Experimental Gerontology 183 (2023) 112325

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Smaller grey matter volume in the central olfactory system in mild cognitive impairment

Benoît Jobin [a,b,c,*], Benjamin Boller [a,b], Johannes Frasnelli [c,d], The CIMA-Q group [1]

[a] Department of Psychology, Université du Québec à Trois-Rivières, Qc, Canada
[b] Research Centre of the Institut universitaire de Gériatrie de Montréal, Qc, Canada
[c] Research Centre of the Hôpital du Sacré-Cœur de Montréal, Qc, Canada
[d] Department of Anatomy, Université du Québec à Trois-Rivières, Qc, Canada

ARTICLE INFO

Section Editor: Tibor Hortobagyi

Keywords:
Olfactory cortex
Volumetry
Mild cognitive impairment
Subjective cognitive decline
MRI
Episodic memory

ABSTRACT

One of the major challenges in the diagnosis of Alzheimer's disease (AD) is to increase the specificity of the early diagnosis. While episodic memory impairment is a sensitive AD marker, other measures are needed to improve diagnostic specificity. A promising biomarker might be a cerebral atrophy of the central olfactory processing areas in the early stages of the disease since an impairment of olfactory identification is present at the clinical stage of AD. Our goal was therefore, (1) to evaluate the grey matter volume (GMV) of central olfactory processing regions in prodromal AD and (2) to assess its association with episodic memory. We included 34 cognitively normal healthy controls (HC), 92 individuals with subjective cognitive decline (SCD), and 40 with mild cognitive impairment (MCI). We performed regions of interest analysis (ROI) using two different approaches, allowing to extract GMV from (1) atlas-based *anatomical ROIs* and from (2) functional and non-functional subregions of these ROIs (*olfactory ROIs* and *non-olfactory ROIs*). Participants with MCI exhibited smaller *olfactory ROIs* GMV, including significant reductions in the piriform cortex, amygdala, entorhinal cortex, and left hippocampus compared to other groups ($p \leq 0.05$, corrected). No significant effect was found regarding *anatomical* or *non-olfactory* ROIs GMV. The left hippocampus olfactory ROI GMV was correlated with episodic memory performance ($p < 0.05$ corrected). Limbic/medial-temporal olfactory processing areas are specifically atrophied at the MCI stage, and the degree of atrophy might predict cognitive decline in AD early stages.

1. Introduction

Alzheimer's disease (AD) begins with a silent phase that spans over decades, during which an accumulation of neurofibrillary tau and β-amyloid depositions lead progressively to dementia. On the neuropathological level, tau tangles spread to the trans-entorhinal regions, then to the limbic regions, before expanding to the neocortex (Braak and Braak, 1991). β-amyloid plaques, on the other hand, accumulate first in the neocortex, then in the allocortex regions such as the entorhinal cortex and the hippocampus, then in subcortical nuclei, the brainstem, and finally in the pons and the cerebellum (Thal et al., 2002). These neuropathologies also correlate with other underlying molecular damages such as caspase activation, which is another factor leading to neuronal death (Rohn et al., 2001). These brain damages occur during a prodromal phase in which the patient typically develops progressively a subjective cognitive decline (SCD) – a preclinical stage in which individuals report complaints of subjective cognitive decline while maintaining normal performance on clinical cognitive assessments (Jessen et al., 2014, 2020). Then, the progression of the disease leads to mild cognitive impairment (MCI), typically including an episodic memory deficit, before leading to dementia, at which point the cognitive impairment is significant enough to impact daily life functionally (Albert et al., 2011; Jack et al., 2018; Sperling et al., 2011).

The amnesic form of MCI is considered a risk factor for developing AD dementia (Petersen et al., 2001). Among neuropsychological tests, performance on verbal episodic memory measures is the most accurate

* Corresponding author at: 3351 Boulevard des Forges, C.P. 500 Trois-Rivières (Québec) G9A 5H7, Local 3470 Léon-Provencher, Canada.
E-mail address: benoit.jobin@uqtr.ca (B. Jobin).

[1] The data used in this article were obtained from the Consortium for the Early Identification of Alzheimer's Disease-Quebec (CIMA-Q; cima-q.ca). As such, the investigators within the CIMA-Q contributed to the design, implementation, and acquisition of clinical, cognitive, and neuroimaging data. A list of the CIMA-Q investigators is available on cima-q.ca.

https://doi.org/10.1016/j.exger.2023.112325
Received 6 October 2023; Received in revised form 2 November 2023; Accepted 7 November 2023
Available online 11 November 2023

to predict the progression from MCI to AD dementia type (Belleville et al., 2017). Nevertheless, episodic memory impairment is not specific to AD, and a significant proportion of patients with an amnesic MCI will not convert to AD dementia type (Vos et al., 2013). As an example, results from a study showed that 31 % of patients diagnosed with amnesic MCI did *not* convert to dementia after six years of follow-up (Mauri et al., 2012).

Combining episodic memory decline with other behavioral markers may improve the early detection of AD; for this, olfactory impairment is a prime candidate. During the prodromal phase of AD, olfactory decline appears among the first behavioral symptoms within the disease progression (Murphy, 2019). Indeed, olfactory impairment is a clinical symptom of AD (Mesholam et al., 1998; Rahayel et al., 2012; Silva et al., 2018; Velayudhan, 2015; Velayudhan et al., 2013) and is already present as episodic memory impairment appears at the MCI stage of the disease (Bahar-Fuchs et al., 2010; Devanand et al., 2010; Djordjevic et al., 2008; Eibenstein et al., 2005; Jung et al., 2019; Roalf et al., 2017; Seligman et al., 2013; Vyhnalek et al., 2015). While episodic memory and olfactory identification are associated during aging (Chen et al., 2018; Devanand et al., 2010; Jobin et al., 2023; Larsson et al., 2016; Tonacci et al., 2017; Wehling et al., 2010), the olfactory decline may begin even before the appearance of memory deficits. Indeed, individuals with SCD can exhibit reduced olfactory identification abilities (Chen et al., 2021; Sohrabi et al., 2009) although memory impairments are per definition absent in this group. Further, in cognitively normal older adults, olfactory performance helps to predict future cognitive decline (Devanand et al., 2015; Dintica et al., 2019; Growdon et al., 2015; Olofsson et al., 2020; Sohrabi et al., 2012; Windon et al., 2019) and conversion to MCI (Roberts et al., 2016; Wheeler and Murphy, 2021; Wilson et al., 2007). Accordingly, olfactory impairment is considered a preclinical marker of AD.

In contrast to the olfactory impairment associated with other conditions such as Parkinson's disease, olfactory impairment within AD is characterized by a particular pattern where olfactory identification is more impaired than olfactory threshold or olfactory discrimination (Rahayel et al., 2012). This pattern can already be observed in MCI (Roalf et al., 2017). Such early olfactory identification impairment could result from damage to limbic and medial temporal lobe structures, as these regions are mainly involved in the identification of odors (Devanand et al., 2010; Hagemeier et al., 2016; Kjelvik et al., 2014, 2021; Kose et al., 2021; Murphy et al., 2003; Patin and Pause, 2015; Yoshii et al., 2019; Yu et al., 2019). Pathologically, tau tangles accumulate first in the trans-entorhinal region (Braak and Braak, 1991); tau accumulation is one of the leading causes of neuronal death and a predictor of brain atrophy in AD (Malpetti et al., 2022; Planche et al., 2022). Although the olfactory bulb is also affected by tau pathology in early Braak stages (Kovacs et al., 1999), a post-mortem histological study showed that olfactory bulb tau pathology failed to predict olfactory identification (Tremblay et al., 2022), while other studies showed that olfactory identification would be associated with cerebrospinal fluid (CSF) tau pathology (Lafaille-Magnan et al., 2017; Reijs et al., 2017; Tu et al., 2020) and with tau pathology within medial-temporal lobe regions (Klein et al., 2021; Risacher et al., 2017). Accordingly, limbic and medial-temporal structures of the primary olfactory cortex (POC), which includes the piriform cortex, the amygdala, the olfactory nucleus, the olfactory tubercle, and the entorhinal cortex, are atrophied in patients with AD, raising the hypothesis that POC atrophy may be present as early as the MCI stage and being one of the main causes of the early olfactory identification impairment (Jobin et al., 2021a).

While several regions are involved in central olfactory processing (e.g., amygdala, piriform cortex, entorhinal cortex, parahippocampal gyrus, orbitofrontal cortex, insula, caudate, hippocampus, cingulate; Lundström et al., 2011; Seubert et al., 2013; Torske et al., 2021), neuropathological and behavioral evidence suggests that damage to limbic and medial-temporal olfactory regions is the first to appear during AD. Over time, odor identification and episodic memory have the same trajectories within aging (Dintica et al., 2021). According to the common cause hypothesis, damages to shared limbic and medial-temporal regions involved in both capacities would explain the relationship and similar trajectories between memory and olfactory declines in aging (Baltes and Lindenberger, 1997; Dulay and Murphy, 2002).

In the present study, we aimed to (1) compare and characterize grey matter volume (GMV) of the central olfactory structures of three groups, namely a control group of cognitively normal healthy older adults without cognitive complaints (HC), a group of older adults with SCD, and a group of older adults with MCI. Compared to cognitively normal controls, we hypothesized that older adults with SCD or MCI have smaller GMV of olfactory structures in the limbic system and medial-temporal lobe. We also aimed to compare the GMV of subregions of these structures across the three groups. Accordingly, we aimed to compare (2a) the olfactory subregions of these structures, i.e., areas that are activated during olfactory stimulation, and (2b) the non-olfactory subregions of these structures, i.e., areas that do not activate to olfactory stimulation, among the three groups. Here, we also predicted smaller GMV in olfactory subregions of these structures in SCD or MCI groups compared to HC participants. Finally, we aimed to (3) determine if the GMV of central olfactory areas is correlated to verbal episodic memory performance, the most accurate cognitive predictor of AD (Belleville et al., 2017). We hypothesized that GMV of olfactory medial temporal and limbic regions correlates with verbal episodic memory performance.

2. Materials and methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the research center of the *Institut universitaire de gériatrie de Montréal*. After a detailed explanation of the study, all participants provided written consent before enrolling in the study.

2.1. Participants

The data were obtained from the Consortium for the Early Identification of Alzheimer's Disease-Quebec (CIMA-Q, Belleville et al., 2019), established in 2013 with initial FRQS-Pfizer funding. The primary objective of CIMA-Q was to establish a cohort of older adults characterized clinically, cognitively, and by neuroimaging and blood sampling, with the following goals: (1) to establish an early diagnosis of Alzheimer's disease; (2) to make a well-characterized cohort available to the scientific community; and (3) to identify novel therapeutic targets to prevent or slow cognitive decline and Alzheimer's disease (4) via subsequent clinical studies. The designated principal investigator and director of CIMA-Q is Dr. Sylvie Belleville from the Research Centre of the *Institut universitaire de gériatrie de Montréal*, a research organization of the Centre Intégré Universitaire de Santé et de Services Sociaux du Centre-sud-de-l'île de Montréal. CIMA-Q represents the joint efforts of many Quebec-based co-principal investigators and researchers affiliated with Université Laval, McGill University, Université de Montréal, and Université de Sherbrooke.

Since 2014, CIMA-Q has recruited a longitudinal cohort of 350 cognitively normal participants, with SCD, with MCI, or with Alzheimer's type dementia. In the current study, we included all eligible participants who underwent MRI examination between 2014 and March 2020 ($n = 166$). All participants were community-dwelling older adults aged 65 or over, living independently from Montreal, Sherbrooke, and Quebec City in Canada. All participants underwent a complete comprehensive neuropsychological evaluation and were evaluated by expert physicians who classified participants across the AD spectrum, from cognitively normal HC to SCD, MCI, and clinically probable AD.

