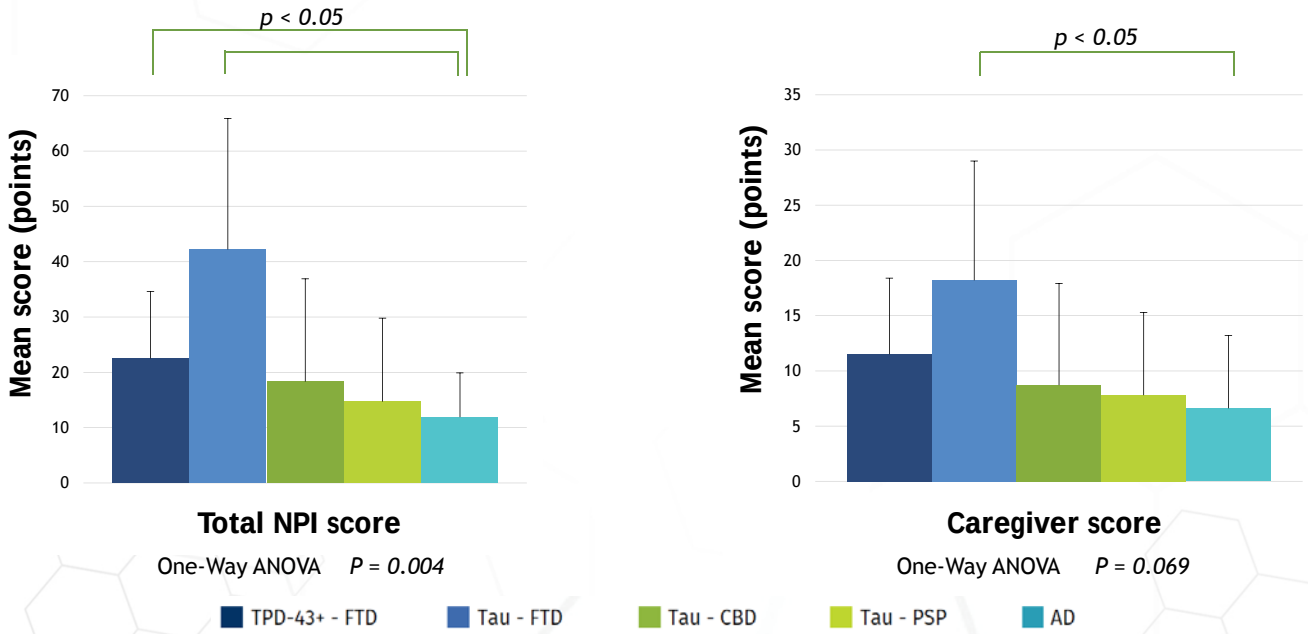
Demographic and Clinical Characteristics

Characteristic	FTLD-TDP 43 FTD (n = 17)	FLTD-tau FTD (n = 10)	FTLD-tau CBD (n = 11)	FTLD-tau PSP (n = 15)	AD (n = 15)	HC (n = 35)	P - value*
Female, n (%)	8 (47%)	4 (40%)	8 (73%)	6 (40%)	5 (33%)	14 (40%)	0.449
Hand dominance, R/L/A	16/0/1	7/2/1	10/1/0	13/1/1	15/0/0	16/0/1	0.512
Education in years, mean (SD)	14.4 (3.3)	15.4 (4.1)	13.5 (3.2)	15.3 (3.2)	16.0 (5.5)	14.4 (3.3)	0.465
Age at baseline, mean (SD)	66.8 (9.5)	67.4 (9.6)	67.4 (6.6)	71.4 (5.3)	69.1 (10.0)	71.2 (7.8)	0.381
Age at onset of symptoms, mean (SD)	63.6 (9.3)	63.5 (11.1)	63.9 (6.0)	68.3 (5.8)	65.6 (10.5)	..	0.549
Disease duration, mean (SD)	3.2 (1.4)	3.9 (3.7)	3.6 (1.7)	3.1 (1.7)	3.6 (2.2)	..	0.881
MMSE (/30), mean (SD)	21.8 (7.0)	16.9 (10.6)	21.9 (5.8)	24.1 (6.2)	19.9 (6.4)	28.9 (0.9)	<0.0001
Genotype APOE ε4+, n/N (%)	6/12 (50%)	1/9 (11%)	0/8 (0%)	2/12 (17%)	6/13 (46%)	2/6 (33%)	0.067
Vascular risk factors, n (%)							
Hypertension	5 (29%)	2 (20%)	3 (27%)	5 (33%)	4 (27%)	9 (26%)	0.988
Hyperlipidemia	4 (24%)	0 (0%)	3 (27%)	2 (13%)	6 (40%)	1 (3%)	0.008
Diabetes mellitus	0 (0%)	1 (10%)	2 (18%)	0 (0%)	0 (0%)	0 (0%)	0.018

