Investigating the contribution of White Matter Hyperintensities to Neuropsychiatric Symptoms and Social Cognition Deficits in Patients with Neurodegenerative Diseases

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Background

- Neurodegenerative diseases are associated with neuropsychiatric symptoms (NPS) and social cognition deficits in addition to cognitive impairment[1].
- NPS and social cognition deficits contribute to caregiver burden and patient distress[2].
- White matter hyperintensities (WMH) likely reflect ischemic damage and are related to vascular risk factors.
- WMH have been implicated in NPS: increased frontal WMH volumes with worse depression and delusions in patients with Alzheimer's disease, vascular dementia, and dementia with Lewy bodies[3,4]; negative association between WMH and social cognition in patients with small vessel disease[5].

Objective

- To examine the associations between WMH, NPS, and social cognition amongst patients with neurodegenerative diseases.

Methods

- Subjects: 126 Alzheimer's Disease/Mild Cognitive Impairment (AD/MCI), 155 Vascular Cognitive Impairment (VCI), 140 Parkinson's Disease (PD), 52 Frontotemporal Dementia (FTD), and 40 Amyotrophic Lateral Sclerosis (ALS) patients underwent baseline MRI and assessment as part of the Ontario Neurodegenerative Disease Research Initiative (ONDRI) study, a research program investigating five neurodegenerative diseases (http://ondri.ca/).
- NPS was measured using Neuropsychiatric Inventory (NPI)[6].
- Social Cognition was measured using:
  - Revised Self-monitoring Scale (RSMS): Socioemotional sensitivity[7].
  - Interpersonal Reactivity Index (IRI) filled out by informant (other) and patient (self): Empathy[8].
  - Social Norms Questionnaire (SNQ): Social norm adherence[9].
- WMH volumes were measured using a previously validated MRI-based volumetric method [Fig.1][10], and subdivided by hemispheric lobes.
- Global cognition was measured using Montreal Cognitive Assessment (MoCA) [11].
- WMH was corrected for hemispheric lobes and log transformed.
  - e.g. (RightFrontalWMH/TotalRightFrontalVolume)*100
- Analysis of Variance (ANOVA) was used to analyze continuous variables and Chi-square for categorical variables.
- Linear regression was used to determine which variable of WMH, Age, Neurocognition, Diagnosis, and Gender contributed most to NPS and social cognition deficits.

Results

Table1. Demographic and Clinical characteristics between Diagnostic groups. **Post-hoc analyses: a.** AD/MCI>PD; AD/MCI>ALS; VCI>ALS; PD>ALS; FTD>ALS. **b.** AD/MCI>FTD; PD>FTD; PD>ALS. **c.** AD/MCI<VCI; AD/MCI<PD; AD/MCI<ALS; VCI>FTD; PD>FTD; FTD<ALS.

	AD/MCI (N=126) Mean (SD)	VCI (N=155) Mean(SD)	PD (N=140) Mean(SD)	FTD (N=52) Mean(SD)	ALS (N=40) Mean (SD)	p value
Age (years)	71.02 (8.16)	69.35 (7.36)	67.93 (6.35)	67.81 (7.12)	61.99 (8.74)	< 0.001[a]
Gender (M:F)	69:59	106:49	109:31	33:19	24:16	= 0.002
Education	15.23 (3.07)	14.69 (2.88)	15.49 (2.73)	13.88 (2.73)	13.83 (2.88)	< 0.001[b]
MoCA Total	22.67 (2.99)	25.29 (2.99)	25.84 (2.57)	21.48 (3.96)	25.46 (2.84)	< 0.001[c]