All recruitment procedures, clinical, cognitive, and neuropsychiatric measurement, as well as all inclusion and exclusion criteria, were described (Belleville et al., 2019). Participants from the MCI group

(Montreal Cognitive Assessment, MoCA, Nasreddine et al., 2005, score between 26 and 20) met the National Institute on Aging and the Alzheimer's Association (NIA-AA) clinical criteria for MCI (Albert et al., 2011): (1) a reported cognitive decline; (2) an objective cognitive impairment typically in episodic memory, (3) the preservation of independence in functional abilities, and (4) the absence of dementia. Participants from the SCD group (MoCA score ≥ 26) met the criteria of the Subjective Cognitive Decline Initiative (Jessen et al., 2014): (1) a reported cognitive decline and (2) cognitive performance within the normal range. Cognitively normal controls participants (MoCA score ≥ 26) (1) reported no cognitive complaint and (2) had a cognitive performance within the normal range. Verbal episodic memory performance measured by the Logical Memory II subtest of the Wechsler Memory Scale (Wechsler, 1997) and general cognitive performance measured by the MoCA are presented in Table 1.

Table 1
Characteristics of participants in each group. Note: Values are means (SD). Analysis of variance was performed, followed by post-hoc pairwise comparisons with Holm-Bonferroni correction. A Chi-Square test of independence was performed for sex. Volumetric data represent volumes in mL divided by total intracranial volume. Volumetric analyses of variance were also performed, followed by post-hoc ANCOVAs controlling for age with Holm-Bonferroni correction. Abbreviations: HC = cognitively normal healthy controls, SCD = subjective cognitive decline, MCI = mild cognitive impairment. MoCA = Montreal Cognitive Assessment. n.a. = No post-hoc performed when the main group effect was non-significant. a Data missing for two subjects. b Data missing for four subjects. * indicates statistically significant effects after adjustment for multiple comparisons (Holm-Bonferroni corrected).

				p values		
	HC ($n = 34$)	SCD ($n = 92$)	MCI ($n = 40$)	HC vs. SCD	HC vs. MCI	SCD vs. MCI
Age in years	72.08 (5.51)	72.18 (4.76)	75.22 (5.11)	0.93	0.008*	0.002*
Female/Male	25/9	63/29	18/22	0.58	0.013	0.011
Years of Education	15.88 (3.69)	15.05 (3.09)	14.30 (3.12)	n.a.	n.a.	n.a.
Logical Memory II delayed free recall	14.74 (4.67)	14.20 (3.86)	10.13 (4.42)	0.52	< 0.001*	< 0.001*
MoCA	28.35 (1.37)	27.66 (1.41)	24.52 (2.34)	0.04	< 0.001*	< 0.001*
Memoria, free word recall[a]	8.18 (1.87)	7.33 (2.10)	6.07 (2.56)	0.055	< 0.001*	0.009*
Face-Name Test, delayed free recall[b]	5.35 (1.77)	4.68 (2.43)	2.95 (2.31)	0.15	< 0.001*	< 0.001*
Piriform cortex anatomical ROI	0.00123 (0.00010)	0.00123 (0.00010)	0.00116 (0.00009)	n.a.	n.a.	n.a.
Piriform cortex olfactory ROI	0.00066 (0.00006)	0.00066 (0.00006)	0.00062 (0.00006)	0.79	0.018*	0.002*
Piriform cortex non-olfactory ROI	0.00057 (0.00005)	0.00057 (0.00005)	0.00054 (0.00005)	n.a.	n.a.	n.a.
Amygdala anatomical ROI	0.00120 (0.00009)	0.00121 (0.00011)	0.00111 (0.00014)	n.a.	n.a.	n.a.
Amygdala olfactory ROI	0.00099 (0.00009)	0.00098 (0.00009)	0.00091 (0.0001)	0.82	0.014*	0.001*
Amygdala non-olfactory ROI	0.00021 (0.00005)	0.00022 (0.00003)	0.00020 (0.00003)	n.a.	n.a.	n.a.
Entorhinal cortex anatomical ROI	0.00275 (0.00025)	0.00273 (0.00028)	0.00257 (0.00033)	n.a.	n.a.	n.a.
Entorhinal cortex olfactory ROI	0.00098 (0.00010)	0.00097 (0.00010)	0.00090 (0.00011)	0.92	0.008*	0.002*
Entorhinal cortex non-olfactory ROI	0.00177 (0.00018)	0.00176 (0.00020)	0.00167 (0.00022)	n.a.	n.a.	n.a.
Left hippocampus anatomical ROI	0.00203 (0.00016)	0.00203 (0.00018)	0.00186 (0.00026)	n.a.	n.a.	n.a.
Left hippocampus olfactory ROI	0.00007 (0.000009)	0.00007 (0.000009)	0.00006 (0.00001)	0.60	0.007*	0.006*
Left hippocampus non-olfactory ROI	0.00196 (0.00016)	0.00196 (0.00018)	0.00180 (0.00026)	n.a.	n.a.	n.a.
Left parahippocampal gyrus anatomical ROI	0.00209 (0.00019)	0.00205 (0.00016)	0.00196 (0.00018)	n.a.	n.a.	n.a.
Left parahippocampal gyrus olfactory ROI	0.00002 (0.000003)	0.00002 (0.000004)	0.00002 (0.000005)	0.89	0.01*	0.004*
Left parahippocampal gyrus non-olfactory ROI	0.00207 (0.00019)	0.00203 (0.00016)	0.00193 (0.00018)	n.a.	n.a.	n.a.
Insula anatomical ROI	0.00750 (0.00060)	0.00757 (0.00060)	0.00728 (0.00066)	n.a.	n.a.	n.a.
Insula olfactory ROI	0.00053 (0.00005)	0.00054 (0.00005)	0.00053 (0.00006)	0.80	0.77	0.94
Insula non-olfactory ROI	0.00696 (0.00055)	0.00703 (0.00058)	0.00675 (0.00062)	n.a.	n.a.	n.a.
Orbitofrontal anatomical ROI	0.00810 (0.00046)	0.00800 (0.00064)	0.00780 (0.00055)	n.a.	n.a.	n.a.
Orbitofrontal olfactory ROI	0.00030 (0.00003)	0.00029 (0.00004)	0.00027 (0.00003)	0.24	0.50	0.04
Orbitofrontal non-olfactory ROI	0.00781 (0.00044)	0.00772 (0.00061)	0.00751 (0.00052)	n.a.	n.a.	n.a.
Left caudate anatomical ROI	0.00177 (0.00018)	0.00123 (0.00009)	0.00116 (0.00009)	n.a.	n.a.	n.a.
Left caudate olfactory ROI	0.000002 (0.0000008)	0.000002 (0.0000009)	0.000002 (0.0000007)	0.46	0.07	0.15
Left caudate non-olfactory ROI	0.00176 (0.00018)	0.00183 (0.00024)	0.00174 (0.00025)	n.a.	n.a.	n.a.

2.2. Design

The CIMA-Q project is a large-scale, multicenter, and longitudinal study including standardized cognitive and neuroimaging assessments (http://www.cima-q.ca/ for more details). After a telephonic pre-screening interview using the Mini-Mental State Examination (t-MMSE; Newkirk et al., 2004), all eligible participants underwent a clinical examination, a neuropsychological assessment, and a neuroanatomical MRI scan. MRI assessments were completed within a maximum of 30 days after the cognitive examination. All measurements from this study have been collected before the COVID-19 pandemic.

2.3. Episodic memory assessment

To reduce circularity issues when testing our hypothesis, we chose a different episodic memory task than those used in the inclusion criteria. Specifically, we used performance at a free word recall task from the Memoria Word Recall test (Chatelois et al., 1993). During the procedure, a 15-word list was presented to the participant on a computer screen displayed in a matrix of 5 rows and 3 columns. After the instructor verbally indicated the word to point on the screen, the participant had to point with his finger the word to remember for subsequent recall. This procedure was repeated 15 times for each word to learn, and for each item, words presentation on the screen was randomized to prevent spatial strategies during encoding. After the 15th word, participants were asked to count upwards to prevent rehearsal and to clear their working memory. Then, the participant was asked to retrieve as many words as possible previously seen during the learning phase. This task is among the most sensitive predictors of progression from MCI to dementia (Belleville et al., 2017).

2.4. Image processing

CIMA-Q used a comprehensive imaging protocol harmonized for manufacturer/software configurations to ensure optimal convergence during analysis (Belleville et al., 2019; Duchesne et al., 2019). In this study, we used anatomical 3D-T1-weighted sequences from this protocol.

We converted all 3D T1-weighted MR images into the Neuroimaging Informatics Technology Initiative (NIFTI) format, and we manually reoriented the anterior commissure as the origin for all images. The images were spatially normalized and segmented into grey matter (GM), white matter (WM), and cerebral spinal fluid (CSF) tissue classes according to the Geodesic Shooting registration approach with default settings in 1.5 mm cubic resolution and MNI space using the CAT12 toolbox (Gaser et al., 2022) implemented in SPM12 (Wellcome Centre of Imaging Neuroscience, Institute of Neurology, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm) and MATLAB software version R2020b (The MathWorks, Natick, MA, USA). GM, WM, and CFS Volumes were summed up to calculate the total intracranial volume (TIV). Moreover, the data quality was obtained from CAT12, and all scans were rated C+ or higher, representing a satisfactory quality level (Gaser et al., 2022). Regarding data quality, an ANOVA revealed no difference between groups regarding the weighted overall image quality (F [2, 165] $= 0.67$; $p = 0.51$).

2.5. GMV extraction

We extracted GMV from regions of interest (ROIs) using the "Estimate Mean Values Inside ROI for External Analysis" CAT12's tool and performed analysis using SPSS software (IBM SPSS Statistics Version 28). We defined ROIs based on a recent activation likelihood estimation (ALE) meta-analysis of 81 studies (Torske et al., 2021), a method previously used by Seubert et al. (2013). The activation mask resulting from this meta-analysis represents significant clusters that are activated during olfactory stimulation, providing a probabilistic map of the central olfactory system (i.e, the amygdala, piriform cortex, medial+posterior orbitofrontal cortex gyrus, insula, left parahippocampal gyrus, left hippocampus, and left caudate). For these last three regions, we were only able to extract the left hemisphere part given the absence of activation in the right hemisphere within these regions in the functional mask (Torske et al., 2021), a similar lateralization effect has been found in Fjaeldstad et al. (2021) regarding the structural connectivity between the olfactory cortex and the left hippocampus (VS the right hippocampus).

ROIs masks were created using an approach combining a functional mask (Torske et al., 2021) and a neuroanatomical atlas (Neuromorphometrics), a technique that has been used in other studies to create ROIs of the central olfactory system (Fjaeldstad et al., 2017, 2021; Postma et al., 2021). Since the piriform cortex is not included in the Neuromorphometrics atlas, we used a mask created by Zhou et al. (2019) which includes the anterior olfactory nucleus, olfactory tubercle, and piriform cortex. First, we extracted GMV from (A) *anatomical ROIs* (i.e., all voxels from different ROIs, based on the anatomical atlas masks). Second, we extracted GMV from another set of ROIs derived on the intersection between the functional mask (Torske et al., 2021) and anatomical regions from the Neuromorphometrics atlas included in CAT12 that is resulting from the OASIS project (http://www.oasis-brains.org/). These (B) *olfactory ROIs* included significant voxels activated by olfactory stimulation from the anatomical ROIs masks. Thus, these novel ROIs represented the parts of anatomical atlas-based regions that are activated during olfactory stimulation (see Fig. 1). Finally, we also extracted (C) *non-olfactory ROIs* GMV (i.e., voxels that are not activated during olfactory stimulation from the same anatomical regions). All GMV extracted were divided by the TIV to control for head size and reported in mL.

