

# LOSS OF SMELL AS A PROGNOSTIC BIOMARKER: OLFACTORY DEFICITS PREDICT COGNITIVE DECLINE AND REVEAL DISTINCT BRAIN NETWORKS IN DLB AND AD

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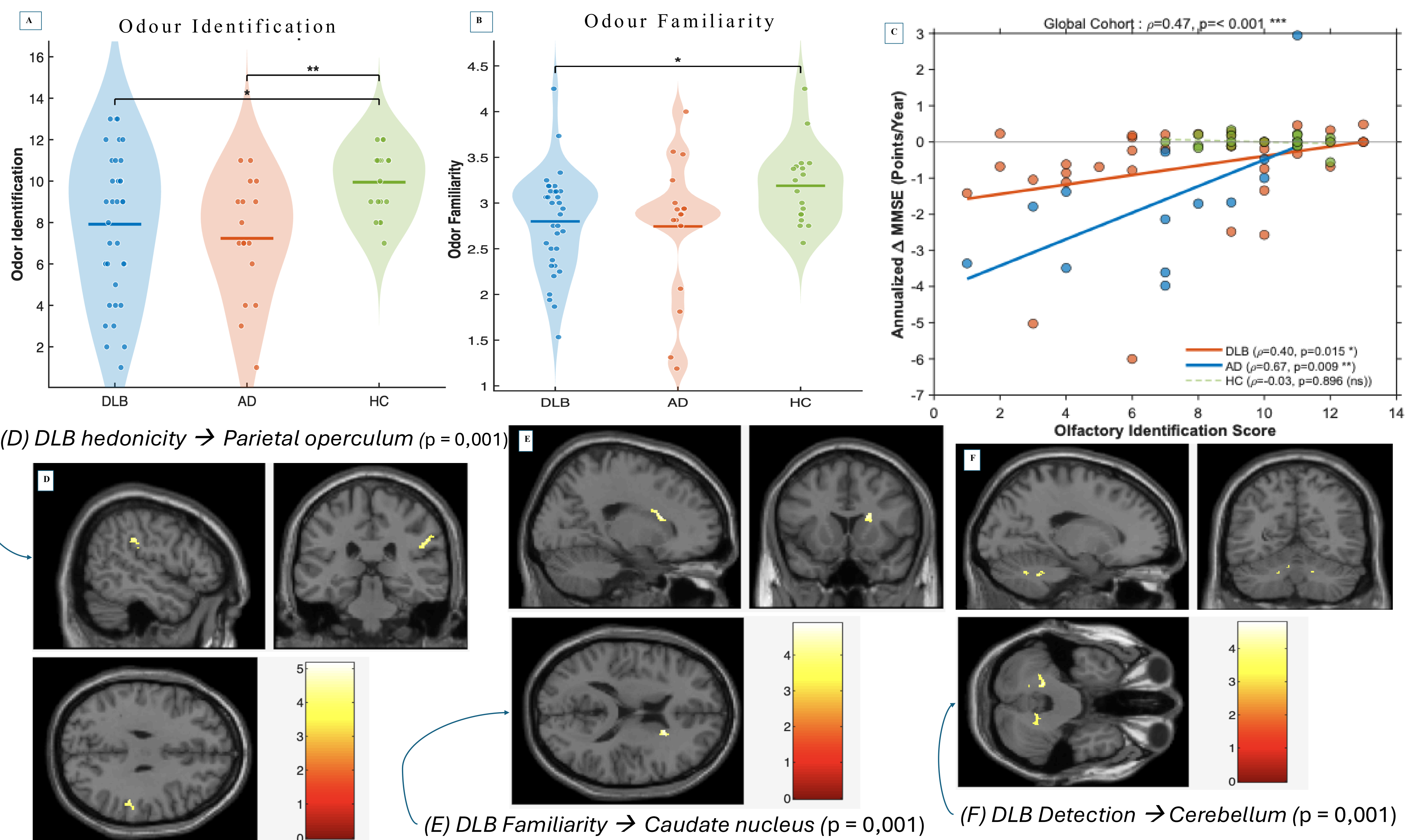
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**Background:** Patients with prodromal DLB exhibit significantly lower olfactory identification abilities than those with prodromal AD or MCI, independent of age, sex, and cognitive function (Williams et al., 2009). However, multidimensional olfactory assessment (including threshold, identification, detection, familiarity, and hedonicity) is not routinely incorporated into clinical workups, limiting the ability to improve early diagnostic accuracy and distinguish prognostic trajectories in DLB and AD.

**Objective:** To determine whether baseline multidimensional olfactory profiles can predict the trajectory of cognitive decline and identify disease-specific neuroanatomical correlates.



## Results:

**Clinical olfactory assessment** (Kruskal-Wallis test).

- Identification: Impaired odour identification in both AD ( $p = 0.003$ ) and DLB ( $p = 0.050$ ) compared to controls.
  - Baseline odour identification strongly predicted the rate of cognitive decline years later across the global cohort (adjusted  $\beta = 0.167$ ,  $p = 0.006$ ; Multiple linear regression), driven by robust trajectory correlations within both the DLB group ( $\rho = 0.398$ ,  $p = 0.015$ ) and the AD group ( $\rho = 0.667$ ,  $p = 0.009$ ) (Spearman rank correlation).
- Familiarity (DLB Specificity): The DLB group showed a significant decrease in subjective odour familiarity compared to controls ( $p = 0.011$ ), whereas the AD group did not ( $p = 0.116$ ).