Image Processing

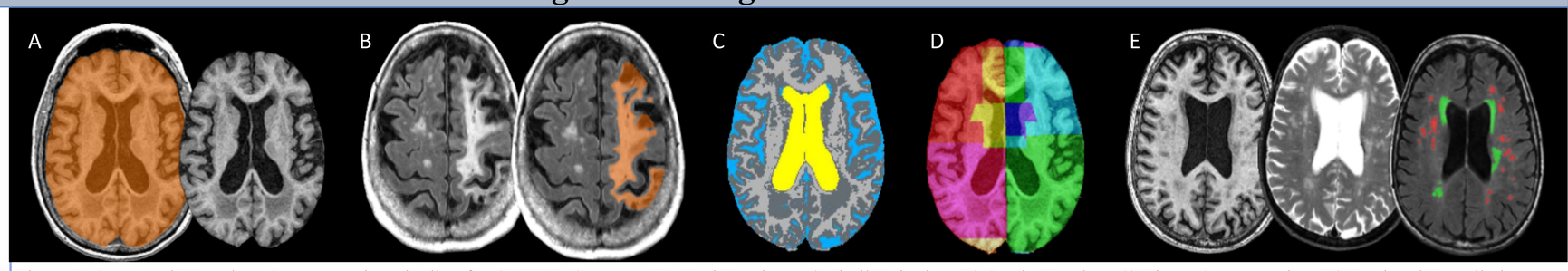

Figure 1. Structural Neuroimaging processing pipeline for ONDRI. *Courtesy:* Dr. Joel Ramirez. A) Skull Stripping; B) Stroke Tracing; C) Tissue Segmentation; D) Regional Parcellation; E) Small Vessel Disease Biomarker Segmentation.

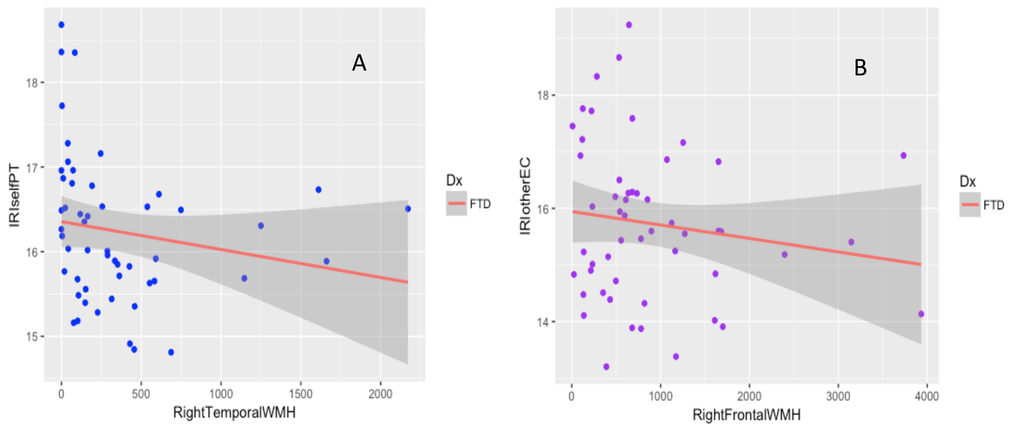

Figure 2. Relationship between White Matter Hyperintensities (WMH) and Empathy in Male FTD. A) Perspective Taking (PT) evaluated by self and Right Temporal WMH; B) Empathic Concern (EC) evaluated by others and Right Frontal WMH. IRI = Interpersonal Reactivity Index.

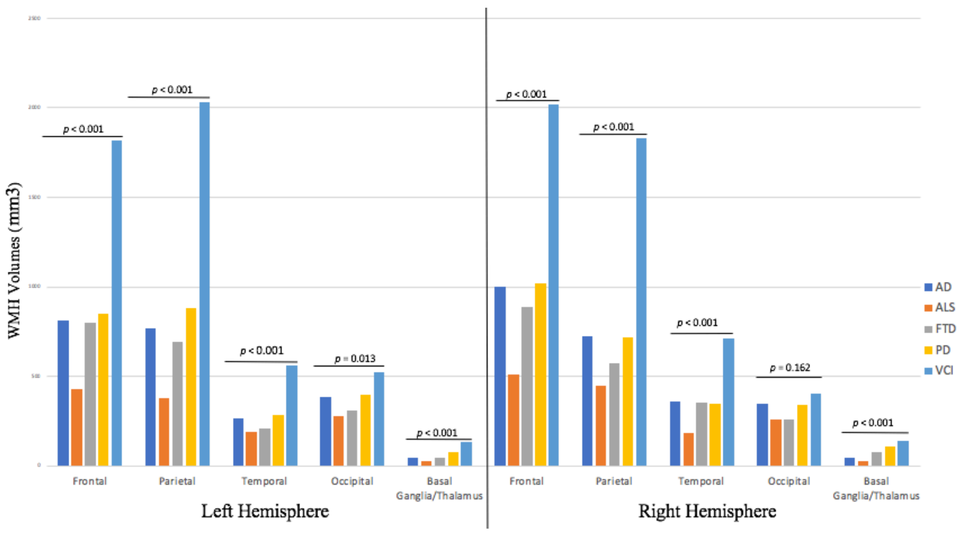

Figure 3. Group Differences in White Matter Hyperintensities.VCI had significantly higher WMH volume compared to other groups, except in the right occipital lobe.