2.6. Statistical analysis

We used the same statistical analysis approach to compare each set of *ROIs* (*anatomical ROIs, olfactory ROIs, non-olfactory ROIs)* GMV between each group (HC, SCD, MCI). We computed Greenhouse-Geisser corrected repeated-measures analysis of variance (rmANOVA) with *region* (height levels: piriform cortex, amygdala, entorhinal cortex, left hippocampus, left parahippocampus, insula, orbitofrontal cortex, left caudate) as within-subject factor and *group* (three levels: HC, SCD, MCI) as between-subject factor. *Education*, *sex* and *age* were used as covariates. When an interaction effect between *region* and *group* was significant, we used ANCOVAs as post-hoc analysis to perform pairwise comparisons comparing GMV of each *ROI* between each group (HC VS SCD, HC VS MCI, SCD VS MCI) using age as a covariate. When an interaction effect between *region* and *sex* was significant, we performed two-way ANCOVAs that included *sex* and *group* (HC, SCD, MCI) as two factors, including age as a covariate. Pairwise comparisons were performed to compare GMV between males and females. Next, when an interaction effect was found between *region* and *age,* we performed Pearson's correlations to assess the relation between different *ROIs* GMV and *age*.

To assess the hemispheric laterality of different bilateral *ROIs* (piriform cortex, amygdala, entorhinal cortex, insula, orbitofrontal cortex), we performed the same analysis (Greenhouse-Geisser corrected rmANOVA), including *side* as a covariate.

We performed Pearson's correlations to verify the relationship between GMV of olfactory ROIs and age or episodic memory performance. Again, we set the alpha value at 0.05 and used Bonferroni-Holm correction for multiple comparisons. Partial correlation analysis was performed to control the effect of pertinent covariates (i.e., age).

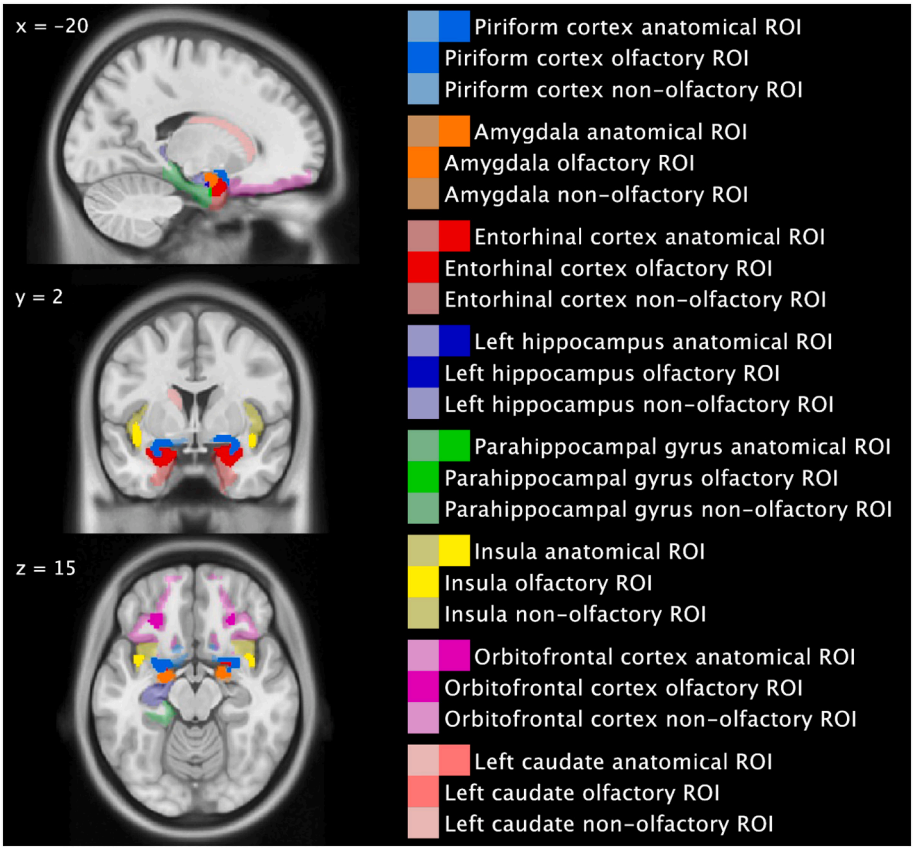

Fig. 1. Defined ROIs used to extract GMV from different ROIs. *Anatomical ROIs* were defined based on the Neuromorphometrics atlas implemented in CAT12 and the piriform cortex mask from Zhou et al., 2019. *Olfactory ROIs* represent significant voxels activated by olfactory stimulation (Torske et al., 2021) within each anatomical ROI. *Non-olfactory ROIs* represent voxels that are not activated during olfactory stimulation within each anatomical ROI. Axes' coordinates follow the MNI system.

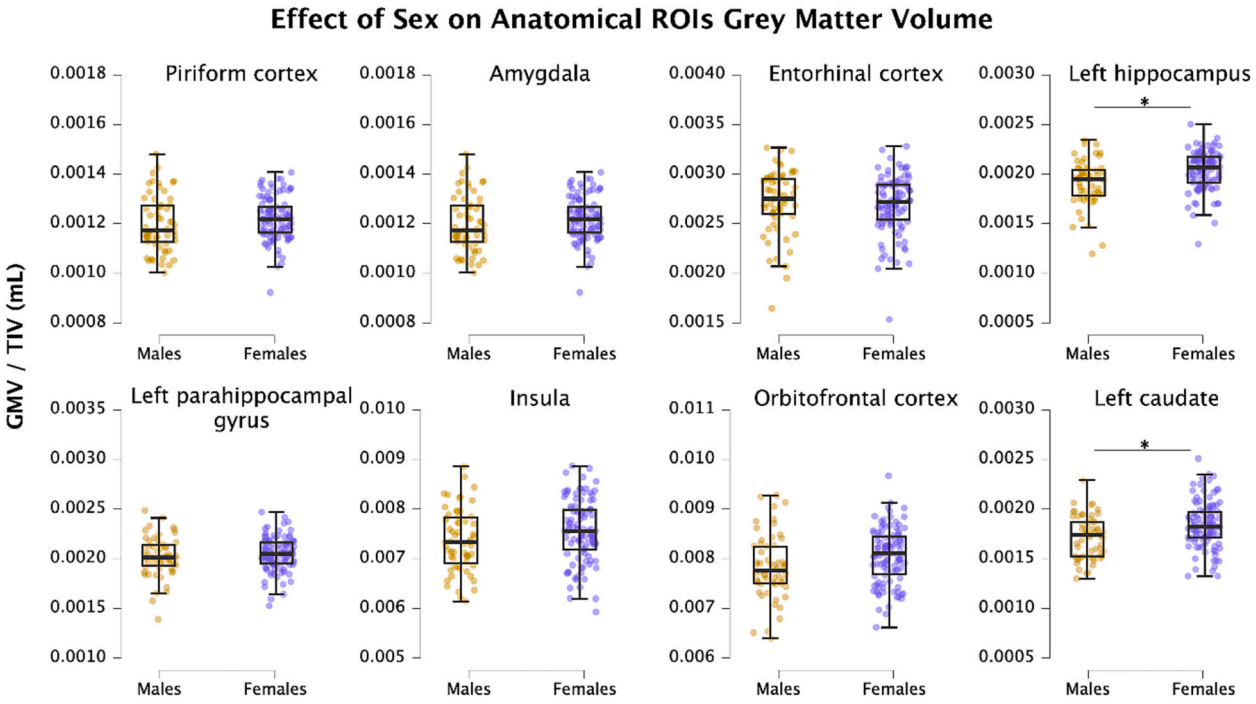

Fig. 2. Post-hoc two-way ANCOVAs comparisons between sex for each anatomical ROI, controlled for age. Males exhibited significantly smaller GMV in the left hippocampus and left caudate compared to females. The boxes represent the interquartile range of GMV distributions, the middle lines represent the median. * indicates statistically significant differences at $p < 0.05$ that resisted to Holm-Bonferroni correction.

3. Results

3.1. GMV of anatomically defined regions (anatomical ROIs)

When comparing GMV from *anatomical ROIs* between the three groups, a rmANOVA revealed no significant interaction between *region* and *group* (F [4.94, 395.26] = 0.867; p = 0.06; partial η^2 = 0.01), nor significant main effect of *group* (F [2, 160] = 2.76; p = 0.06; partial η^2 = 0.03). No significant interaction effects between *region* and *education* (F [2.47, 395.26] = 0.42; p = 0.70; partial η^2 = 0.003), nor main effect of education were found (F [1, 160] = 0.40; p = 0.84; partial $\eta^2 > 0.001$). We found a significant interaction between *region* and *age* (F [2.47, 395.26] = 3.05; p = 0.038; partial η^2 = 0.019). Age was significantly and negatively associated with each ROIs GMV (piriform cortex: $r = -0.25$, p = 0.001); amygdala: $r = -0.33$, $p < 0.001$; *entorhinal* cortex: $r = -0.25$, p = 0.001; left hippocampus: $r = -0.41$, $p < 0.001$), left parahippocampal gyrus ($r = -0.26$, $p < 0.001$), insula ($r = -0.23$, p = 0.003), orbitofrontal cortex ($r = -0.26$, $p < 0.001$), and left caudate ($r = -0.24$, p = 0.002) GMV.

We also found an interaction effect between *region* and *sex* (F [2.47, 395.26] = 3.01; p = 0.036; partial η^2 = 0.019). Two-way ANCOVAs including *group* and *sex* as factors showed significant main effects of *sex* for the left hippocampus (F [1, 159] = 5.88; p = 0.02; partial η^2 = 0.036). and for the left caudate (F [1, 159] = 5.33; p = 0.02; partial η^2 = 0.032). Post-hoc pairwise analysis revealed smaller left hippocampus (p = 0.02) and left caudate (p = 0.02) GMV in males compared to females (Fig. 2). No significant interaction effects were found between *group* and *sex* nor main effect of *sex* for other anatomical ROIs ($p > 0.05$).

Regarding laterality, we did not find a significant interaction effect between *region*, *group*, and *side* (F [4.02, 321.24] = 0.59; p = 0.67; partial η^2 = 0.007).

3.2. GMV of olfactory regions (olfactory ROIs)

When comparing *olfactory ROIs* GMV between the three groups, the rmANOVA revealed a significant main effect of *group* (F [2, 160] = 5.02; p = 0.008; partial η^2 = 0.059) and *age* (F [2, 160] = 9.76; p = 0.002; partial η^2 = 0.058), significant interactions between *region* and *group* (F [3,45, 275.73] = 4.01; p = 0.006; partial η^2 = 0.048), and significant interaction between *region* and *age* (F [1.72, 275.73] = 9.82; $p > 0.001$; partial η^2 = 0.058). No significant interaction effects between *region* and *sex* (F [1.72, 275.73] = 0.97; p = 0.37; partial η^2 = 0.006) or *education* (F [1.72, 275.73] = 0.44; p = 0.94; partial $\eta^2 > 0.001$) were found, nor main effect of *sex* (F [1, 160] = 0.47; p = 0.83; partial $\eta^2 > 0.001$) or *education* (F [1, 160] = 0.80; p = 0.78; partial η^2 = 0.001). Post-hoc ANCOVAs pairwise comparisons controlled for age revealed smaller GMVs in MCI compared to both SCD and HC in the piriform cortex, amygdala, entorhinal cortex, and the left hippocampus ($p \leq 0.05$), but not for the left parahippocampal gyrus, the insula, the orbitofrontal cortex, and the left caudate ($p > 0.05$) (Fig. 3).

