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Background

- Data supporting clinical and biological differences between early-onset Alzheimer's Disease (EOAD, age < 65) and late-onset AD (LOAD, age ≥ 65) are accumulating based on cognitive profiles ⁽¹⁻²⁾, cortical atrophy ⁽³⁻⁴⁾ and hypometabolism ⁽⁵⁾.
- [¹¹C]UCB-J is a radiotracer targeting the **synaptic vesicle glycoprotein 2A (SV2A)**. Its properties are favourable for quantifying synaptic density in AD.⁽⁶⁾
- We used [¹¹C]UCB-J PET to investigate the extent and distribution of synaptic loss in EOAD and LOAD in order to test the hypothesis of distinct regional patterns.

Materials and Methods

- **Early stage AD patients** (CDR = 0.5-1) with a clinical and biological diagnosis based on CSF biomarkers, divided in **25 EOAD** patients and **30 LOAD** patients, and **29 age-matched healthy controls** were included and underwent [¹¹C]UCB-J PET imaging (*Table 1*). (*Three subjects were excluded prior to analysis.*)
- **Standardised uptake value ratio (SUVr)** was calculated using the whole cerebellum as the reference region for the **time window between 50 and 70 min post-injection** (see Poster P4-07). We defined **14 cortical meta-regions-of-interest (ROI)**.
- We **compared SUVr values** between EOAD and LOAD and between each patient subgroup and age-matched controls.
- We calculated a **temporal / parietal SUVr ratio**.
- We then explored the **effect of the ApoE4 genotype** on tracer uptake in each patient subgroup, and **correlations of regional tracer uptake with MMSE and CDR-SB**.

	EOAD patients (n=25)	LOAD patients (n=30)	Controls (n=29)
Age (years)	62.4 ± 6.8 *	76.3 ± 3.2 *	68.0 ± 9.6 (<65 yo: 57.8 ± 3.4, n=12 >65 yo: 75.1 ± 4.8, n=17)
Sex (M, %)	13 (52%)	14 (47%)	12 (41%)
Education (years)	13.3 ± 2.4 *	13.9 ± 3.3	15.0 ± 2.0
Apo E genotype ‡ (n E4 carriers, %)	14 * (58%)	26 * (87%)	9 (31%)
MMSE (/30)	23.0 ± 3.2 *	25.1 ± 2.7 *	29.3 ± 0.8
CDR (0 / 0.5 / 1) (% CDR = 0.5)	0 / 21 / 4 * (84%)	0 / 28 / 2 * (93%)	29 / 0 / 0 (0%)
CDR-SB (/18)	2.8 ± 1.3 *	2.6 ± 1.3 *	0 ± 0

Table 1: Characteristics of participants

* Data available for 24 EOAD, 30 LOAD and 29 Controls

* significantly different from control group (p-value < 0.05)

Results

Synaptic loss in subgroups, SUVr_(50-70 min) (Figure 1)

- Each patient subgroup showed lower tracer uptake than age-matched controls in the **temporo-parietal regions**
 - parietal predominance in EOAD
 - temporal predominance in LOAD.
- Comparison between EOAD and LOAD showed no significant difference.

Temporal / Lateral parietal ratio (Figure 2)

- Ratio was higher in EOAD than in LOAD (p=0.003).

