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ORIGINAL ARTICLE

Gray matter and episodic memory associations with olfaction in middle-aged to older adults

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Abstract

Background: Age-related declines in olfaction contribute to low quality of life and appear to occur with declines in cognitive function, including diminished episodic memory. We tested the hypothesis that low gray matter volume within cortical regions that support olfaction and episodic memory can explain age-related differences in olfactory and episodic memory functions.

Methods: T1-weighted images, Sniffin' Sticks olfactory measures, and the NIH Toolbox-Cognition Battery were administered to 131 middle-aged to older adults (50–86 years; 66% female). Correlation was used to examine the associations between these measures. A network-based image processing approach was then used to examine the degree to which spatial patterns of gray matter variance were related to the olfactory and cognitive measures. Structural equation modeling was used to characterize the relative specificity of olfactory, cognitive, gray matter, and aging associations.

Results: Olfactory threshold, discrimination, and identification exhibited small to medium effect size associations with episodic memory performance (rs = 0.27–0.42, ps < 0.002). Gray matter volume within medial temporal and orbitofrontal cortex was also related to olfactory (discrimination and identification) and episodic memory function (rs = 0.21–0.36, ps < 0.019). Age and episodic memory explained the same variance in olfaction that was explained by the medial temporal and orbitofrontal pattern of gray matter volume.

Conclusions: The results of this cross-sectional study suggest that identifying mechanisms contributing to differences in medial temporal and orbitofrontal cortex will advance our understanding of co-morbid olfactory and cognitive declines.

KEYWORDS
imaging, olfaction, olfactory disorders

1 | INTRODUCTION

The high rate of olfactory dysfunction (OD) among older adults[1–3] appears to be due in part to age-related changes in central nervous system structure and function, as demonstrated by OD associations with neurodegenerative disorders.[4–7] There is limited understanding about the mechanisms of central OD, including the specific neural systems where age-related declines contribute to OD and perhaps co-morbid cognitive dysfunction.

OD in older adults appears to occur with diminished cognitive functions.[8–10] Decline in episodic memory, in particular, has been associated with worse olfactory function.[10–12] These findings are consistent with evidence that better verbal episodic memory may be a protective factor for preserved olfactory function.[13] Other cognitive functions have been inconsistently associated with olfactory function, including different measures of executive function,[9,10,12] which may be associated with declines in frontal and medial temporal cortices that support these functions.

Medial temporal (piriform) and orbitofrontal cortex are targets in the olfactory pathway[14] for understanding OD and cognitive changes with aging because these regions exhibit structural declines with age[15,16] and because of their roles in encoding the identity[17] and associative significance of odorants.[18] A meta-analysis of studies examining congenital and acquired OD associations with cortical gray matter morphology demonstrated consistent associations between OD and orbitofrontal and anterior insula, and cerebellar gray matter volumes across a small number of studies involving varied etiologies for OD.[19] The directionality of these effects was not always consistent. Some studies demonstrated more gray matter volume, whereas others demonstrated lower gray matter volume with OD. These inconsistent voxel-based morphometry findings may reflect relatively modest sample sizes across studies, and perhaps varied etiologies for OD.[20] Age may also be critical for the location and direction of brain structure associations with olfaction. The previous voxel-based gray matter studies included samples composed largely of middle-aged participants. That is, we have relatively limited understanding if the gray matter findings from these studies would also be observed in older adult participants.

The goal of this study was to test the overarching hypothesis that olfactory and memory performance in middle-aged to older adults can be explained by age-related differences in gray matter structure within primary and secondary olfactory cortices that also support memory functions.[21–24] This multidimensional and transdiagnostic hypothesis was tested with a well-powered sample of middle-aged to older adults using an image processing data reduction method to limit the number of statistical comparisons. This approach identified spatial patterns of voxel-based gray matter volume across the brain and is conceptually aligned with a neural system premise that specific spatial patterns of cortical decline occur in older adults with olfactory and cognitive losses.