Regarding the interaction between *age* and *region*, linear Pearson's correlations showed that age was significantly and negatively associated with piriform cortex ($r = -0.26$, $p < 0.001$), amygdala ($r = -0.35$, $p < 0.001$), entorhinal cortex ($r = -0.27$, $p < 0.001$), left hippocampus ($r = -0.22$, p = 0.005), and orbitofrontal cortex ($r = -0.34$, $p < 0.001$) GMV.

Regarding *olfactory ROIs* laterality, we did not find a significant interaction effect between *region*, *group*, and *side* (F [3.47, 277.51] = 1.06; p = 0.37; partial η^2 = 0.01).

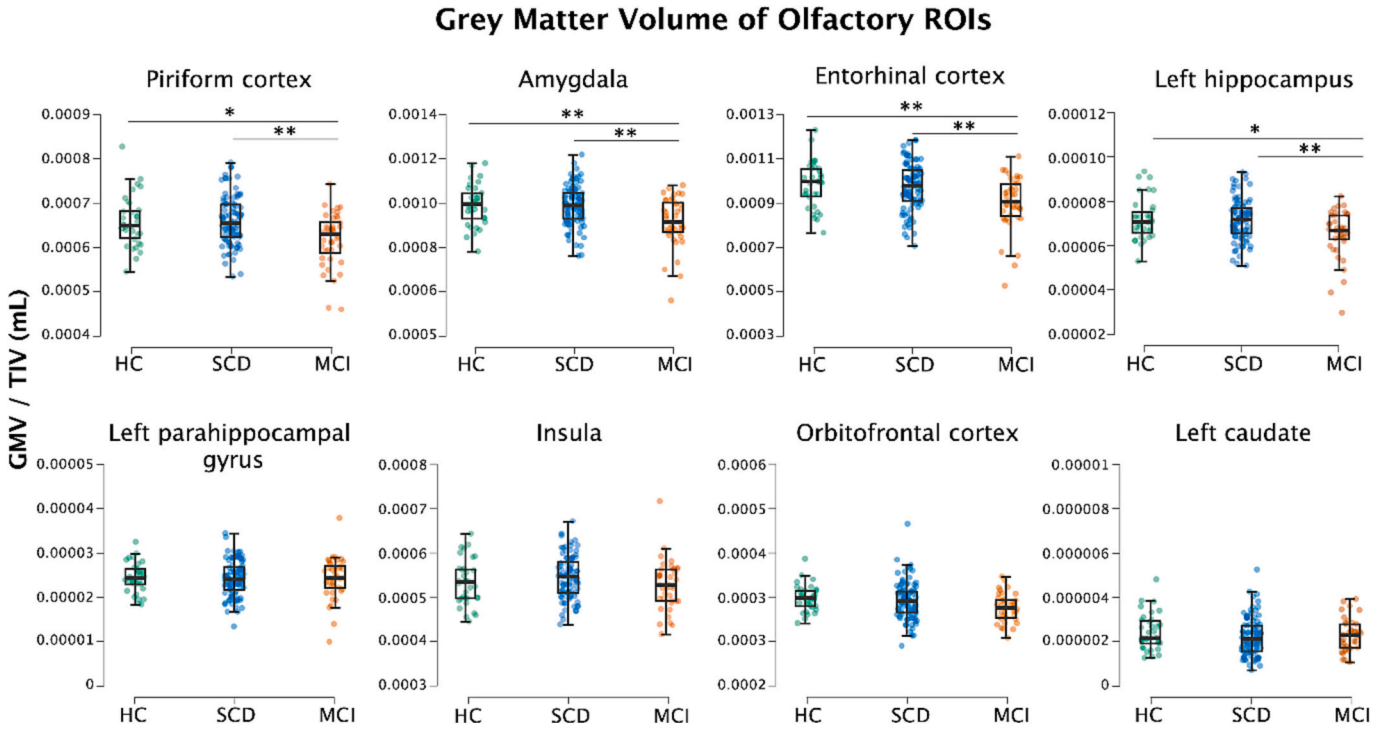

Fig. 3. Post-hoc ANCOVAs pairwise comparisons for each olfactory ROI between the three groups (HC, SCD, MCI), controlled for age. MCI group exhibited significantly smaller GMV in the piriform cortex, amygdala, entorhinal cortex, and left hippocampus compared to HC and SCD groups. The boxes represent the interquartile range of GMV distributions, the middle lines represent the median. p-values for each pairwise comparison: Piriform cortex: HC VS SCD p = 0.82, HC VS MCI p = 0.014, SCD VS MCI p = 0.001; Amygdala: HC VS SCD p = 0.92, HC VS MCI p = 0.008, SCD VS MCI p = 0.002; Entorhinal cortex: HC VS SCD p = 0.60, HC VS MCI p = 0.007, SCD VS MCI p = 0.006; Left hippocampus: HC VS SCD p = 0.89, HC VS MCI p = 0.01, SCD VS MCI p = 0.004; Left parahippocampal gyrus: HC VS SCD p = 0.80, HC VS MCI p = 0.77, SCD VS MCI p = 0.94; Insula: HC VS SCD p = 0.24, HC VS MCI p = 0.49, SCD VS MCI p = 0.04; Orbitofrontal cortex: HC VS SCD p = 0.46, HC VS MCI p = 0.07, SCD VS MCI p = 0.15; Left caudate: HC VS SCD p = 0.20, HC VS MCI p = 0.59, SCD VS MCI p = 0.51.
* indicates statistically significant difference at $p < 0.05$ that resisted to Holm-Bonferroni correction; ** indicates statistically significant difference at $p < 0.01$ that resisted to Holm-Bonferroni correction.

3.3. GMV of non-olfactory regions (non-olfactory ROIs)

In contrast, when comparing *non-olfactory ROIs* GMV between the three groups, a rmANOVA revealed no significant interaction between *region* and *group* (F [4.76, 380.63] = 0.87; $p = 0.49$; partial $\eta^2 = 0.011$), nor main effect of group (F [2, 161] = 2.21; $p = 0.11$; partial $\eta^2 = 0.027$). No significant interaction effects between *region* and *sex* (F [4.76, 380.63] = 0.87; $p = 0.50$; partial $\eta^2 = 0.017$) or *education* (F [2.40, 380.63] = 0.46; $p = 0.68$; partial $\eta^2 = 0.003$) were found, nor main effect of *sex* (F [1, 160] = 2.85; $p = 0.09$; partial $\eta^2 = 0.018$) or *education* (F [1, 160] = 0.03; $p = 0.86$; partial $\eta^2 > 0.001$). However, we found a significant interaction between *region* and *age* (F [2.38, 380.63] = 4.13; $p = 0.012$; partial $\eta^2 = 0.025$). Age was significantly and negatively associated with the entorhinal cortex ($r = -0.22$, $p = 0.005$), left hippocampus ($r = -0.41$, $p < 0.001$), left parahippocampal gyrus ($r = -0.27$, $p < 0.001$), insula ($r = -0.24$, $p = 0.002$), orbitofrontal cortex ($r = -0.25$, $p = 0.001$), and left caudate ($r = -0.24$, $p = 0.002$) GMV. Regarding laterality, we did not find a significant interaction effect between *region*, *group*, and *side* ($p = 0.60$).

3.4. Relationship between olfactory ROIs GMV and episodic memory performance

When analyzing the relationship between *olfactory ROIs'* GMV and episodic memory performance in the whole sample ($n = 166$), we observed significant linear correlations between Memoria free word recall scores and the piriform cortex ($r = 0.21$, $p = 0.007$), amygdala ($r = 0.25$, $p = 0.001$), and left hippocampus ($r = 0.26$, $p < 0.001$) GMV. After controlling for age using a partial correlation, only the left hippocampus GMV remained significantly correlated to episodic memory performance after correction ($r = 0.22$, $p = 0.005$). When analyzing the relationship between olfactory ROIs and episodic memory by groups (HC, SCD, MCI), no significant correlations were found between GMV and episodic memory, although there was a trend within the MCI group (HC: $r = 0.23$, $p = 0.20$; SCD: $r = 0.04$, $p = 0.74$; MCI: $r = 0.31$, $p = 0.056$) (Fig. 4).

When performing the same partial correlation analysis with *anatomical ROIs* and *non-olfactory ROIs*, we obtained the same pattern where only left hippocampus GMV remained significantly correlated to episodic memory performance after correction (*anatomical ROI:* $r = 0.30$, $p < 0.0.001$; *non-olfactory ROI:* $r = 0.29$, $p < 0.0.001$). When performing the analysis by groups (HC, SCD, MCI), we did not find any significant correlations were found between GMV and episodic memory ($p > 0.05$).

4. Discussion

In this study, we examined GMV of central olfactory structures and its relationship with episodic memory performance in individuals at risk of AD dementia. We found that GMV of piriform cortex, amygdala, entorhinal cortex, and left hippocampus olfactory subregions were smaller in the MCI group compared to both other groups. We also found that this neurodegenerative pattern is specific to olfactory processing areas since we did not find similar effects outside defined olfactory ROIs (*non-olfactory ROIs*) within the same regions, nor when using whole regions GMV (*anatomical ROIs)*. Finally, the GMV of the left hippocampus ROIs correlated with episodic memory performance.

Consistent with previous reports (Chen et al., 2021; Jobin et al., 2021a; Lu et al., 2019; Vasavada et al., 2015), these results suggest that atrophy of central olfactory processing areas is present in individuals with MCI. More specifically, our data suggest a distinct and specific structural atrophy pattern where temporal-medial and limbic olfactory

