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Major depression disorder with a late age-of-onset as a biological model to detect the brain features of depression in Alzheimer's disease and behavioral variant of frontotemporal dementia

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INTRODUCTION AND OBJECTIVES

In Alzheimer's disease (AD) and behavioural variant of frontotemporal dementia (bvFTD), depression is a frequent symptom. Whether depressive symptoms are a patient reaction to cognitive decline or are intrinsic to neurodegeneration is still poorly understood. Patients with a late age-of-onset major depressive disorder (lo-MDD) may represent a model to understand the nature of depressive symptoms in AD and bvFTD.

The aims of this study were:

✓ to detect the structural brain signatures of lo-MDD patients relative to healthy controls (TRAINING-dataset), and

✓to test the ability of such measures to predict the presence of depression in AD and bvFTD patients as well as in an independent group of controls (TESTING-dataset).

METHODS

TRAINING-dataset: 15 lo-MDD and 28 healthy controls.

TESTING-dataset: 61 AD, 27 bvFTD, and an independent group of 20 age-matched healthy controls (**Tab.1**).

Table 1. Sociodemographic and clinical features of patients and controls.

TRAINING DATASET			
	MDD	**HC**	**p**
N	15	28	
Age at MRI	56.5 ± 3.0	54.7 ± 5.6	0.27
Education	3.4 ± 1.0	4.5 ± 1.1	0.04
Gender, females	12 (80%)	25 (89%)	0.65
Age at Onset	54.1 ± 3.4	-	-
Disease duration, months	37.7 ± 35.4	-	-
HAMD	22.5 ± 3.8	-	-
HAMA	22.5 ± 8.7	-	-
TESTING DATASET			
	EOAD	**bvFTD**	**HC**
N	61	27	20
N with depressive symptoms#	34 (56%)	14 (52%)	4 (20%)*
Age at MRI	59.7 ± 4.1	57.7 ± 8.1	61.2 ± 7.0
Education	12.0 ± 2.6	12.3 ± 2.8	11.9 ± 2.8
Gender, females	37 (60%)	11 (41%)	7 (35%)
Age at onset	56.2 ± 4.1	53.9 ± 8.6	-
Disease duration, months	3.6 ± 1.3	3.8 ± 3.0	-
HAMD	4.2 ± 4.0	5.8 ± 4.9	3.9 ± 4.6
HAMA	4.6 ± 2.9	5.4 ± 4.3	3.3 ± 0.7
CDR	1.8 ± 0.8*	1.3 ± 0.6	-
CSF, $A\beta_{42}$	418.7 ± 100.2*	1090.6 ± 227.6	-
CSF, T-tau	567.0 ± 273.8*	248.3 ± 104.4	-
CSF, p-tau	81.97 ± 35.74*	49.8 ± 21.3	-

Values are means ± standard deviations or frequencies (%). P values refer to T-test models. *=p<0.05 *vs* the other group/s. Education scale: 1= no school; 2= primary school; 3= high school; 4= college; 5= university degree; 6= master degree or doctoral degree. Abbreviations. Aβ42=Amyloid β42; CDR=Clinical Dementia Rating; CSF=Cerebrospinal Fluid; HAMA=Hamilton Anxiety Rating scale; HAMD= Hamilton Depression Rating scale. MRI=Magnetic Resonance Imaging; T-tau=Total tau; p-tau=phosphorilated tau. #=according to clinical scales, neurologist evaluation and caregiver 's reports.

MRI acquisition

- 1.5 T Philips Medical Systems (Achieva): dual echo, 3D T1-Transient Field Echo (TFE) and diffusion tensor (DT) MRI sequences.

MRI preprocessing

- MRI metrics of cortical thickness (CT) were obtained from atlas-based cortical regions using FreeSurfer 5.3 and the Desikan atlas.
- DT MRI metrics from the major interhemispheric and long association white matter (WM) tracts using probabilistic tractography.