2 | METHODS

2.1 | Participants

This prospective observational study of 135 middle-aged to older adults (mean age = 64.13, ±8.92 years; 66.41% female) was approved by the MUSC Institutional Review Board. Participants were recruited from the Charleston, SC, region using flyers, word of mouth, a community event, during clinical visits, and using medical records of patients who did not opt-out of contact for research participation. Inclusion criteria included age ≥50 years, the ability to follow instructions and understand informed consent in English, and the ability to complete behavioral tasks without assistance. Exclusionary criteria included the use of oral steroids or immunomodulatory medications in the previous 30 days, sarcoidosis or granulomatosis with polyangiitis or immunodeficiency, nasal mass seen with endoscopy, upper respiratory tract infection, a score of ≤22 on the Telephone Interview for Cognitive Status[25] that has been shown in a multi-ethnic sample to accurately distinguish individuals with dementia from those without,[26] a history of dementia or neurodegenerative disease, and claustrophobia or ferrous metal in the body that would prohibit magnetic resonance imaging scanning.

2.2 | Behavioral assessment

The Sniffin' Sticks odor threshold, discrimination, and identification test battery was used to obtain an objective and quantitative measure of olfactory function.[27] The odor threshold is established with 16 dilutions of 2-phenylethanol that are presented using a single-staircase procedure in which participants make a triple-forced choice response selection. Participants with the highest and best threshold score are able to detect the most diluted 2-phenylethanol stimulus (item 16). The odor discrimination test requires participants to identify a unique odorant across three randomly ordered odorant presentations. The odor identification test requires identification of 16 suprathreshold presentations of odorant stimuli. Performance for each test is combined to obtain a total olfactory function score, with higher scores indicating better performance on each test. This total score was used to summarize the extent of OD across the sample. Performance on each

test was examined separately because of the prediction that individual differences in cortical gray matter volume, including within medial temporal regions that support memory functions, would more strongly explain discrimination and identification task performance because of the memory and naming demands of these Sniffin' Sticks tests in comparison to the threshold test.

The NIH Toolbox-Cognition Battery was used to assess cognitive functions. In the current study, we focused on the episodic memory, set-shifting, and vocabulary knowledge tests. The episodic memory and set-shifting measures would be expected to significantly correlate with age in this middle-aged to older adult sample.[28–30] Vocabulary knowledge has been associated with olfactory function,[10,31] but is often relatively preserved with age[28,32,33] and was not expected to explain age-related differences in olfaction. Moreover, ability for all three cognitive constructs could influence the Sniffin' Sticks performance, particularly for the discrimination and identification tasks that require memory for the odorants, the ability to adjust to changing task conditions, and selection of a verbal response. The picture sequence memory test assesses episodic memory by showing participants pictures of various activities and asking them to reproduce the sequence of pictures that was presented. The dimensional change card sort test assesses set-shifting by requiring participants to identify a card sorting rule (e.g., color or shape) that changes or shifts after a number of correct trials. The picture vocabulary test assesses vocabulary knowledge by asking participants to choose one of four pictures that most accurately represents an aurally presented word. The uncorrected standardized scores were used to test the study hypotheses for sensitivity to aging effects for these measures and because the Sniffin' Sticks measures were also uncorrected for age.

2.3 | Neuroimaging

T1-weighted images were collected using a Siemens Prisma 3T system. The CAT12 toolbox was used to produce segmented gray matter images from these T1-weighted images, which were normalized into a common coordinate space using SPM12 iterative DARTEL normalization, modulated to estimate gray matter volume in each voxel, and smoothed with a Gaussian kernel (8 mm full-width half-maximum). GIFT (v3.0b) was then used to reduce the dimensionality of the gray matter images and identify common patterns of gray matter spatial covariance (or gray matter structural networks that exhibit differences with age[34]) using an independent components analysis approach.[35] This approach produces images that represent the relative contribution of each voxel across gray matter regions to the identification of each spatial independent component. These values are summarized across an independent component to provide an estimate of the amount of gray matter volume in the component for each participant. This independent component summary variable was used in the statistical analyses. Additional details about the neuroimaging methods are available in the Supporting Information.

2.4 | Statistical analyses

Four participants had missing behavioral data and thus results for 131 participants are presented. This sample size provided sufficient power and allowed the inclusion of covariates, as determined by a power analysis that demonstrated 64 participants would be necessary for a medium effect size from a meta-analysis of the OD and voxel-based gray matter literature,[19] power = 0.80, and p value of 0.05. The sample of 131 participants allowed for multivariable analyses, including structural equation modeling.