Data are n (%) and mean (SD). All percentages were rounded to the nearest whole number.
* P-value for One-Way ANOVA.

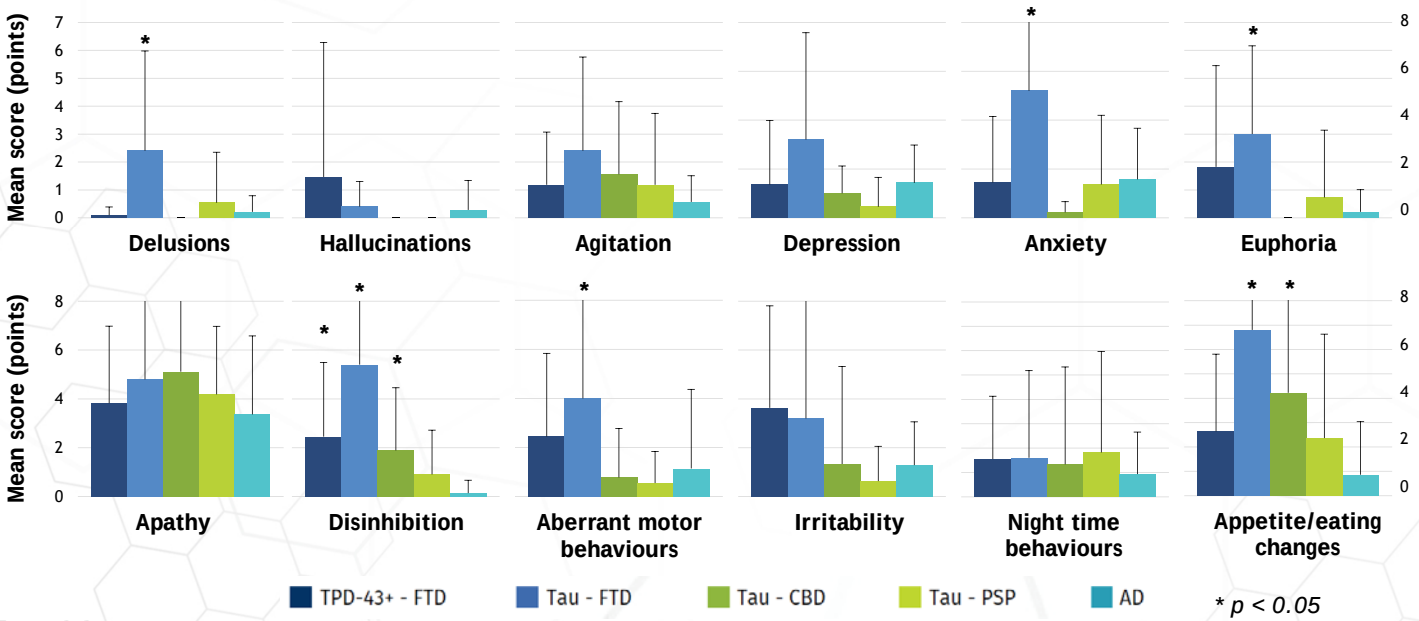
Results

Neuropsychiatric symptoms at baseline



Results