## Neuroimaging results (VBM)

In the DLB group, olfactory deficits were linked to distinct structural brain alterations:

- Hedonicity:** Linked to the right parietal operculum (insula) ( $T = 5.27$ ) (D).
- Familiarity:** Associated with gray matter reduction in the caudate nucleus (striatum) ( $T = 4.92$ ) (E).
- Detection:** Correlated with white matter loss in the bilateral cerebellar pathways ( $T = 4.49$ ) (F).

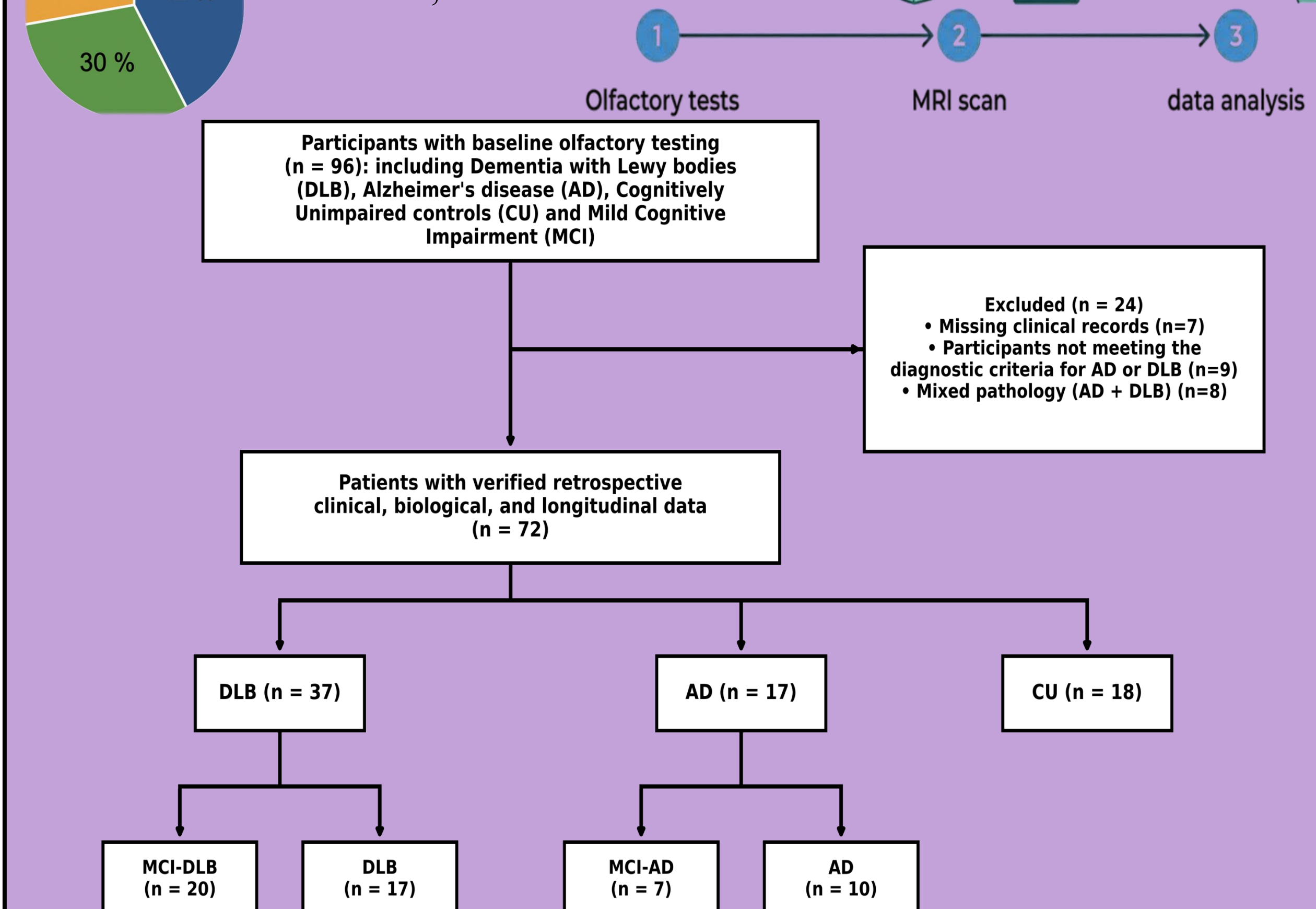
## Methods:

Study Design: Participants ( $N = 72$ ):

DLB,  $n = 37$

AD,  $n = 17$

Controls,  $n = 18$



**Standardized Olfactory Assessment (TOCL):** Detection, thresholds, identification, familiarity, and hedonicity.

**Longitudinal Tracking:** Annual change in the Mini-Mental State Examination ( $\Delta$ MMSE).

**Neuroimaging:** Whole-brain Voxel-Based Morphometry (VBM) on structural MRI ( $n = 62$ ), strictly thresholded at  $p < 0.001$  (uncorrected) with a spatial extent of  $k > 50$  contiguous voxels.

## Conclusions:

Odour identification performance may serve as a prognostic marker of cognitive decline rate in both DLB and AD, with potential clinical utility from the prodromal stages of disease. In DLB, multidimensional odour deficits are associated with central neurodegenerative changes rather than isolated peripheral dysfunction, involving distinct structural alterations within affective (parietal operculum/insula), implicit semantic (caudate), and predictive-attentional (cerebellar) networks.

**Clinical Implication:** Multidimensional smell testing is a sensitive, low-cost tool that could improve early differential diagnosis between DLB and AD. It offers a practical first-line strategy in memory clinics to guide patient diagnosis and better target costly neuroimaging examinations like MRI.

**Next Step:** Correlate central olfactory network atrophy with peripheral  $\alpha$ -synuclein pathology using RT-QuIC on olfactory mucosa, establishing a direct link between synucleinopathy load and structural neurodegeneration.