Each Sniffin' Stick and NIH Toolbox test was examined separately and visually inspected to evaluate normality. Non-parametric Spearman correlations were used to examine relationships between variables because some did not exhibit a normal distribution (e.g., episodic memory, Kolmogorov–Smirnov: $D = 1$, $p < 2.2e\text{-}16$). The R COCOR library[36] was used to examine the relative magnitude of associations.[37] Specifically, we compared the cognition associations with olfactory function and determined if age exhibited a significantly larger association with medial temporal and orbitofrontal cortex compared to other brain regions. Structural equation modeling was also performed to examine the relative contributions of gray matter, episodic memory, and age for predicting variance of a latent variable representing olfaction. Years of education and sex were also included in these analyses because OD is more common among men and participants with lower socioeconomic position,[38] as defined using years of education. When appropriate, Bonferroni correction for multiple comparisons was performed to establish statistical significance using a p value threshold of 0.05 and Cohen's d effect sizes are presented to evaluate results.

3 | RESULTS

3.1 | Age associations with olfactory and cognitive abilities

The oldest adults exhibited poorer (lower) olfactory thresholds, discrimination, and identification (Table 1, Figure 1). In addition, women exhibited significantly better olfactory performance than men (Table 1). Figure 1 presents

TABLE 1 Demographic, Sniffin' Sticks (SS), NIH Toolbox (TBX), and medial temporal and orbitofrontal cortex (MTC-OFC) gray matter volume descriptive statistics and Spearman rho associations.

Variable	*M*	SD	1	2	3	4	5	6	7	8	9	10
1. Age	64.13	8.92										
2. Sex (1: male; 2: female)	1.66	0.47	−0.257** [−0.410, −0.089]									
3. Education (years)	5.22	0.94	0.031 [−0.141, 0.202]	−0.111 [−0.277, 0.062]								
4. SS TDI	29.56	7.89	−0.399** [−0.534, −0.245]	0.234** [0.065, 0.39]	0.083 [−0.089, 0.251]							
5. SS threshold	7.23	3.83	−0.292** [−0.442, −0.127]	0.188* [0.017, 0.348]	0.051 [−0.122, 0.22]	0.802** [0.731, 0.856]						
6. SS discrimination	10.91	2.99	−0.338** [−0.482, −0.177]	0.176* [0.004, 0.337]	0.106 [−0.066, 0.273]	0.786** [0.710, 0.843]	0.400** [0.246, 0.535]					
7. SS identification	11.43	2.83	−0.366** [−0.506, −0.208]	0.232** [0.063, 0.388]	0.116 [−0.056, 0.282]	0.686** [0.583, 0.767]	0.312** [0.148, 0.459]	0.573** [0.445, 0.678]				
8. TBX episodic memory	99.97	15.5	−0.374** [−0.512, −0.216]	0.019 [−0.153, 0.19]	0.218* [0.048, 0.376]	0.403** [0.249, 0.537]	0.266** [0.099, 0.419]	0.417** [0.265, 0.549]	0.338** [0.177, 0.482]			
9. TBX set-shifting	102.86	9.4	−0.317** [−0.464, −0.154]	0.013 [−0.159, 0.184]	0.124 [−0.049, 0.289]	0.358** [0.199, 0.499]	0.216* [0.046, 0.373]	0.329** [0.167, 0.474]	0.405** [0.251, 0.539]	0.408** [0.255, 0.542]		
10. TBX picture vocabulary	113.13	9.55	0.061 [−0.111, 0.23]	−0.117 [−0.283, 0.056]	0.422** [0.27, 0.553]	0.010 [−0.162, 0.181]	−0.040 [−0.21, 0.132]	0.042 [−0.13, 0.212]	0.069 [−0.103, 0.238]	0.205* [0.034, 0.363]	0.374** [0.216, 0.512]	
11. IC3 MTC-OFC	−0.03	0.99	−0.568** [−0.674, −0.439]	0.211* [0.041, 0.369]	0.016 [−0.156, 0.187]	0.203* [0.032, 0.362]	0.135 [−0.038, 0.299]	0.226** [0.057, 0.383]	0.205** [0.035, 0.364]	0.359** [0.200, 0.500]	0.280** [0.113, 0.430]	−0.055 [−0.224, 0.118]

Note: *M* and SD are used to represent mean and standard deviation, respectively. Values in square brackets indicate the 95% confidence interval for each correlation.
Abbreviation: SS TDI, Sniffin' Sticks total score (Threshold, Discrimination, Identifiation).
*$p < 0.05$;
**$p < 0.01$.