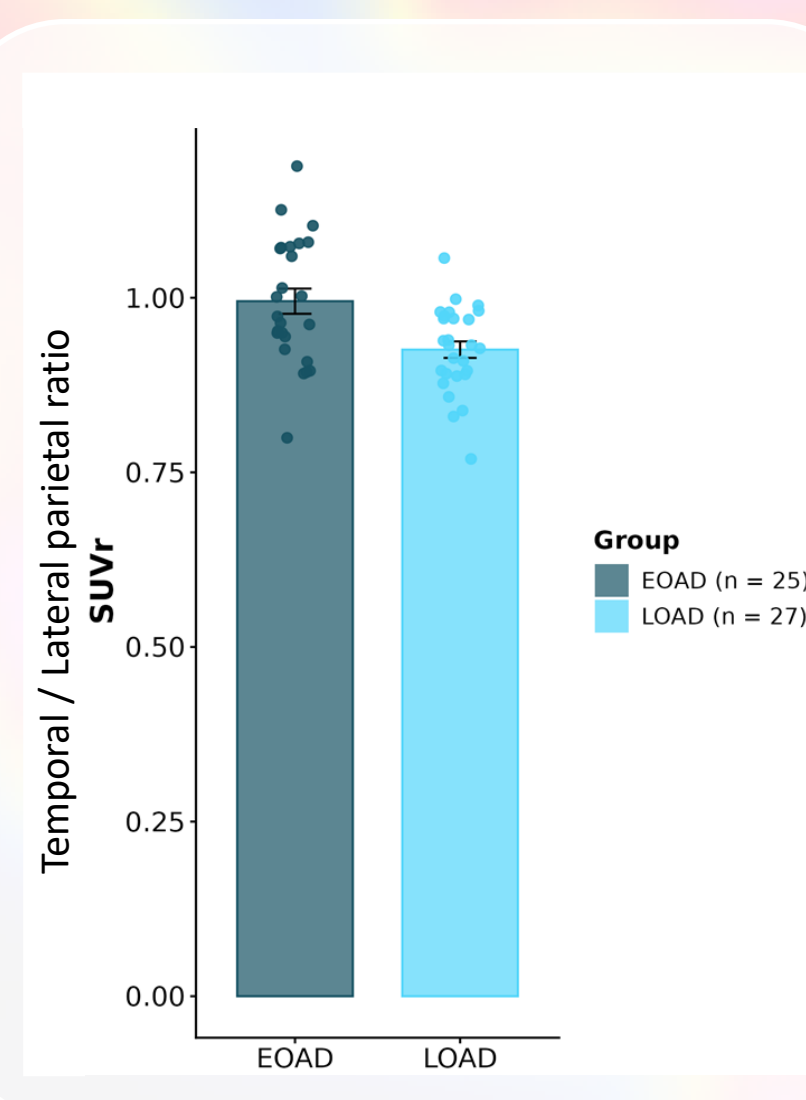


Figure 2: Barplots of the ratio between SUVr in an inferomedial temporal meta-region and in the lateral parietal region in EOAD and LOAD.