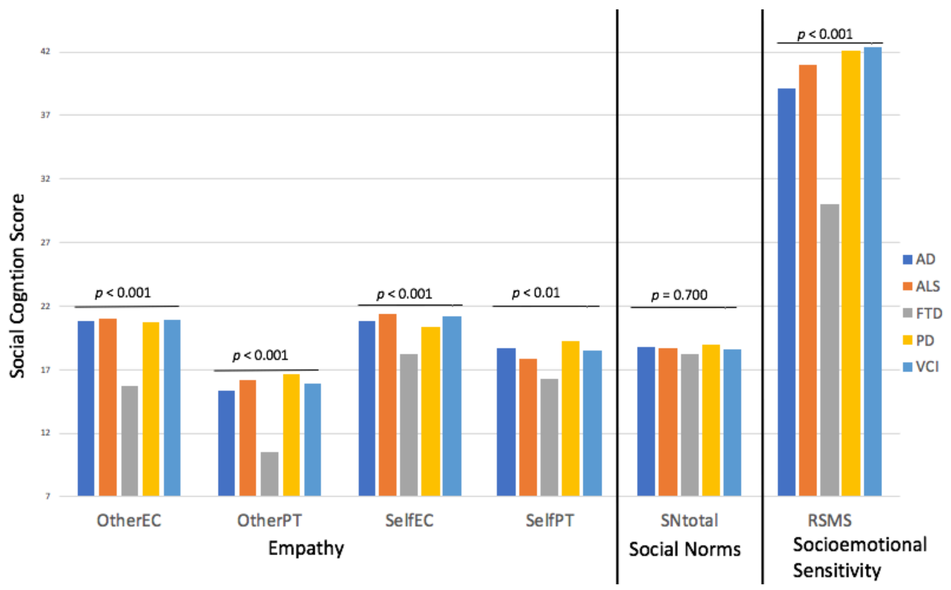

Figure 4. Group Differences in Social Cognition Measures. FTD scored significantly lower on empathy and social behaviours compared to other groups. PT= Perspective Taking; EC = Empathic Concern; SN = Social Norms; RSMS = Revised Self-monitoring Scale

- Severity of NPS and caregiver distress were significantly higher in FTD ($p < 0.001$), compared to other groups.
- Being male, having FTD, and right temporal WMH is associated with decreased perspective taking (according to self) (β = -1.47, $p < 0.001$; β = -1.99, $p < 0.01$; β = -0.37, $p = 0.029$), respectively. Fig. 2A.
- Being male, having FTD, and right frontal WMH is associated with decreased empathic concern (according to informant) (β = -2.46, $p < 0.001$; β = -4.31, $p < 0.001$; β = -0.73, $p = 0.046$), respectively. Fig. 2B.
- Having FTD is associated with lower scores in socioemotional sensitivity (RSMS: β = -8.71, $p < 0.001$).
- Being male and having FTD is associated with increased NPS severity (β =1.57, $p < 0.001$; β = 3.47, $p < 0.001$), respectively. Increased age and better cognition is associated with decreased NPS severity (β = -0.09, $p < 0.01$; β = -0.23, $p < 0.001$), respectively.
- Being male and having FTD is associated with increased NPS caregiver distress (β = 2.41, $p < 0.001$; β = 3.61, $p < 0.001$), respectively. Increased age and better cognition is associated with decreased NPS caregiver distress (β = -0.16, $p < 0.001$; β = -0.27, $p < 0.01$), respectively.

Conclusions

- FTD has worse social cognition (lack of empathy and less socioemotional sensitivity) and more neuropsychiatric symptoms. Increased WMH in right frontal and temporal lobes contributed to deficits in social cognition.
- Our findings suggest that WMH may contribute to social cognition deficits in FTD and warrants further study.

Acknowledgements

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