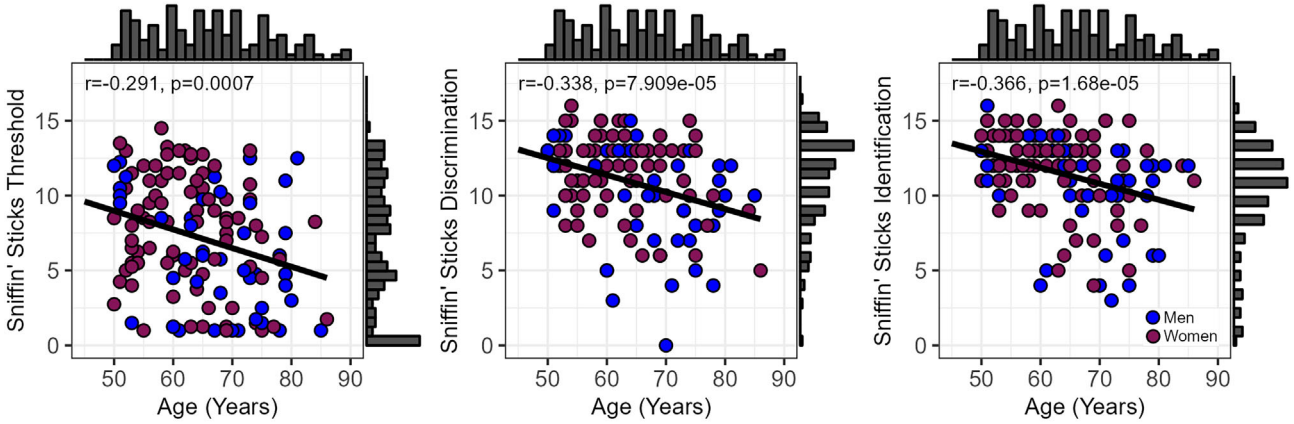

FIGURE 1 Increasing age predicts lower olfactory thresholds, discrimination, and identification. Olfactory function was also better in women compared to men. Age and olfactory function histograms are presented along the corresponding parallel axis.