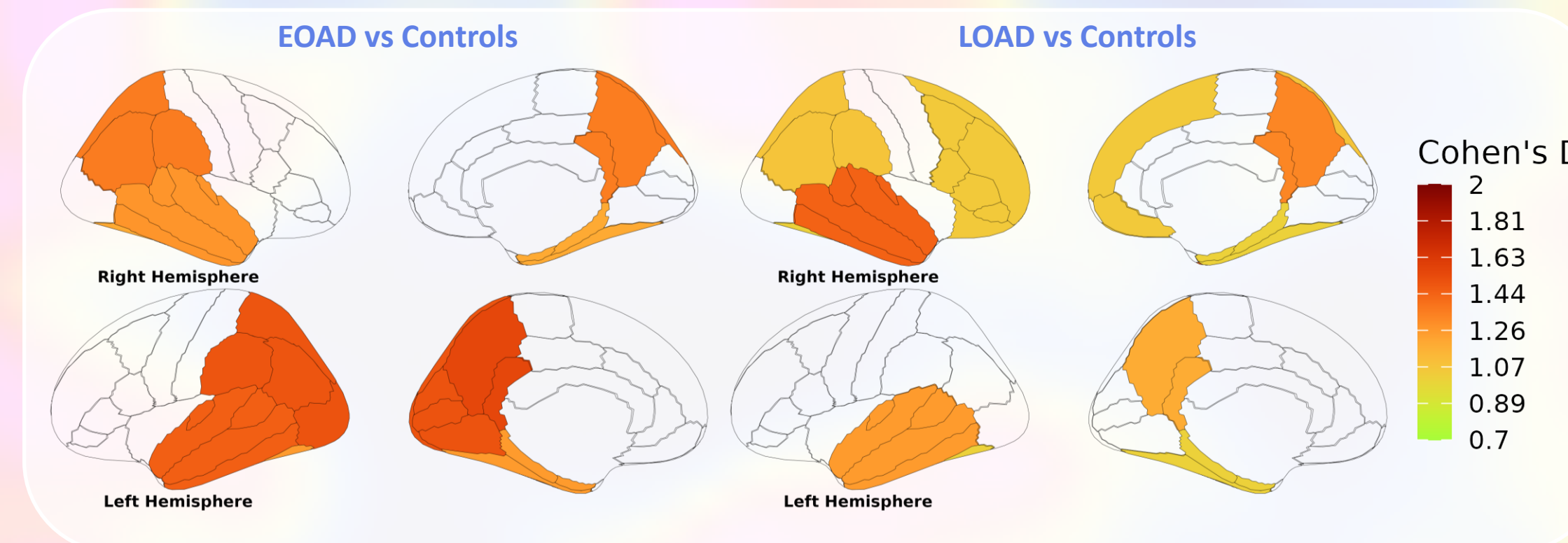


Figure 1: Comparison of each patient subgroup with age-matched controls. Effect sizes expressed as Cohen's d in regions where the difference is significant. (p<0.05 after Bonferroni correction for multiple comparisons)

Association of APOE4 genotype, MMSE and CDR-SB with regional tracer uptake (Figure 3)

- No significant difference in tracer binding between patients carrying at least one **APOE4 allele** and those carrying none, both in EOAD (n=14 and 10) and LOAD (n=23 and 4).
- **MMSE and CDR-SB were correlated with tracer binding only in LOAD patients** : In the right temporal ROI for MMSE and in the temporal and frontal ROIs for CDR-SB.