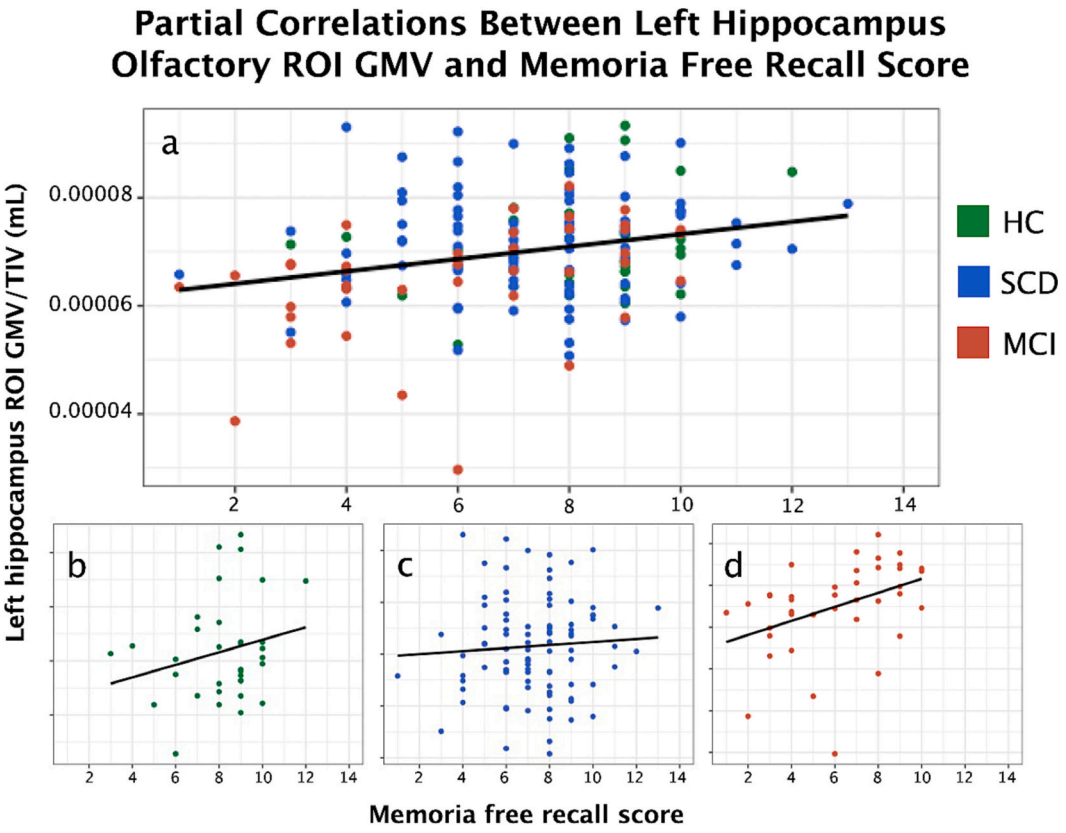

Fig. 4. Partial correlations between left hippocampus olfactory ROI and Memoria free recall score. a. represents a partial positive correlation ($r = 0.22$, $p = 0.005$) between left hippocampus olfactory ROI GMV and Memoria free recall score, controlling for age, for the whole sample. The three other panels represent the same analysis by group (b. HC, c. SCD, d. MCI respectively), without statistically significant effects (all $p > 0.05$).

processing areas are damaged early in the prodromal stage of AD. This pattern is consistent with the Braak staging of neurofibrillary changes, where tau tangles appear very early within trans-entorhinal and then in limbic regions before expanding to isocortical areas of the brain (Braak and Braak, 1991), supporting the hypothesis that olfactory impairment observed in prodromal AD reflects early neuronal damage caused by tau pathology in medial-temporal and limbic regions of the brain. Indeed, several studies have linked CSF and PET tau levels to olfactory performance in healthy older adults (Lafaille-Magnan et al., 2017; Risacher et al., 2017; Tu et al., 2020) and in mixed AD-continuum groups (Klein et al., 2021; Reijs et al., 2017).

The observed atrophy pattern of the central olfactory processing areas occurring first in the temporal-medial and limbic areas is also consistent with a newly proposed model (Planche et al., 2022) suggesting that atrophy progression in AD starts in (1) the hippocampus and amygdala; before progressing to (2) the middle temporal gyrus; (3) entorhinal cortex, parahippocampal cortex and other temporal areas; (4) striatum and thalamus, and (5) middle frontal, cingular, parietal and insular cortex. It is important to point out that Planche's model does not include the piriform cortex. However, given its anatomical and functional connections with the amygdala, entorhinal cortex, and hippocampus (Carmichael et al., 1994; Zhou et al., 2019, 2021), our observation of atrophied piriform cortex is in line with the model. These two models (Braak and Braak, 1991; Planche et al., 2022) demonstrated that key primary olfactory cortex structures are among the first to be damaged in AD.

Furthermore, damages to the olfactory system in AD could even be detected earlier, as recent studies showed that caspase activation, a molecular pathology that precedes and leads to tau-tangles (de Calignon et al., 2010), is present in the human anterior olfactory nucleus, is related to cognitive performance (Foveau et al., 2016), cooccurs with olfactory bulb atrophy, and is correlated to olfactory performance in Huntington's Disease murine model (Lessard-Beaudoin et al., 2019; Laroche et al., 2020). Future studies need to investigate caspase activation and its relationship to olfactory performance in AD models.

On a behavioral level, early atrophy of medial-temporal and limbic olfactory regions could explain why olfactory identification is early impaired during AD development (Rahayel et al., 2012; Roalf et al., 2017). Indeed, damage to medial-temporal and limbic olfactory regions is associated with a reduced olfactory identification performance, as smaller hippocampal volumes are related to worse olfactory identification performance in community-dwelling older adults (Devanand et al., 2010; Kose et al., 2021) and in patients with MCI or AD (Hagemeier et al., 2016; Kjelvik et al., 2014; Murphy et al., 2003; Yoshii et al., 2019; Yu et al., 2019). Although the amygdala has been associated with emotional processing and aversive stimuli (Patin and Pause, 2015), its volume is also linked to olfactory identification performance in older adults (Kose et al., 2021). Further, the primary olfactory cortex (including piriform cortex, amygdala, anterior olfactory nucleus, and olfactory tubercle) is smaller in AD and MCI compared to healthy older adults (Al-Otaibi et al., 2021; Vasavada et al., 2015) and the piriform cortex is less activated during an olfactory identification task in patients with amnesic MCI or AD (Kjelvik et al., 2021). The olfactory orbitalfrontal/insular regions are also activated during an odor identification task (Suzuki et al., 2001; Wang et al., 2005). Although we did not detect any significantly smaller volume in these regions, neuronal damage to the primary olfactory regions probably prevents the proper transmission of olfactory information to these regions, which would also impair olfactory identification performance. Indeed, previous work demonstrated that olfactory quality coding is already disrupted at the piriform cortex processing level and mediates olfactory deficits in AD (Li et al., 2010). Finally, the olfactory system impairment in neurodegenerative diseases is complex and damage to more peripheral olfactory structures such as the olfactory bulb or olfactory neuroepithelium could also contribute to olfactory impairment in AD. While neurofibrillary tangles are present in the first Braak's stages (0–1) in the olfactory bulbs (Kovács et al., 2001) and the olfactory bulb volume is smaller in MCI patients (Jobin et al., 2021a), amyloid-β aggregates accumulate in the olfactory mucosa of MCI patients (Ayala-Grosso et al., 2015; Dibattista et al., 2020 for a review).

Our findings indicate that damage to the central olfactory system is first observable during the MCI stage of Alzheimer's disease. However, evidence suggests that sensory decline may begin before the onset of MCI. Older adults with SCD show a trend for worse olfactory identification performance compared to healthy controls (Jobin et al., 2021b). In the same vein, individuals with SCD or MCI exhibit reduced capacity to identify odors, combined with a reduced GMV of the bilateral hippocampus, bilateral parahippocampal gyrus, entorhinal cortex, right gyrus rectus, left caudate nucleus, and left putamen, and reduced functional connectivity between left and right hippocampus compared to healthy older participants (Chen et al., 2021). In our study, we did not find any significant difference between SCD and HC groups regarding GMV of olfactory regions. This result may be due to the large heterogeneity of the SCD population and the lack of specificity of the SCD symptom to predict who will convert to AD in community-based cohorts (Slot et al., 2019). Longitudinal studies involving cognitively normal older adults positive to tau and β-amyloid biomarkers should verify whether olfactory decline, and its associated structural and functional damage, start before or at the same time as the onset of memory impairment. Future studies should also include participants from large and publicly available cohorts, such as the ADNI cohort, to replicate the cross-sectional results of this study.

Age was also independently significantly associated with piriform cortex, amygdala, entorhinal cortex, left hippocampus, and orbitofrontal cortex olfactory ROIs GVM. These relationships are unsurprising as olfaction declines with age (Doty and Kamath, 2014; Mackay-Sim et al., 2006; Oleszkiewicz et al., 2019). Interestingly, except for the orbitofrontal cortex, all these structures were also independently smaller in the MCI when controlling for age using post-hoc ANCOVAs, suggesting a more severe alteration in MCI that might be due to AD within the limbic/medial-temporal olfactory system.

Our results show that left hippocampus and left caudate *anatomical ROIs* were smaller in males compared to females. These results are consistent with previous reports suggesting greater atrophy in males for temporal regions (Brun et al., 2009), the hippocampus (Jack et al., 2015; Murphy, 1996) in older adults, and the left caudate (Persson et al., 2018). Interestingly, males typically exhibit lower olfactory performance than females (Sorokowski et al., 2019), which may be explained by endocrine-related effects on brain regions involved in olfaction, including the hippocampus (Doty and Cameron, 2009). Indeed, sex hormones such as estrogen are neuroprotective for the hippocampus during adult life (Zárate et al., 2017; Siddiqui et al., 2016). Their reduction during menopause accelerates aging, which explains why females are more at risk of AD and decline to the dementia stage more quickly than males (Li and Singh, 2014; Yue et al., 2005).

After controlling for age, verbal episodic memory performance was correlated with the left hippocampus olfactory ROIs GMV. This significant correlation is not surprising since the left hippocampus is involved in both olfactory and memory functions (Gabrieli et al., 1997; Hummel et al., 2010; Kjelvik et al., 2021; Lundström et al., 2011; Squire and Zola, 1996; Squire and Zola-Morgan, 1991; Zald and Pardo, 2000), and that episodic memory and olfactory functions are associated in the healthy older adult population (Chen et al., 2018; Devanand et al., 2010; Jobin et al., 2023; Larsson et al., 2016; Tonacci et al., 2017; Wehling et al., 2010). This could suggest an overlap between olfactory and memory functions within the left hippocampus, which would support the common cause hypothesis (Baltes and Lindenberger, 1997) suggesting that both sensory and cognitive declines related to aging stem from a shared factor—the deterioration of common cerebral structures. In line with the common cause hypothesis, our results also support the hypothesis of a common trajectory of olfactory and memory decline within aging due to damages in shared medial-temporal regions (Dintica et al., 2021).

This study has certain limitations. The main limitation of this study is the lack of behavioral olfactory testing, which prevents the evaluation of the association between olfactory function and both structural and memory measures. Future studies should include olfactory measures, such as olfactory identification and olfactory threshold assessments. Another limitation is that most participants were recruited from the community, which are less impaired and less likely to convert to dementia than patients from memory clinics (Farias et al., 2009; Slot et al., 2019). This suggests that the observed effect may be even bigger among the clientele of memory clinics.

5. Conclusion

Limbic and medial-temporal olfactory processing areas are smaller in patients with MCI compared to participants with SCD and controls. Moreover, the olfactory processing area of the left hippocampus correlated with episodic memory performance, suggesting a potential overlap between olfactory and memory functions within this region.

CRediT authorship contribution statement

B. Jobin: Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft. **B. Boller:** Conceptualization, Funding acquisition, Resources, Methodology, Supervision, Writing – review & editing. **J. Frasnelli:** Conceptualization, Funding acquisition, Resources, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

We would like to thank Gabrielle Ciquier for English editing. This work was supported by grants from the Canadian Institutes of Health Research (JF; Grant number: PJT-173514), the Fonds de Recherche Québec Santé (JF, grant number: 283144 - chercheur boursier Junior 2) and the Research Centre of the Institut Universitaire de gériatrie de Montréal (BB, Grant for pilot project). BJ is supported by scholarships from the Canadian Institutes of Health Research and the Fonds de recherche Québec Santé.

References

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7 (3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008.

Al-Otaibi, M., Lessard-Beaudoin, M., Castellano, C.-A., Gris, D., Cunnane, S.C., Graham, R.K., 2021. Volumetric MRI demonstrates atrophy of the olfactory cortex in AD. Curr. Alzheimer Res. 17 (10), 904–915. https://doi.org/10.2174/1567205017666201215120909.