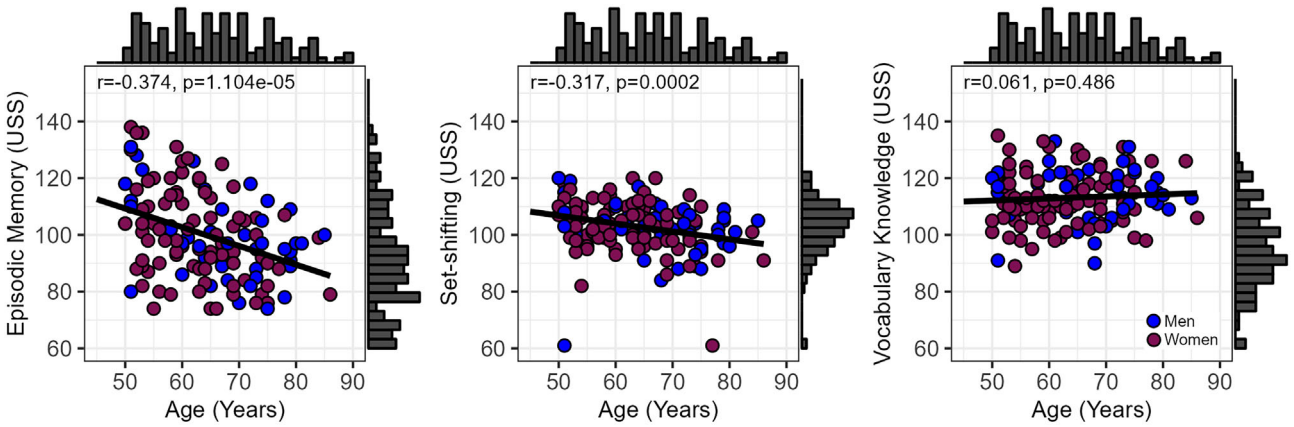

FIGURE 2 Increasing age predicts lower episodic memory and set-shifting, but not vocabulary knowledge. These cognitive measures did not significantly differ between women and men. Age and cognitive function histograms are presented along the corresponding parallel axis.

the associations between age and each olfactory measure for women and men. Thus, we observed expected age-dependent influences on olfactory test performance in the current sample, with 56.5% of participants exhibiting evidence of normosmia based on having a Sniffin' Sticks total score greater than 30.75.[39]

The oldest adults also exhibited significantly worse episodic memory and set-shifting, but vocabulary knowledge was not significantly associated with age (Table 1). There were no sex differences in any of these cognitive measures, as shown in Figure 2. However, more years of education was significantly associated with better performance for episodic memory and vocabulary knowledge (Table 1). These results demonstrate that the current sample is representative of older adults who experience cognitive declines for memory and executive functions, while exhibiting preservation of lexical knowledge.

3.2 | Olfactory and cognitive ability covariance

Table 1 also shows that the olfactory measures exhibited small to medium effect size associations with the episodic memory and set-shifting measures. While age and education were significantly associated with episodic memory and set-shifting, multiple regression showed that the olfactory discrimination association with episodic memory remained significant after controlling for age, education, and sex with Bonferroni correction for nine comparisons across the olfactory and cognitive measures ($t_{(4,126)} = 3.80$, Cohen's $d = 0.68$ [CI 0.32, 1.03], $p = 0.0002$). However, there was no significant difference in the strength of association between olfactory discrimination and episodic memory versus set-shifting ($Z = 1.15$, $p = 0.125$). That is, olfactory and cognitive functions covaried across participants owing to age and education, but these demographic

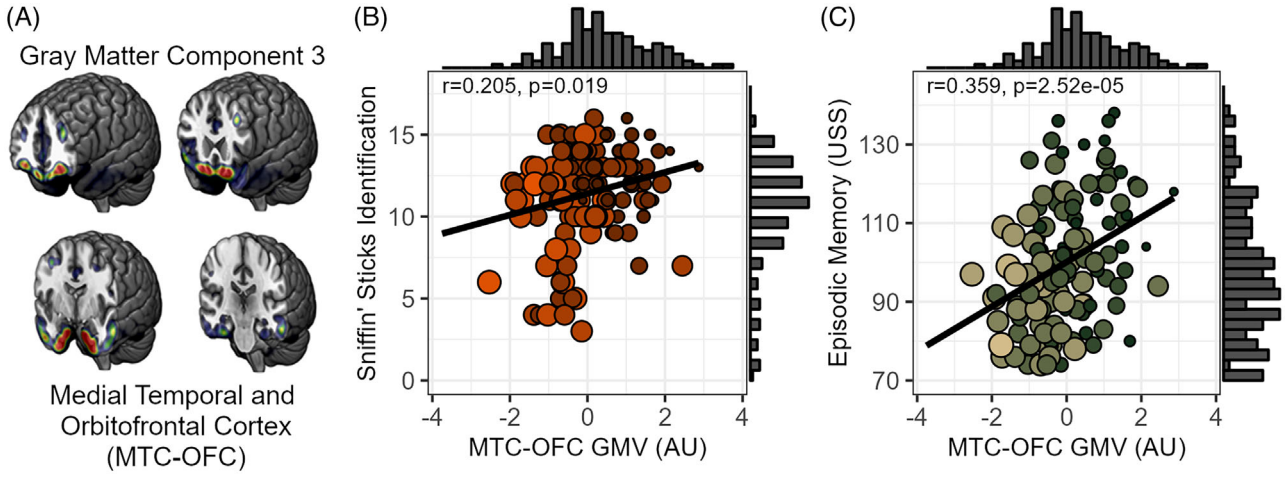

FIGURE 3 Medial temporal and orbitofrontal cortex (MTC-OFC) gray matter volume (GMV) predicts olfactory stimulus identification and episodic memory. Color overlay indicates MTC-OFC regions that exhibited covarying gray matter volume (A). Lower MTC-OFC gray matter volume was observed in the oldest adults (symbol size and color) who also had low olfactory identification (B) and episodic memory (C). MTC-OFC, olfactory identification, and episodic memory histograms are presented along their corresponding parallel axis. AU: scaled arbitrary unit.