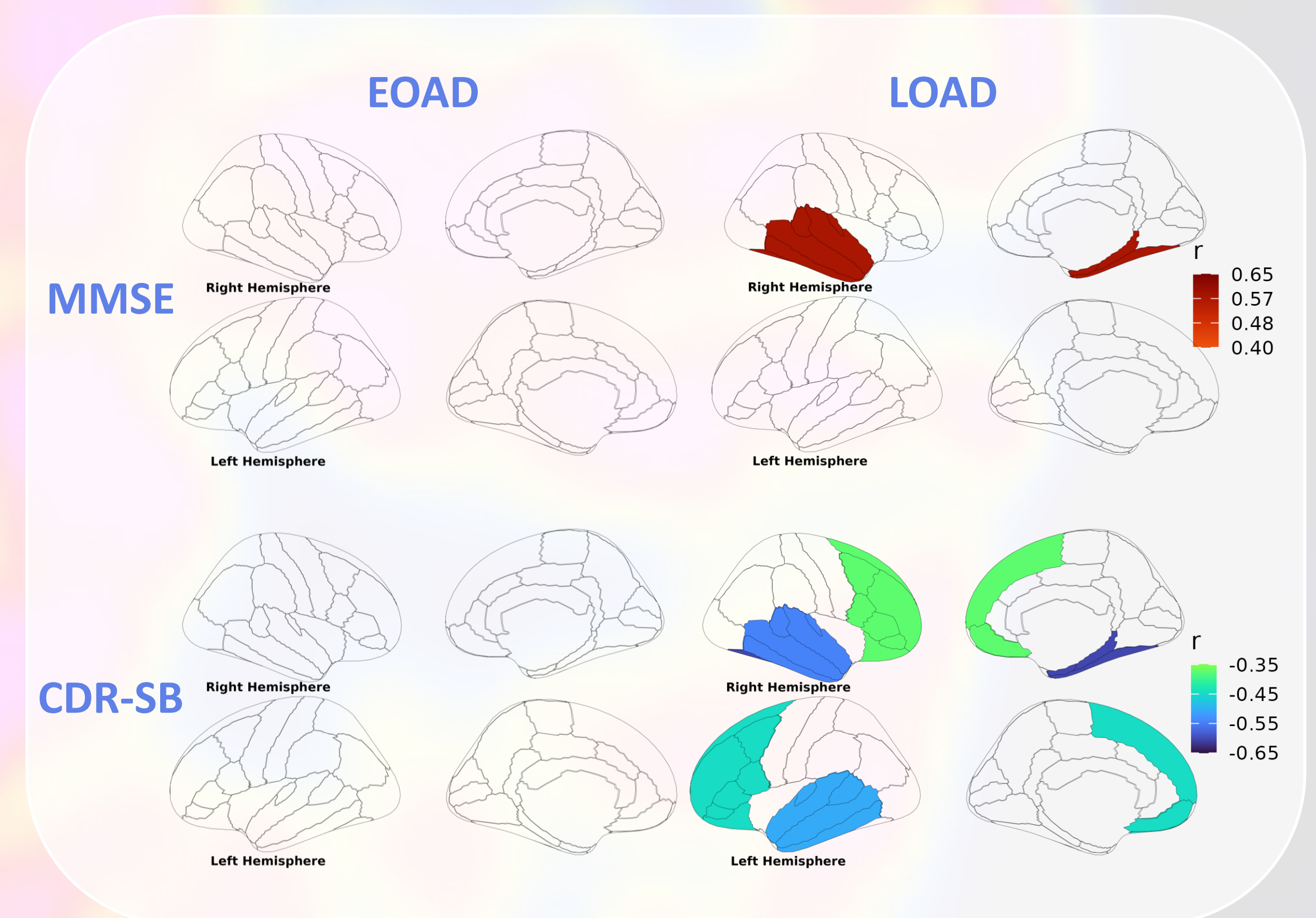


Figure 3: Correlations between SUVr and MMSE / CDR-SB in EOAD and LOAD. Representation of correlation coefficients r in ROIs where they are significant (p<0.05 after Bonferroni correction for multiple comparisons)

Conclusion

- ⇒ Alteration in synaptic density in AD patients showed a parietal predominance in EOAD and a temporal predominance in LOAD. These results are consistent with previous clinical and neuropathological data showing a difference in the distribution of neurodegeneration and tau pathology depending on the age of symptom onset, and highlight the potential of synaptic PET imaging to capture phenotypic variations in AD.
- ⇒ Further analysis is needed to understand the link between synaptic loss, proteinopathies, and clinical symptoms, in order to improve the design of therapeutic trials.

- Mendez MF. Early-Onset Alzheimer's Disease. Neurol Clin. 2017;35(2):263–281. doi: 10.1016/j.ncl.2017.01.005.
- Tort-Merino A, Falgàs N, Allen IE, et al. Early-onset Alzheimer's disease shows a distinct neuropsychological profile and more aggressive trajectories of cognitive decline than late-onset. Ann Clin Transl Neurol. 2022;9(12):1962–1973. doi: 10.1002/acn3.51689.
- Dickerson BC, Brickhouse M, McGinnis S, Wolk DA, Initiative ADN. Alzheimer's disease: The influence of age on clinical heterogeneity through the human brain connectome. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2017;6(1):122–135. doi: 10.1016/j.dadm.2016.12.007.
- Hamelin L, Bertoux M, Bottlaender M, et al. Sulcal morphology as a new imaging marker for the diagnosis of early onset Alzheimer's disease. Neurobiology of Aging. 2015;36(11):2932–2939. doi: 10.1016/j.neurobiolaging.2015.04.019.
- Kim EJ, Cho SS, Jeong Y, et al. Glucose metabolism in early onset versus late onset Alzheimer's disease: an SPM analysis of 120 patients. Brain. 2005;128(8):1790–1801. doi: 10.1093/brain/awh539.
- Finnema SJ, Nabulsi NB, Eid T, et al. Imaging synaptic density in the living human brain. Sci Transl Med. 2016;8(348). doi: 10.1126/scitranslmed.aaf6667.