Ayala-Grosso, C.A., Pieruzzini, R., Diaz-Solano, D., Wittig, O., Abrante, L., Vargas, L., Cardier, J., 2015. Amyloid-Aβ peptide in olfactory mucosa and mesenchymal stromal cells of mild cognitive impairment and Alzheimer's Disease patients: amyloid in olfactory mucosa of Alzheimer Disease. Brain Pathol. 25 (2), 136–145. https://doi.org/10.1111/bpa.12169.

Bahar-Fuchs, A., Moss, S., Rowe, C., Savage, G., 2010. Olfactory performance in AD, aMCI, and healthy ageing: a unirhinal approach. Chem. Senses 35 (9), 855–862. https://doi.org/10.1093/chemse/bjq094.

Baltes, P.B., Lindenberger, U., 1997. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? Psychol. Aging 12 (1), 12. https://doi.org/10.1037/0882-7974.12.1.12.

Belleville, S., Fouquet, C., Hudon, C., Zomahoun, H.T.V., Croteau, J., 2017. Neuropsychological measures that predict progression from mild cognitive impairment to Alzheimer's type dementia in older adults: a systematic review and meta-analysis. Neuropsychol. Rev. 27 (4), 328–353. https://doi.org/10.1007/s11065-017-9361-5.

Belleville, S., LeBlanc, A.C., Kergoat, M., Calon, F., Gaudreau, P., Hébert, S.S., Hudon, C., Leclerc, N., Mechawar, N., Duchesne, S., Gauthier, S., Consortium for the Early Identification of Alzheimer's disease-Quebec (CIMA-Q), Bellec, P., Belleville, S., Bocti, C., Calon, F., Chertkow, H., Collins, L., Cunnane, S., Villalpando, J.M., 2019. The consortium for the early identification of Alzheimer's disease–Quebec (CIMA-Q). Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 11 (1), 787–796. https://doi.org/10.1016/j.dadm.2019.07.003.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82 (4), 239–259. https://doi.org/10.1007/BF00308809.

Brun, C.C., Leporé, N., Luders, E., Chou, Y.-Y., Madsen, S.K., Toga, A.W., Thompson, P. M., 2009. Sex differences in brain structure in auditory and cingulate regions. NeuroReport 20 (10), 930–935. https://doi.org/10.1097/WNR.0b013e32832c5e65.

Carmichael, S.T., Clugnet, M.-C., Price, J.L., 1994. Central olfactory connections in the macaque monkey. J. Comp. Neurol. 346 (3), 403–434. https://doi.org/10.1002/cne.903460306.

Chatelois, J., Pineau, H., Belleville, S., Peretz, I., Lussier, I., Fontaine, F.S., Renaseau-Leclerc, C., 1993. Batterie informatisée d'évaluation de la mémoire inspirée de l'approche cognitive. Can. Psychol. 34 (1), 45. https://doi.org/10.1037/h0078803.

Chen, B., Zhong, X., Mai, N., Peng, Q., Zhang, M., Chen, X., Wu, Z., Zou, L., Liang, W., Ouyang, C., Wu, Y., Ning, Y., 2018. Interactive effect of depression and cognitive impairment on olfactory identification in elderly people. J. Alzheimers Dis. 66 (4), 1645–1655. https://doi.org/10.3233/JAD-180760.

Chen, B., Wang, Q., Zhong, X., Mai, N., Zhang, M., Zhou, H., Haehner, A., Chen, X., Wu, Z., Auber, L.A., Rao, D., Liu, W., Zheng, J., Lin, L., Li, N., Chen, S., Chen, B., Hummel, T., Ning, Y., 2021. Structural and functional abnormalities of olfactory-related regions in subjective cognitive decline, mild cognitive impairment, and Alzheimer's Disease. Int. J. Neuropsychopharmacol. pyab091 https://doi.org/10.1093/ijnp/pyab091.

De Calignon, A., Fox, L.M., Pitstick, R., Carlson, G.A., Bacskai, B.J., Spires-Jones, T.L., Hyman, B.T., 2010. Caspase activation precedes and leads to tangles. Nature 464 (7292), 1201–1204. https://doi.org/10.1038/nature08890.

Devanand, D.P., Tabert, M.H., Cuasay, K., Manly, J.J., Schupf, N., Brickman, A.M., Andrews, H., Brown, T.R., DeCarli, C., Mayeux, R., 2010. Olfactory identification deficits and MCI in a multi-ethnic elderly community sample. Neurobiol. Aging 31 (9), 1593–1600. https://doi.org/10.1016/j.neurobiolaging.2008.09.008.

Devanand, D.P., Lee, S., Manly, J., Andrews, H., Schupf, N., Doty, R.L., Stern, Y., Zahodne, L.B., Louis, E.D., Mayeux, R., 2015. Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. Neurology 84 (2), 182–189. https://doi.org/10.1212/WNL.0000000000001132.

Dibattista, M., Pifferi, S., Menini, A., Reisert, J., 2020. Alzheimer's Disease: what can we learn from the peripheral olfactory system? Front. Neurosci. 14, 440. https://doi.org/10.3389/fnins.2020.00440.

Dintica, C.S., Marseglia, A., Rizzuto, D., Wang, R., Seubert, J., Arfanakis, K., Bennett, D. A., Xu, W., 2019. Impaired olfaction is associated with cognitive decline and neurodegeneration in the brain. Neurology 92 (7), e700–e709. https://doi.org/10.1212/WNL.0000000000006919.

Dintica, C.S., Haaksma, M.L., Olofsson, J.K., Bennett, D.A., Xu, W., 2021. Joint trajectories of episodic memory and odor identification in older adults: patterns and predictors. Aging 13 (13), 17080–17096. https://doi.org/10.18632/aging.203280.

Djordjevic, J., Jones-Gotman, M., De Sousa, K., Chertkow, H., 2008. Olfaction in patients with mild cognitive impairment and Alzheimer's disease. Neurobiol. Aging 29 (5), 693–706. https://doi.org/10.1016/j.neurobiolaging.2006.11.014.

Doty, R.L., Cameron, E.L., 2009. Sex differences and reproductive hormone influences on human odor perception. Physiol. Behav. 97 (2), 213–228. https://doi.org/10.1016/j.physbeh.2009.02.032.

Doty, R.L., Kamath, V., 2014. The influences of age on olfaction: a review. Front. Psychol. 5 https://doi.org/10.3389/fpsyg.2014.00020.

Duchesne, S., Chouinard, I., Potvin, O., Fonov, V.S., Khademi, A., Bartha, R., Bellec, P., Collins, D.L., Descoteaux, M., Hoge, R., McCreary, C.R., Ramirez, J., Scott, C.J.M., Smith, E.E., Strother, S.C., Black, S.E., for the CIMA-Q group and the CCNA group, 2019. The Canadian dementia imaging protocol: harmonizing national cohorts. J. Magn. Reson. Imaging 49 (2), 456–465. https://doi.org/10.1002/jmri.26197.

Dulay, M.F., Murphy, C., 2002. Olfactory acuity and cognitive function converge in older adulthood: support for the common cause hypothesis. Psychol. Aging 17 (3), 392–404. https://doi.org/10.1037/0882-7974.17.3.392.

Eibenstein, A., Fioretti, A.B., Simaskou, M.N., Sucapane, P., Mearelli, S., Mina, C., Amabile, G., Fusetti, M., 2005. Olfactory screening test in mild cognitive impairment. Neurol. Sci. 26 (3), 156–160. https://doi.org/10.1007/s10072-005-0453-2.

Farias, S.T., Mungas, D., Reed, B.R., Harvey, D., DeCarli, C., 2009. Progression of mild cognitive impairment to dementia in clinic-vs community-based cohorts. Arch. Neurol. 66 (9), 1151–1157. https://doi.org/10.1001/archneurol.2009.106.

Fjaeldstad, A., Fernandes, H.M., Van Hartevelt, T., Gleesborg, C., Møller, A., Ovesen, T., Kringelbach, M., 2017. Brain fingerprints of olfaction: a novel structural method for assessing olfactory cortical networks in health and disease. Sci. Rep. 7 (1), 1–13. https://doi.org/10.1038/srep42534.

Fjaeldstad, A.W., Ovesen, T., Dalby, R.B., 2021. Cortical atrophy, White matter lesions, and bulb configuration in patients with idiopathic olfactory loss and other causes of olfactory loss. ORL 1–9. https://doi.org/10.1159/000520567.

Foveau, B., Albrecht, S., Bennett, D.A., Correa, J.A., LeBlanc, A.C., 2016. Increased Caspase-6 activity in the human anterior olfactory nuclei of the olfactory bulb is associated with cognitive impairment. Acta Neuropathol. Commun. 4 (1), 127. https://doi.org/10.1186/s40478-016-0400-x.

Gabrieli, J.D.E., Brewer, J.B., Desmond, J.E., Glover, G.H., 1997. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science, New Series 276 (5310), 264–266.

Gaser, C., Dahnke, R., Thompson, P.M., Kurth, F., Luders, E., Alzheimer's Disease Neuroimaging Initiative, 2022. CAT – a computational anatomy toolbox for the analysis of structural MRI data [preprint]. Neuroscience. https://doi.org/10.1101/2022.06.11.495736.

Growdon, M.E., Schultz, A.P., Dagley, A.S., Amariglio, R.E., Hedden, T., Rentz, D.M., Johnson, K.A., Sperling, R.A., Albers, M.W., Marshall, G.A., 2015. Odor identification and Alzheimer disease biomarkers in clinically normal elderly. Neurology 84 (21), 2153–2160. https://doi.org/10.1212/WNL.0000000000001614.

Hagemeier, J., Woodward, M.R., Rafique, U.A., Amrutkar, C.V., Bergsland, N., Dwyer, M. G., Benedict, R., Zivadinov, R., Szigeti, K., 2016. Odor identification deficit in mild cognitive impairment and Alzheimer's disease is associated with hippocampal and deep gray matter atrophy. Psychiatry Res. Neuroimaging 255, 87–93. https://doi.org/10.1016/j.pscychresns.2016.08.003.

Hummel, T., Fliessbach, K., Abele, M., Okulla, T., Reden, J., Reichmann, H., Wüllner, U., Haehner, A., 2010. Olfactory fMRI in patients with Parkinson's Disease. Front. Integr. Neurosci. 4 https://doi.org/10.3389/fnint.2010.00125.

Jack, C.R., Wiste, H.J., Weigand, S.D., Knopman, D.S., Vemuri, P., Mielke, M.M., Lowe, V., Senjem, M.L., Gunter, J.L., Machulda, M.M., Gregg, B.E., Pankratz, V.S., Rocca, W.A., Petersen, R.C., 2015. Age, sex, and *APOE* ε4 effects on memory, brain structure, and β-amyloid across the adult life span. JAMA Neurol. 72 (5), 511. https://doi.org/10.1001/jamaneurol.2014.4821.

Jack, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Silverberg, N., 2018. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 14 (4), 535–562. https://doi.org/10.1016/j.jalz.2018.02.018.

Jessen, F., Amariglio, R.E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K.A., van der Flier, W.M., Glodzik, L., van Harten, A.C., de Leon, M.J., McHugh, P., Mielke, M.M., Molinuevo, J.L., Mosconi, L., Osorio, R.S., Perrotin, A., Wagner, M., 2014. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 10 (6), 844–852. https://doi.org/10.1016/j.jalz.2014.01.001.

Jessen, F., Kleineidam, L., Wolfsgruber, S., Bickel, H., Brettschneider, C., Fuchs, A., Kaduszkiewicz, H., König, H., Mallon, T., Mamone, S., Pabst, A., Pentzek, M., Roehr, S., Weeg, D., Jochen, W., Weyerer, S., Wiese, B., Maier, W., Scherer, M., Wagner, M., 2020. Prediction of dementia of Alzheimer type by different types of subjective cognitive decline. Alzheimers Dement. 16 (12), 1745–1749. https://doi.org/10.1002/alz.12163.