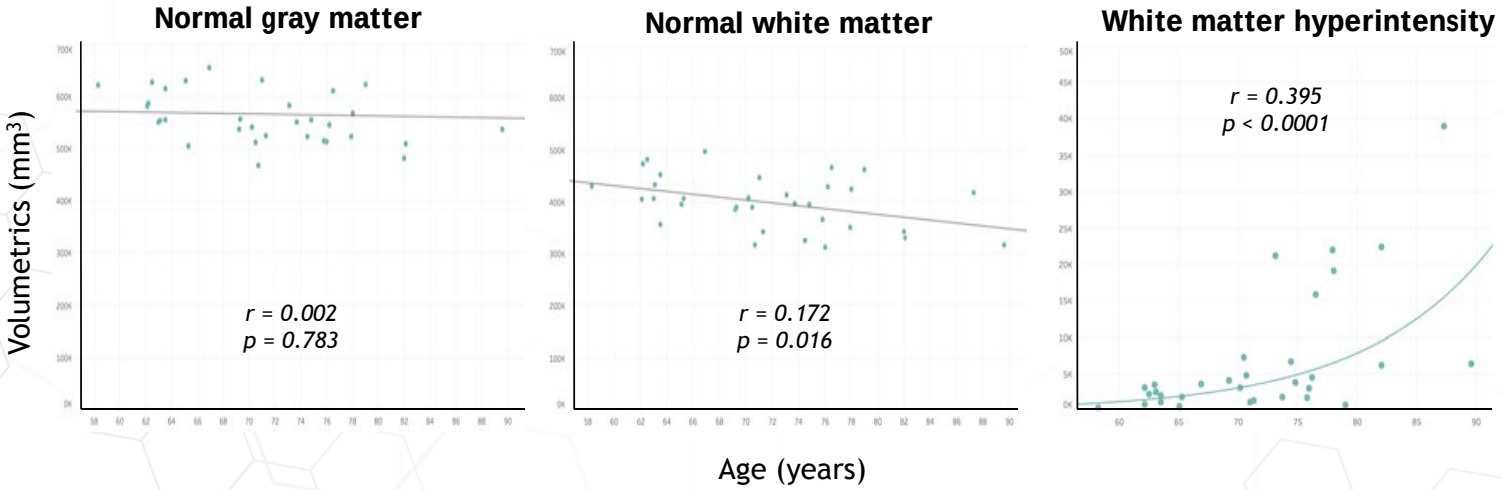
Neuropsychiatric symptoms at baseline



Results

Volumetrics at baseline

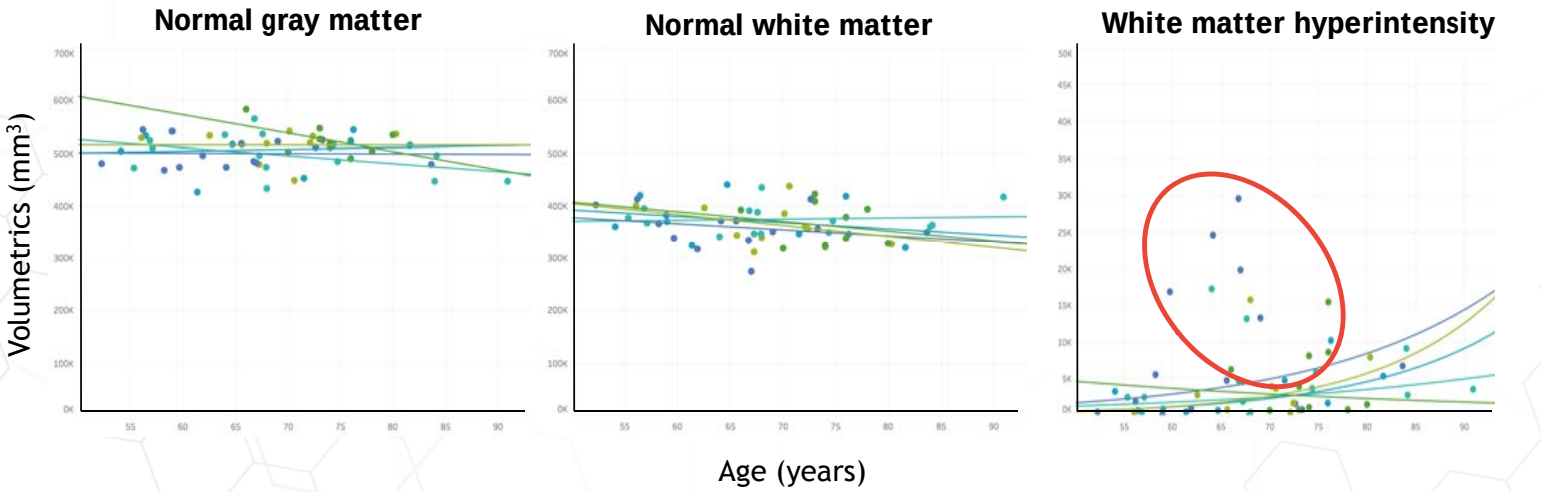
Healthy controls



Results

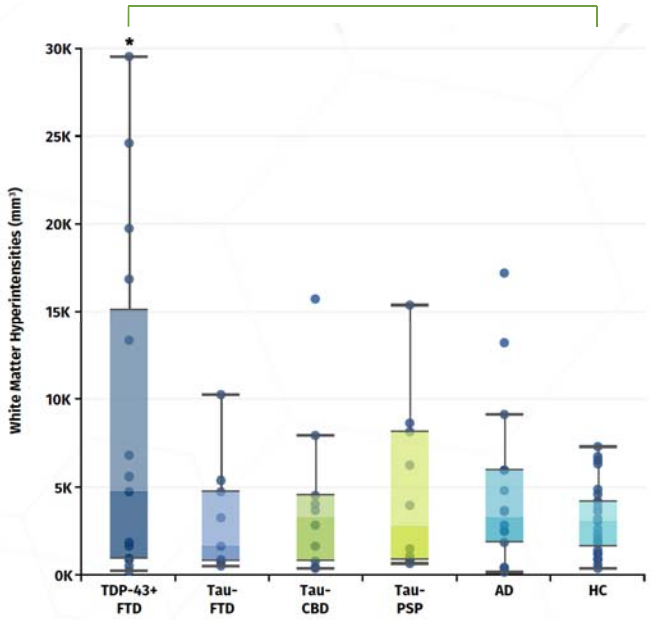