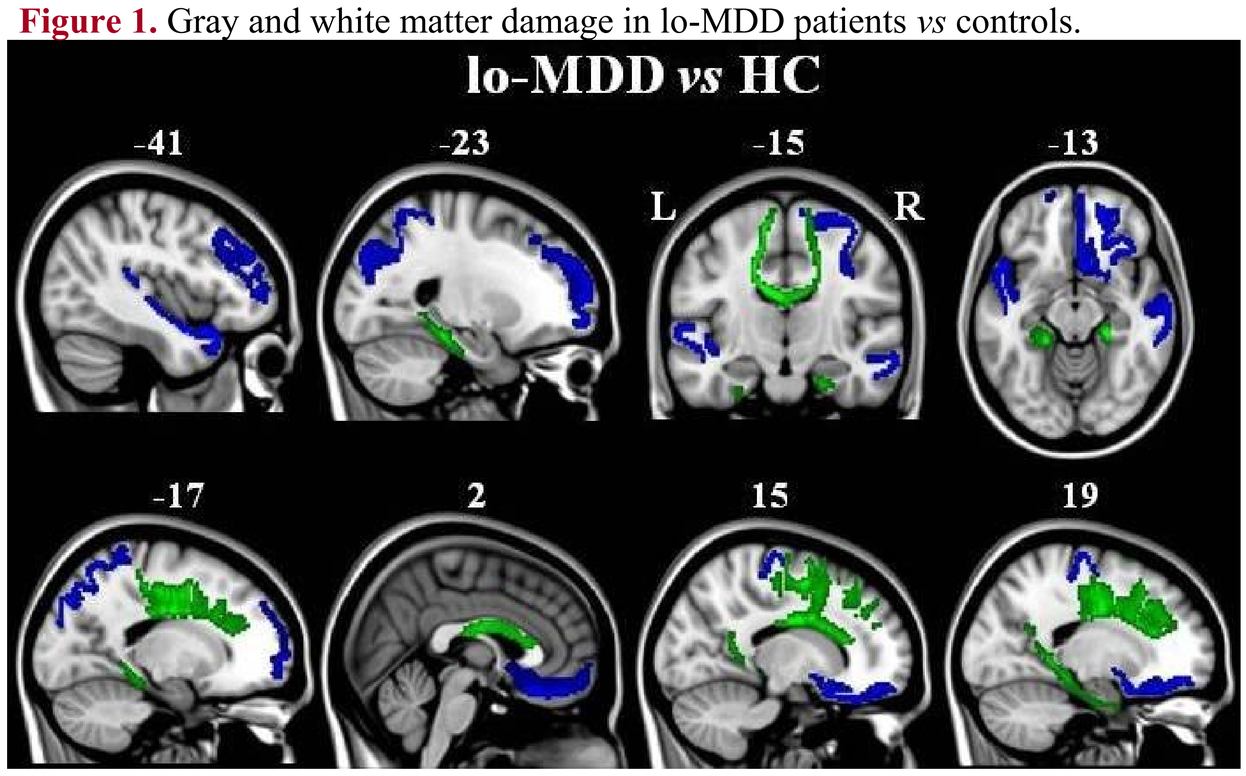
Statistical analysis

- Using T-test models, MRI metrics of CT and WM tracts were compared between groups in the **TRAINING-dataset** to identify signatures of depression.
- Using a ROC curve analysis, CT and DT MRI measures found to be significantly different between TRAINING-dataset groups were used for the classification of depressed/non-depressed outcome (defined according to clinical scales, neurological evaluation and caregiver's reports) of the **TESTING-dataset**.

RESULTS

TRAINING-dataset. Compared with controls, lo-MDD patients showed reduced WM integrity of the body of the corpus callosum and of the parahippocampal tract bilaterally (**Fig.1**, green colour), and reduced CT of the left rostral middle frontal cortex, left superior temporal and parietal gyri, right medial and lateral orbitofrontal cortex, and right precentral and middle temporal gyri (**Fig.1**, blue colour).

Figure 1. Gray and white matter damage in lo-MDD patients *vs* controls.



Colours indicate cortical thinning (blue) and white matter tract damage (green). Results are overlaid on the Montreal Neurological Institute standard brain and shown at p<0.05 uncorrected; R=right; L=left. In sagittal views, negative numbers denote the left side.

TESTING-dataset (Tab.2). ROC curve analysis demonstrated that the best models to predict the presence of depression are: in all subjects, a model combining CT and DT MRI measures ("GM+WM model"); in controls, the model combining CT measures ("GM model"); in AD, the "GM+WM model", although it adds low prediction power respect to the "GM model" alone; and in bvFTD, the "GM+WM model" which adds higher power of prediction respect to each other model alone.

Table 2. ROC curve findings for the classification of depression in the TESTING sample.

	AUC	**Specificity**	**Sensitivity**
All subjects			
GM model	0.66	0.80	0.50
WM model	0.62	0.82	0.47
GM+WM model	0.71	0.88	0.49
Controls			
GM model	0.84	0.69	1.00
WM model	0.77	0.53	1.00
AD patients			
GM model	0.73	0.74	0.71
WM model	0.68	0.67	0.76
GM+WM model	0.76	0.79	0.72
bvFTD patients			
GM model	0.71	0.38	1.00
WM model	0.62	0.36	1.00
GM+WM model	0.92	0.91	0.83

AUC=Area Under the Curve; GM=gray matter; WM=white matter; GM model=model combining cortical thickness (CT) measures; WM model=model combining diffusion tensor (DT) MRI measures; GM+WM model=model combining CT and DT MRI measures.

CONCLUSIONS

✓ Lo-MDD is a good model to understand the nature of depression in AD and bvFTD.

✓ Depression seems to be inherently associated with neurodegeneration in both diseases.

✓ The discrimination accuracies obtained suggest that models combining CT measures in AD and CT+WM metrics in bvFTD are potentially relevant for depression detection in these disorders.