Jobin, B., Boller, B., Frasnelli, J., 2021a. Volumetry of olfactory structures in mild cognitive impairment and Alzheimer's Disease: a systematic review and a meta-analysis. Brain Sci. 11 (8), 1010. https://doi.org/10.3390/brainsci11081010.

Jobin, B., Zahal, R., Bussières, E.-L., Frasnelli, J., Boller, B., 2021b. Olfactory identification in subjective cognitive decline: a meta-analysis. J. Alzheimers Dis. 79 (4), 1497–1507. https://doi.org/10.3233/JAD-201022.

Jobin, B., Roy-Côté, F., Frasnelli, J., Boller, B., 2023. Olfaction and declarative memory in aging: a meta-analysis. Chem. Senses bjad045. https://doi.org/10.1093/chemse/bjad045.

Jung, H.J., Shin, I.-S., Lee, J.-E., 2019. Olfactory function in mild cognitive impairment and Alzheimer's disease: a meta-analysis: olfactory function deficit in MCI and AD. Laryngoscope 129 (2), 362–369. https://doi.org/10.1002/lary.27399.

Kjelvik, G., Saltvedt, I., White, L.R., Stenumgård, P., Sletvold, O., Engedal, K., Skåtun, K., Lyngvær, A.K., Steffenach, H.A., Håberg, A.K., 2014. The brain structural and cognitive basis of odor identification deficits in mild cognitive impairment and Alzheimer's disease. BMC Neurol. 14 (1), 168. https://doi.org/10.1186/s12883-014-0168-1.

Kjelvik, G., Evensmoen, H.R., Hummel, T., Engedal, K., Selbæk, G., Saltvedt, I., Håberg, A.K., 2021. The human brain representation of odor identification in amnestic mild cognitive impairment and Alzheimer's dementia of mild degree. Front. Neurol. 11, 1779. https://doi.org/10.3389/fneur.2020.607566.

Klein, J., Yan, X., Johnson, A., Tomljanovic, Z., Zou, J., Polly, K., Honig, L.S., Brickman, A.M., Stern, Y., Devanand, D.P., Lee, S., Kreisl, W.C., 2021. Olfactory impairment is related to tau pathology and neuroinflammation in Alzheimer's Disease. J. Alzheimers Dis. 80 (3), 1051–1065. https://doi.org/10.3233/JAD-201149.

Kose, Y., Hatamoto, Y., Takae, R., Tomiga, Y., Yasukata, J., Komiyama, T., Higaki, Y., 2021. Association between the inability to identify particular odors and physical performance, cognitive function, and/or brain atrophy in community-dwelling older adults from the Fukuoka Island City study. BMC Geriatr. 21 (1), 421. https://doi.org/10.1186/s12877-021-02363-y.

Kovács, Cairns, Lantos, 1999. β-Amyloid deposition and neurofibrillary tangle formation in the olfactory bulb in ageing and Alzheimer's disease. Neuropathol. Appl. Neurobiol. 25 (6), 481–491. https://doi.org/10.1046/j.1365-2990.1999.00208.x.

Kovács, T., Cairns, N.J., Lantos, P.L., 2001. Olfactory centres in Alzheimer's disease: olfactory bulb is involved in early Braak's stages. Neuroreport 12 (2), 285–288. https://doi.org/10.1097/00001756-200102120-00021.

Lafaille-Magnan, M.-E., Poirier, J., Etienne, P., Tremblay-Mercier, J., Frenette, J., Rosa-Neto, P., Breitner, J.C.S., For the PREVENT-AD Research Group, 2017. Odor identification as a biomarker of preclinical AD in older adults at risk. Neurology 89 (4), 327–335. https://doi.org/10.1212/WNL.0000000000004159.

Laroche, M., Lessard-Beaudoin, M., Garcia-Miralles, M., Kreidy, C., Peachey, E., Leavitt, B.R., Pouladi, M.A., Graham, R.K., 2020. Early deficits in olfaction are associated with structural and molecular alterations in the olfactory system of a Huntington disease mouse model. Hum. Mol. Genet. 29 (13), 2134–2147. https://doi.org/10.1093/hmg/ddaa099.

Larsson, M., Hedner, M., Papenberg, G., Seubert, J., Bäckman, L., Laukka, E.J., 2016. Olfactory memory in the old and very old: relations to episodic and semantic memory and APOE genotype. Neurobiol. Aging 38, 118–126. https://doi.org/10.1016/j.neurobiolaging.2015.11.012.

Lessard-Beaudoin, M., Yu-Taeger, L., Laroche, M., Singer, E., Riess, O., Nguyen, H.H.P., Graham, R.K., 2019. Olfactory bulb atrophy and caspase activation observed in the BACHD rat models of Huntington disease. Neurobiol. Dis. 125, 219–231. https://doi.org/10.1016/j.nbd.2019.02.002.

Li, R., Singh, M., 2014. Sex differences in cognitive impairment and Alzheimer's disease. Front. Neuroendocrinol. 35 (3), 385–403. https://doi.org/10.1016/j.yfrne.2014.01.002.

Li, W., Howard, J.D., Gottfried, J.A., 2010. Disruption of odour quality coding in piriform cortex mediates olfactory deficits in Alzheimer's disease. Brain 133 (9), 2714–2726. https://doi.org/10.1093/brain/awq209.

Lu, Testa, Jordan, Elyan, Kanekar, Wang, Eslinger, Yang, Zhang, Karunanayaka, 2019. Functional connectivity between the resting-state olfactory network and the Hippocampus in Alzheimer's Disease. Brain Sci. 9 (12), 338. https://doi.org/10.3390/brainsci9120338.

Lundstrom, J.N., Boesveldt, S., Albrecht, J., 2011. Central processing of the chemical senses: an overview. ACS Chem. Neurosci. 2 (1), 5–16. https://doi.org/10.1021/cn1000843.

Mackay-Sim, A., Royet, J.-P., Doherty, P., 2006. Structure and function of the olfactory system. In: Brewer, W.J., Castle, D., Pantelis, C. (Eds.), Olfaction and the Brain. Cambridge University Press, pp. 3–27. https://doi.org/10.1017/CBO9780511543623.003.

Malpetti, M., La Joie, R., Rabinovici, G.D., 2022. Tau beats amyloid in predicting brain atrophy in Alzheimer disease: implications for prognosis and clinical trials. J. Nucl. Med. 63 (6), 830–832. https://doi.org/10.2967/jnumed.121.263694.

Mauri, M., Sinforiani, E., Zucchella, C., Cuzzoni, M.G., Bono, G., 2012. Progression to dementia in a population with amnestic mild cognitive impairment: clinical variables associated with conversion. Funct. Neurol. 27 (1), 49–54.

Mesholam, R.I., Moberg, P.J., Mahr, R.N., Doty, R.L., 1998. Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. Arch. Neurol. 55 (1), 84. https://doi.org/10.1001/archneur.55.1.84.

Murphy, D.G.M., 1996. Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging. Arch. Gen. Psychiatry 53 (7), 585. https://doi.org/10.1001/archpsyc.1996.01830070031007.

Murphy, C., 2019. Olfactory and other sensory impairments in Alzheimer disease. Nat. Rev. Neurol. 15 (1), 11–24. https://doi.org/10.1038/s41582-018-0097-5.

Murphy, C., Jernigan, T.L., Fennema-Notestine, C., 2003. Left hippocampal volume loss in Alzheimer's disease is reflected in performance on odor identification: a structural MRI study. J. Int. Neuropsychol. Soc. 9 (3), 459–471. https://doi.org/10.1017/S1355617703930116.

Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment: MOCA: a BRIEF SCREENING TOOL FOR MCI. J. Am. Geriatr. Soc. 53 (4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x.

Newkirk, L.A., Kim, J.M., Thompson, J.M., Tinklenberg, J.R., Yesavage, J.A., Taylor, J.L., 2004. Validation of a 26-point telephone version of the mini-mental state examination. J. Geriatr. Psychiatry Neurol. 17 (2), 81–87. https://doi.org/10.1177/0891988704264534.

Oleszkiewicz, A., Schriever, V., Croy, I., Hähner, A., Hummel, T., 2019. Updated Sniffin'Sticks normative data based on an extended sample of 9139 subjects. Eur. Arch. Otorhinolaryngol. 276 (3), 719–728. https://doi.org/10.1007/s00405-018-5248-1.

Olofsson, J.K., Larsson, M., Roa, C., Wilson, D.A., Jonsson Laukka, E., 2020. Interaction between odor identification deficit and APOE4 predicts 6-year cognitive decline in elderly individuals. Behav. Genet. 50 (1), 3–13. https://doi.org/10.1007/s10519-019-09980-9.

Patin, A., Pause, B.M., 2015. Human amygdala activations during nasal chemoreception. Neuropsychologia 78, 171–194. https://doi.org/10.1016/j.neuropsychologia.2015.10.009.

Persson, K., Bohbot, V.D., Bogdanovic, N., Selbæk, G., Brækhus, A., Engedal, K., 2018. Finding of increased caudate nucleus in patients with Alzheimer's disease. Acta Neurol. Scand. 137 (2), 224–232. https://doi.org/10.1111/ane.12800.

Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., Ritchie, K., Rossor, M., Thal, L., Winblad, B., 2001. Current concepts in mild cognitive impairment. Arch. Neurol. 58 (12), 1985. https://doi.org/10.1001/archneur.58.12.1985.

Planche, V., Manjon, J.V., Mansencal, B., Lanuza, E., Tourdias, T., Catheline, G., Coupé, P., 2022. Structural progression of Alzheimer's disease over decades: the MRI staging scheme. Brain Communications 4 (3), fcac109. https://doi.org/10.1093/braincomms/fcac109.

Postma, E.M., Smeets, P.A.M., Boek, W.M., Boesveldt, S., 2021. Investigating morphological changes in the brain in relation to etiology and duration of olfactory dysfunction with voxel-based morphometry. Sci. Rep. 11 (1), 12704. https://doi.org/10.1038/s41598-021-92224-w.

Rahayel, S., Frasnelli, J., Joubert, S., 2012. The effect of Alzheimer's disease and Parkinson's disease on olfaction: a meta-analysis. Behav. Brain Res. 231 (1), 60–74. https://doi.org/10.1016/j.bbr.2012.02.047.

Reijs, B.L.R., Ramakers, I.H.G.B., Elias-Sonnenschein, L., Teunissen, C.E., Koel-Simmelink, M., Tsolaki, M., Wahlund, L.-O., Waldemar, G., Hausner, L., Johannsen, P., Vanderstichele, H., Verhey, F., Devanand, D.P., Visser, P.J., 2017.