Volumetrics at baseline

Neurodegenerative disorders



Results

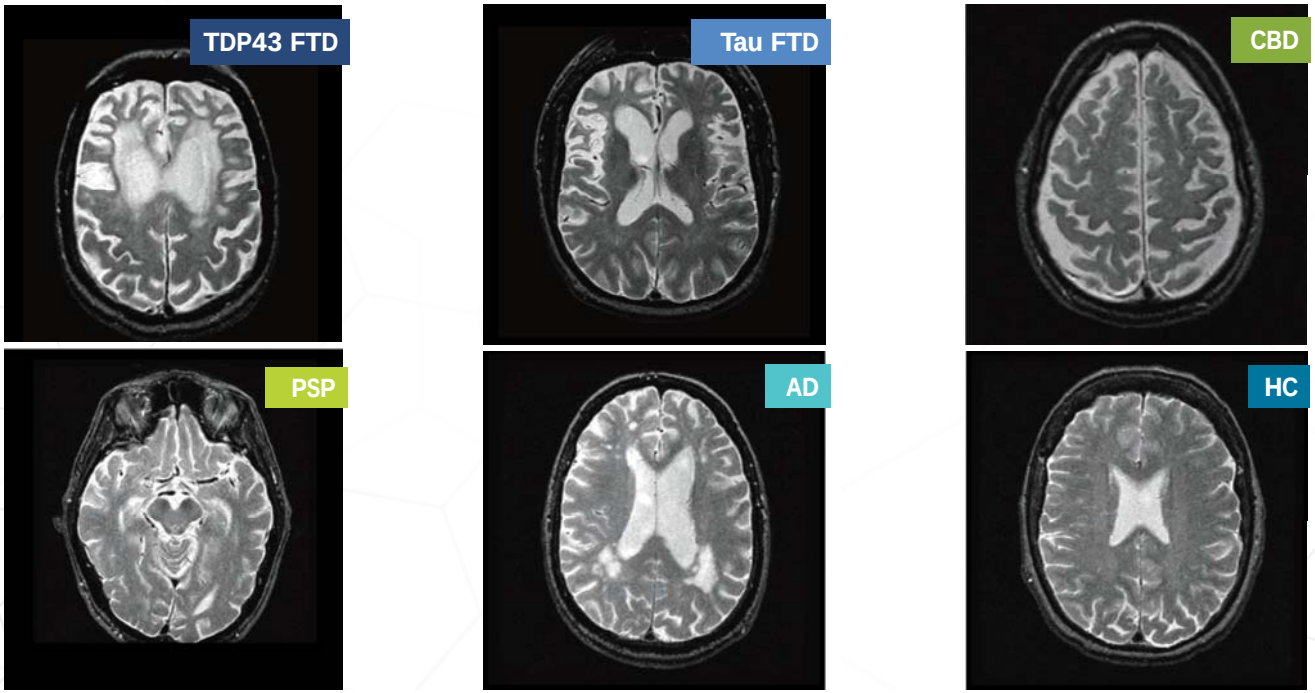
White Matter Hyperintensities



Data were adjusted for total intracranial volume. * Student's T-test $p < 0.05$ compared to HC.