variables did not fully explain the episodic memory and olfactory function associations.

3.3 | Gray matter associations with olfactory and memory abilities

We then examined the extent to which variation in gray matter volume explained individual differences in the olfactory and cognitive measures. Ten independent components or spatially covarying patterns of gray matter volume were identified (Supporting Information Figure S1, with Montreal Neurological Institute coordinates in Supporting Information Table S1), which accounted for 46% of the variance in voxel-wise gray matter volume across participants. One of the components included medial temporal and orbitofrontal cortex (MTC-OFC; Figure 3A), which exhibited a stronger association with age than the other components (e.g., MTC-OFC versus a cerebellar component [IC2 in Supporting Information Table S2]: $Z = -1.988$ $p = 0.034$). Gray matter volume in these MTC-OFC regions was lower in participants who were older, had poorer olfactory discrimination and identification, and had lower episodic memory and set-shifting (Table 1; Figure 3). Figure 3B,C presents the MTC-OFC association with olfactory identification and episodic memory. Supporting Information Table S2 presents Spearman correlations between all of the gray matter components and behavioral measures.

To examine the specificity of the MTC-OFC gray matter associations with olfactory function, a series of structural equation models were examined where MTC-OFC, years of education, and sex were consistently in the model as predictors of a latent olfaction measure composed of the discrimination and identification measures. These two Sniffin' Sticks measures were used for the latent olfaction variable because the MTC-OFC gray matter volume measure was most strongly related to these two olfactory measures and was non-significantly associated with the threshold measure. Models were also examined in which episodic memory or age were included as predictors of olfaction to demonstrate the change in MTC-OFC prediction with these variables in the model. MTC-OFC, education, and sex each explained unique variance in olfaction when these were the only predictors in the model (Figure 4A). MTC-OFC was a non-significant predictor of olfaction when episodic memory (Figure 4B) or age (Figure 4C) was included in the model, but these models did not provide better fits of the data relative to the initial model (Figure 4A). Table 2 presents the statistical parameters for these three analyses.

Together, these regression and correlation results demonstrate that MTC-OFC explains age-dependent variation in olfactory discrimination and identification functions. While some of this age-dependent variation appears to influence episodic memory function, episodic memory also explained unique variation in olfactory discrimination.

4 | DISCUSSION

This study examined the hypothesis that age-related differences in olfaction and memory abilities covary because of

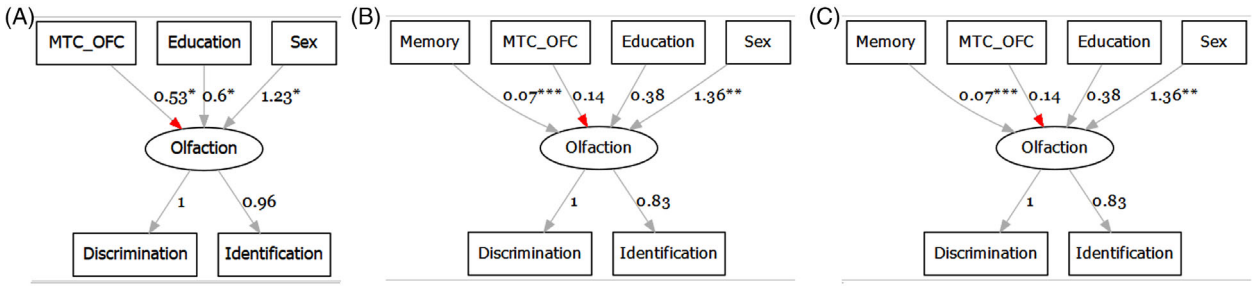

FIGURE 4 Medial temporal and orbitofrontal cortex (MTC-OFC) gray matter volume predicts olfactory stimulus discrimination and identification when controlling for education and sex (A), but not when controlling for episodic memory (B) or age (C). The red arrow head identifies the path from MTC-OFC to the olfaction latent variable composed of the Sniffin' Sticks discrimination and identification variables, with the corresponding estimate at the right of the arrow.