Relation of odor identification with Alzheimer's disease markers in cerebrospinal fluid and cognition. J. Alzheimers Dis. 60 (3), 1025–1034. https://doi.org/10.3233/JAD-170564.
Risacher, S.L., Tallman, E.F., West, J.D., Yoder, K.K., Hutchins, G.D., Fletcher, J.W., Gao, S., Kareken, D.A., Farlow, M.R., Apostolova, L.G., 2017. Olfactory identification in subjective cognitive decline and mild cognitive impairment: association with tau but not amyloid positron emission tomography. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 9, 57–66.
Roalf, D.R., Moberg, M.J., Turetsky, B.I., Brennan, L., Kabadi, S., Wolk, D.A., Moberg, P. J., 2017. A quantitative meta-analysis of olfactory dysfunction in mild cognitive impairment. J. Neurol. Neurosurg. Psychiatry 88 (3), 226–232. https://doi.org/10.1136/jnnp-2016-314638.
Roberts, R.O., Christianson, T.J., Kremers, W.K., Mielke, M.M., Machulda, M.M., Vassilaki, M., Alhurani, R.E., Geda, Y.E., Knopman, D.S., Petersen, R.C., 2016. Association between olfactory dysfunction and amnestic mild cognitive impairment and Alzheimer disease dementia. JAMA Neurol. 73 (1), 93–101.
Rohn, T.T., Head, E., Su, J.H., Anderson, A.J., Bahr, B.A., Cotman, C.W., Cribbs, D.H., 2001. Correlation between caspase activation and neurofibrillary tangle formation in Alzheimer's Disease. Am. J. Pathol. 158 (1), 189–198. https://doi.org/10.1016/S0002-9440(10)63957-0.
Seligman, S.C., Kamath, V., Giovannetti, T., Arnold, S.E., Moberg, P.J., 2013. Olfaction and apathy in Alzheimer's disease, mild cognitive impairment, and healthy older adults. Aging Ment. Health 17 (5), 564–570. https://doi.org/10.1080/13607863.2013.768208.
Seubert, J., Freiherr, J., Djordjevic, J., Lundström, J.N., 2013. Statistical localization of human olfactory cortex. Neuroimage 66, 333–342.
Siddiqui, A.N., Siddiqui, N., Khan, R.A., Kalam, A., Jabir, N.R., Kamal, M.A., Firoz, C.K., Tabrez, S., 2016. Neuroprotective role of steroidal sex hormones: an overview. CNS Neurosci. Ther. 22 (5), 342–350. https://doi.org/10.1111/cns.12538.
Silva, M. de M. e, Mercer, P.B.S., Witt, M.C.Z., Pessoa, R.R., 2018. Olfactory dysfunction in Alzheimer's disease systematic review and meta-analysis. Dementia & Neuropsychologia 12 (2), 123–132. https://doi.org/10.1590/1980-57642018dn12-020004.
Slot, R.E.R., Sikkes, S.A.M., Berkhof, J., Brodaty, H., Buckley, R., Cavedo, E., Dardiotis, E., Guillo-Benarous, F., Hampel, H., Kochan, N.A., Lista, S., Luck, T., Maruff, P., Molinuevo, J.L., Kornhuber, J., Reisberg, B., Riedel-Heller, S.G., Risacher, S.L., Roehr, S., van der Flier, W.M., 2019. Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia. Alzheimers Dement. 15 (3), 465–476. https://doi.org/10.1016/j.jalz.2018.10.003.
Sohrabi, H.R., Bates, K.A., Rodrigues, M., Taddei, K., Laws, S.M., Lautenschlager, N.T., Dhaliwal, S.S., Johnston, A.N., Mackay-Sim, A., Gandy, S., 2009. Olfactory dysfunction is associated with subjective memory complaints in community-dwelling elderly individuals. J. Alzheimers Dis. 17 (1), 135–142.
Sohrabi, H.R., Bates, K.A., Weinborn, M.G., Johnston, A.N.B., Bahramian, A., Taddei, K., Martins, R.N., 2012. Olfactory discrimination predicts cognitive decline among community-dwelling older adults. Transl. Psychiatry 2 (5), e118. https://doi.org/10.1038/tp.2012.43.
Sorokowski, P., Karwowski, M., Misiak, M., Marczak, M.K., Dziekan, M., Hummel, T., Sorokowska, A., 2019. Sex differences in human olfaction: a meta-analysis. Front. Psychol. 10, 242. https://doi.org/10.3389/fpsyg.2019.00242.
Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack, C.R., Kaye, J., Montine, T.J., Park, D.C., Reiman, E.M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M.C., Thies, B., Morrison-Bogorad, M., Phelps, C.H., 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7 (3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003.
Squire, L.R., Zola, S.M., 1996. Structure and function of declarative and nondeclarative memory systems. Proc. Natl. Acad. Sci. 93 (24), 13515–13522. https://doi.org/10.1073/pnas.93.24.13515.
Squire, L.R., Zola-Morgan, S., 1991. The medial temporal lobe memory system. Science, New Series 253 (5026), 1380–1386. https://doi.org/10.1126/science.1896849.
Suzuki, Y., Critchley, H.D., Suckling, J., Fukuda, R., Williams, S.C.R., Andrew, C., Howard, R., Ouldred, E., Bryant, C., Swift, C.G., Jackson, S.H.D., 2001. Functional magnetic resonance imaging of odor identification: the effect of aging. J. Gerontol. A Biol. Sci. Med. Sci. 56 (12), M756–M760. https://doi.org/10.1093/gerona/56.12.M756.
Thal, D.R., Rüb, U., Orantes, M., Braak, H., 2002. Phases of Aβ-deposition in the human brain and its relevance for the development of AD. Neurology 58 (12), 1791–1800. https://doi.org/10.1212/wnl.58.12.1791.
Tonacci, A., Bruno, R.M., Ghiadoni, L., Pratali, L., Berardi, N., Tognoni, G., Cintoli, S., Volpi, L., Bonuccelli, U., Sicari, R., Taddei, S., Maffei, L., Picano, E., 2017. Olfactory evaluation in mild cognitive impairment: correlation with neurocognitive performance and endothelial function. Eur. J. Neurosci. 45 (10), 1279–1288. https://doi.org/10.1111/ejn.13565.
Torske, A., Koch, K., Eickhoff, S., Freiherr, J., 2021. Localizing the human brain response to olfactory stimulation: a meta-analytic approach. Neurosci. Biobehav. Rev. S0149763421005832 https://doi.org/10.1016/j.neubiorev.2021.12.035.
Tremblay, C., Serrano, G.E., Intorcia, A.J., Sue, L.I., Wilson, J.R., Adler, C.H., Shill, H.A., Driver-Dunckley, E., Mehta, S.H., Beach, T.G., 2022. Effect of olfactory bulb pathology on olfactory function in normal aging. Brain Pathol. https://doi.org/10.1111/bpa.13075.
Tu, L., Lv, X., Fan, Z., Zhang, M., Wang, H., Yu, X., 2020. Association of odor identification ability with amyloid-β and tau burden: a systematic review and meta-analysis. Front. Neurosci. 14, 586330 https://doi.org/10.3389/fnins.2020.586330.
Vasavada, M.M., Wang, J., Eslinger, P.J., Gill, D.J., Sun, X., Karunanayaka, P., Yang, Q. X., 2015. Olfactory cortex degeneration in Alzheimer's disease and mild cognitive impairment. J. Alzheimers Dis. 45 (3), 947–958. https://doi.org/10.3233/JAD-141947.
Velayudhan, L., 2015. Smell identification function and Alzheimer's disease: a selective review. Curr. Opin. Psychiatry 28 (2), 173–179. https://doi.org/10.1097/YCO.0000000000000146.
Velayudhan, L., Pritchard, M., Powell, J.F., Proitsi, P., Lovestone, S., 2013. Smell identification function as a severity and progression marker in Alzheimer's disease. Int. Psychogeriatr. 25 (7), 1157–1166. https://doi.org/10.1017/S1041610213000446.
Vos, S.J., Van Rossum, I.A., Verhey, F., Knol, D.L., Soininen, H., Wahlund, L.-O., Hampel, H., Tsolaki, M., Minthon, L., Frisoni, G.B., 2013. Prediction of Alzheimer disease in subjects with amnestic and nonamnestic MCI. Neurology 80 (12), 1124–1132. https://doi.org/10.1212/WNL.0b013e318288690c.
Vyhnalek, M., Magerova, H., Andel, R., Nikolai, T., Kadlecova, A., Laczo, J., Hort, J., 2015. Olfactory identification in amnestic and non-amnestic mild cognitive impairment and its neuropsychological correlates. J. Neurol. Sci. 349 (1–2), 179–184. https://doi.org/10.1016/j.jns.2015.01.014.
Wang, J., Eslinger, P.J., Smith, M.B., Yang, Q.X., 2005. Functional magnetic resonance imaging study of human olfaction and normal aging. J. Gerontol. A Biol. Sci. Med. Sci. 60 (4), 510–514. https://doi.org/10.1093/gerona/60.4.510.
Wechsler, D., 1997. Weschsler adult intelligence scale-III. The Psychological Corporation, San Antonio, TX.
Wehling, E.I., Nordin, S., Espeseth, T., Reinvang, I., Lundervold, A.J., 2010. Familiarity, cued and free odor identification and their association with cognitive functioning in middle aged and older adults. Aging Neuropsychol. Cognit. 17 (2), 205–219. https://doi.org/10.1080/13825580903042684.
Wheeler, P.L., Murphy, C., 2021. Olfactory measures as predictors of conversion to mild cognitive impairment and Alzheimer's Disease. Brain Sci. 11 (11), 1391. https://doi.org/10.3390/brainsci11111391.
Wilson, R.S., Schneider, J.A., Arnold, S.E., Tang, Y., Boyle, P.A., Bennett, D.A., 2007. Olfactory identification and incidence of mild cognitive impairment in older age. Arch. Gen. Psychiatry 64 (7), 802. https://doi.org/10.1001/archpsyc.64.7.802.
Windon, M.J., Kim, S.J., Oh, E.S., Lin, S.Y., 2019. Predictive value of olfactory impairment for cognitive decline among cognitively normal adults. Laryngoscope 130 (4), 840–847. https://doi.org/10.1002/lary.28166.
Yoshii, F., Onaka, H., Kohara, S., Ryo, M., Takahashi, W., 2019. Association of smell identification deficit with Alzheimer's disease assessment scale-cognitive subscale, Japanese version scores and brain atrophy in patients with dementia. Eur. Neurol. 81 (3–4), 145–151. https://doi.org/10.1159/000501311.
Yu, H., Chen, Z., Zhao, J., Duan, S., Zhao, J., 2019. Olfactory impairment and hippocampal volume in a Chinese MCI clinical sample. Alzheimer Dis. Assoc. Disord. 33 (2), 124–128. https://doi.org/10.1097/WAD.0000000000000305.
Yue, X., Lu, M., Lancaster, T., Cao, P., Honda, S.-I., Staufenbiel, M., Harada, N., Zhong, Z., Shen, Y., Li, R., 2005. Brain estrogen deficiency accelerates Aβ plaque formation in an Alzheimer's disease animal model. Proc. Natl. Acad. Sci. 102 (52), 19198–19203. https://doi.org/10.1073/pnas.0505203102.
Zald, D.H., Pardo, J.V., 2000. Functional neuroimaging of the olfactory system in humans. Int. J. Psychophysiol. 36 (2), 165–181. https://doi.org/10.1016/S0167-8760(99)00110-5.
Zárate, S., Stevnsner, T., Gredilla, R., 2017. Role of estrogen and other sex hormones in brain aging. Neuroprotection and DNA repair. Frontiers in Aging Neurosci. 9, 430. https://doi.org/10.3389/fnagi.2017.00430.
Zhou, G., Lane, G., Cooper, S.L., Kahnt, T., Zelano, C., 2019. Characterizing functional pathways of the human olfactory system. eLife 8, e47177. https://doi.org/10.7554/eLife.47177.
Zhou, G., Olofsson, J.K., Koubeissi, M.Z., Menelaou, G., Rosenow, J., Schuele, S.U., Xu, P., Voss, J.L., Lane, G., Zelano, C., 2021. Human hippocampal connectivity is stronger in olfaction than other sensory systems. Prog. Neurobiol. 102027 https://doi.org/10.1016/j.pneurobio.2021.102027.