Results

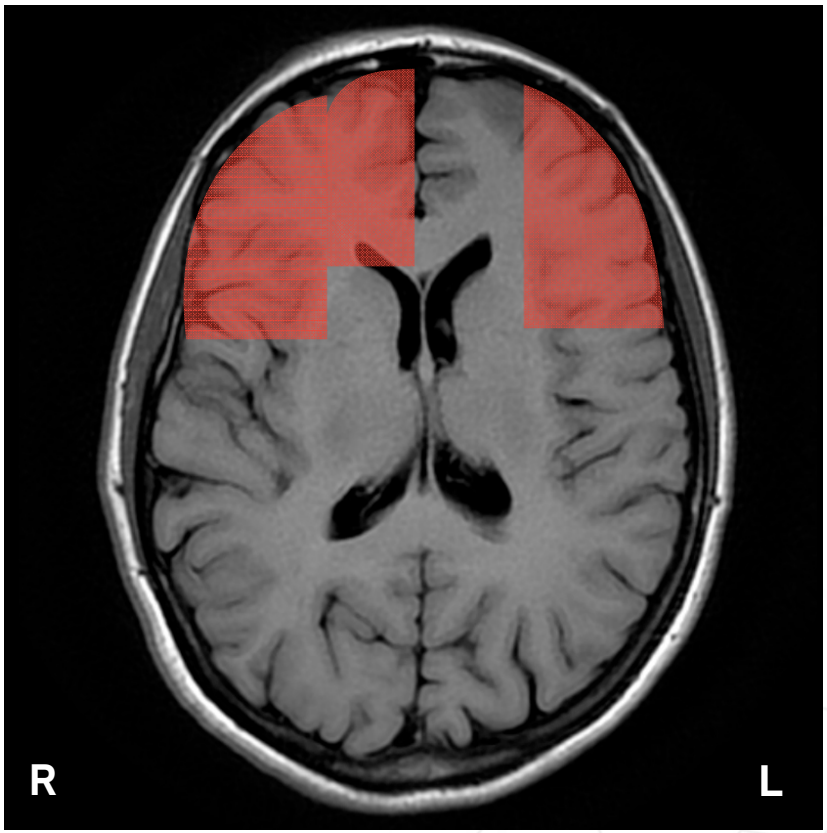
White Matter Hyperintensities



Results

Clinico-radiological Correlations

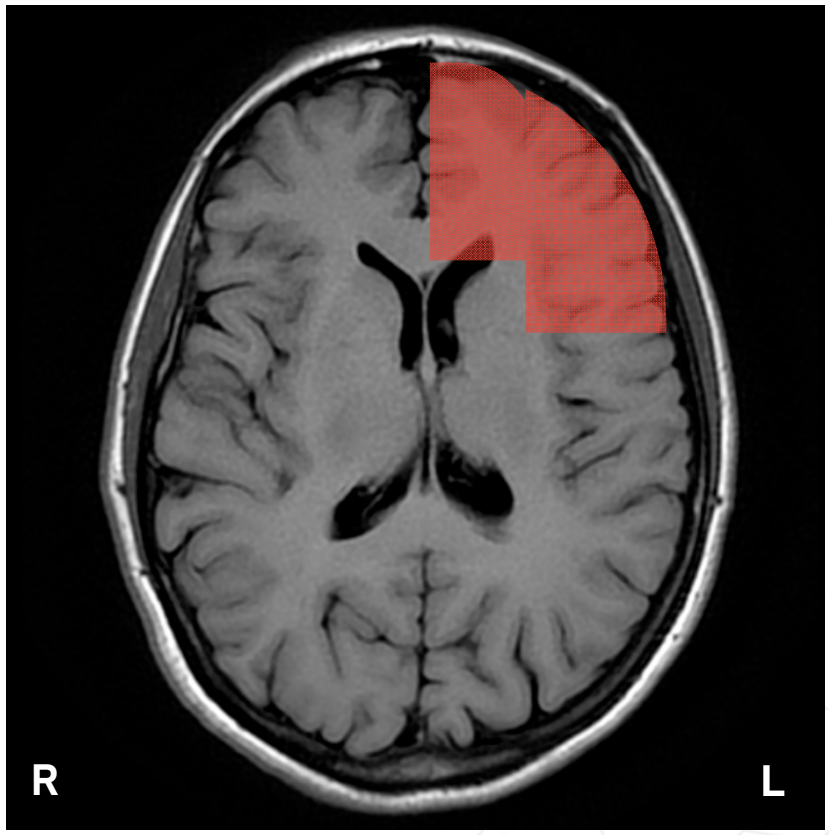
Anxiety & WMH:



Results

Clinico-radiological Correlations

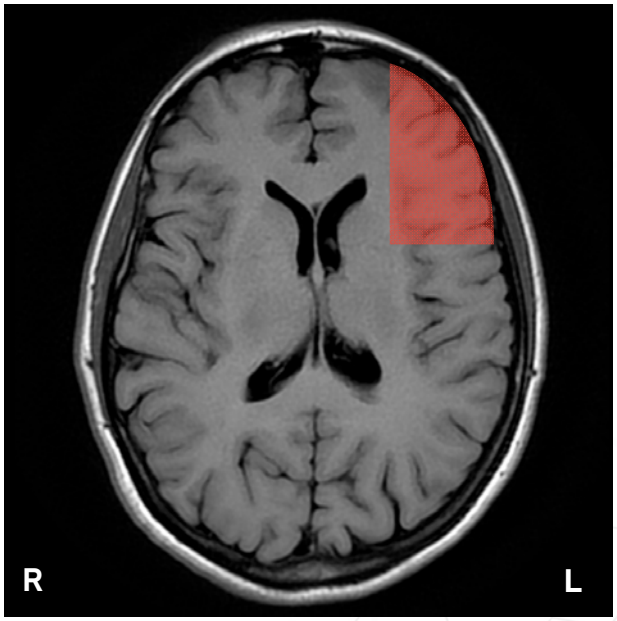
Euphoria & WMH:



Results

Clinico-radiological Correlations

Eating Changes & WMH:



Discussion

Highlights & Interpretation

- FTD due to TDP-43+ was associated with significant increased in total WMHs:
  - Progranulin mutation linked to WMHs[1]
- WMH distribution was different between AD and FTLD pathologies:
  - More frontotemporal regions for TDP-43+
  - More periventricular regions (anteriorly and posteriorly) in AD
- Specific regions of WMHs correlated with specific neuropsychiatric symptoms:
  - Previous positive correlations in psychiatric disorders, such as depression[2] and bipolar disorder[3]
  - White matter changes in frontal region linked to frontostriatal dysfunction[4]

[1] Caroppo *et al.*, *JAMA Neurology*, 2014; [2] Firbank, *et al.*, *American Journal Geriatric Psychiatry*, 2004;
[3] Tighe *et al.*, *Bipolar Disorder*, 2012; [4] MacFall *et al.*, *Biological Psychiatry*, 2000

Discussion

Strengths

- Large cohort of autopsy-confirmed cases of FTLD
- Quantitative measures of white matter hyperintensities

Limitations

- Underpowered for some subgroup comparisons
- Correlation relationships ≠ causation relationships
  - WMHs ➔ neuropsychiatric sx *vs.* neuropsychiatric sx ➔ WMHs ?

Discussion

Future Directions

WMH volumetrics could be used as:

- Diagnostic biomarkers to differentiate between FTD-*tau*, FTD-*TDP-43*, and AD pathologies
- Surrogate markers for pharmacological trials
- Potential predictive markers for clinical response to psychotropic medications

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Thank you!

Questions?