TABLE 2 Structural equation model fit and regression parameters demonstrate the relative contributions of the medial temporal and orbitofrontal cortex (MTC-OFC), episodic memory, and demographic variables for predicting the latent variable olfaction (Sniffin' Sticks discrimination and identification).

Model and fit	Estimate [CI]	Completely standardized solution (Std.lv)	*Z* score	*p* value
Olfaction				
MTC-OFC	0.53 [0.07, 0.98]	0.22	2.28	0.023
Education	0.60 [0.12, 1.08]	0.23	2.44	0.015
Sex	1.23 [0.28, 2.19]	0.24	2.54	0.011
$\chi^2 = 7.48$, $p = 0.187$, RMSEA = 0.062				
Olfaction				
Episodic memory	0.071 [0.04, 0.10]	0.43	4.84	0.000
MTC-OFC	0.144 [−0.29, 0.58]	0.06	0.65	0.514
Education	0.379 [−0.08, 0.84]	0.14	1.62	0.104
Sex	1.357 [0.44, 2.27]	0.25	2.91	0.004
$\chi^2 = 35.06$, $p = 5.82e\text{-}05$, RMSEA = 0.149				
Olfaction				
Age	-0.091 [−0.14, −0.04]	-0.34	-3.55	0.000
MTC-OFC	0.089 [−0.34, 0.52]	0.04	0.41	0.686
Education	0.590 [0.13, 1.05]	0.23	2.49	0.013
Sex	0.988 [0.08, 1.90]	0.20	2.12	0.034
$\chi^2 = 63.74$, $p = 2.54e\text{-}10$, RMSEA = 0.215				

Abbreviation: RMSEA, root mean square error of approximation.

age-related structural declines in orbitofrontal and medial temporal regions that support these functions. Olfactory discrimination and identification were significantly associated with episodic memory in middle-aged to older adults. Moreover, a spatially covarying pattern of MTC-OFC gray matter volume exhibited a significant age-related difference that was significantly associated with olfactory and episodic memory functions. However, the episodic memory and age variables accounted for significant variance in olfaction that was not explained by MTC-OFC gray matter volume, education, and sex. These results suggest that mechanisms of MTC-OFC gray matter volume loss are one source for age-related olfactory and memory dysfunction.

4.1 | Olfaction and cognitive specificity

The results of the current study demonstrate that olfactory discrimination was more strongly related to episodic memory compared to set-shifting, although olfactory threshold, discrimination, and identification exhibited age-related differences. The stronger episodic memory and olfactory function association is consistent with the extant literature on this topic where olfactory and episodic memory associations appear to be more consistently reported[10–12] than other behavioral variables.[9,10,12] However, the strength of olfactory function association with episodic memory and set-shifting did not significantly differ in the current study.

It was clear that vocabulary knowledge, which was unrelated to age, was not significantly associated with olfactory function. That is, limited lexical knowledge did not appear to constrain the ability to discriminate or name odorants, whereas measures of fluid cognition that typically decline with age[40] were predictive of olfactory discrimination and identification but were not predictive of olfactory threshold.

The ability to retrieve the verbal label for an odorant may be one explanation for a memory and olfactory function association. However, the ability to discriminate between odorants does not necessarily require recall of a verbal label and was also associated with episodic memory. We hypothesize that the spatial overlap and adjacency of cortical tissue that supports these functions increases the likelihood that common mechanisms of decline across medial temporal and orbitofrontal regions (e.g., inflammation, intermittent hypoxia, and/or tau accumulation in humans[41–43]) explain why olfaction and memory decline together with age in normative[10–12] and neurodegenerative disorder samples.[11,44] This hypothesis is supported by olfactory loss in animal models of inflammation, intermittent hypoxia, and tau accumulation.[45,46]

4.2 | Gray matter effects

This study was designed with an a priori hypothesis that medial temporal and orbitofrontal gray matter volume would exhibit age-related differences and explain significant variation in episodic memory and olfactory function. The spatial independent component analysis used in this study demonstrated that gray matter volume in these regions covaried together. That is, middle-aged to older adults with lower gray matter volume in medial temporal cortex also had lower orbitofrontal gray matter volume. A similar image analysis approach was taken in a study of anosmia in which a pattern of medial temporal gray matter volume was observed, with the gray matter volume within this structural network differing between controls and anosmics.[47] Our results are also partially consistent with evidence that odorant identification, and not detection threshold, was significantly associated with orbitofrontal gray matter volume in older adults with mild cognitive impairment.[48] Thus, there is replication of medial temporal and orbitofrontal associations with olfactory function across studies when using a similar analysis approach and when considering memory-related declines.

There also was spatial and behavioral specificity of the medial temporal cortex effects. For example, a bilateral hippocampal and inferior temporal gyrus pattern of gray matter covariance (independent component 10 in Supporting Information Figure S1 and Supporting Information Table S2) exhibited $p < 0.05$ (uncorrected) associations with age, sex, set-shifting, and vocabulary knowledge, but did not appear to be related to episodic memory or olfactory function. This component spatially overlapped with the MTC-OFC component with respect to anterior medial temporal and hippocampal regions, but did not include orbitofrontal cortex and included more posterior cortical regions that were not included in the MTC-OFC component. It appears that orbitofrontal cortex and its association with medial temporal cortex was critical for the olfaction and episodic memory associations.

4.3 | Peripheral losses

Sniffin' Sticks threshold scores exhibited a non-significant association with MTC-OFC volume. This result suggests that the olfactory discrimination and identification results were not due to peripheral etiologies of olfactory dysfunction, such as sinusitis or rhinitis, altered nasal airflow and/or olfactory mucus or olfactory neuroepithelium by impeding delivery of odorant molecules to the olfactory cleft.[49,50] While these peripheral etiologies and gradual loss of olfactory sensory neurons[51] would affect thresholds, suprathreshold presentation of the stimuli should result in normal discrimination and identification scores if central processing pathways are intact. Isolated threshold loss that can precede the loss of discrimination and/or identification has been shown previously for sinusitis patients.[52] However, there appeared to be stronger age influences on olfactory discrimination and identification than thresholds (Table 1). It is possible that the relatively increased task demands of the olfactory discrimination and identification tests compared to the threshold test, as described earlier, increased sensitivity for observing age-related gray matter associations with discrimination and identification.

4.4 | Strengths, limitations, and future directions

One important consideration when interpreting the results of this study is that olfactory and cognitive measures in this study were obtained with the widely used Sniffin' Sticks and NIH Toolbox tests, which should enhance the potential for replication of results from this study, including because the tests exhibit relatively high test–retest reliability.[28,53] We also note that episodic memory had more explanatory power in predicting olfaction than the MTC-OFC measure (Table 2), which appears to reflect the greater sensitivity of episodic memory than MTC-OFC gray matter volume for predicting olfaction.

The significant but limited explanatory power of the MTC-OFC measure (e.g., explained 6.3% of the variance in olfactory identification) could reflect the sensitivity of the 1 mm resolution, segmented, and spatially smoothed gray matter measurement and/or that other anatomical measures may be more critical. For example, the MTC-OFC gray matter effects may be observed as a consequence of myelin and axonal declines across fibers that connect MTC-OFC regions due to inflammatory and/or small vessel disease effects in white matter.[54] We also note that other independent gray matter components exhibited small to medium effect bivariate associations with olfactory function, including a component that includes cerebellar regions that were linked to OD in previous studies.[19] However, we did not have a priori hypotheses about these other regions and any functional linkage to olfaction and memory is more indirect than the MTC-OFC regions. We also note that larger effect sizes may have been observed with a voxel-wise approach. The independent component approach used in the current study provided a weighted gray matter volume estimate across the space of each component. This approach demonstrated that a common pattern of gray matter volume variance across brain regions could explain olfactory and episodic memory function, while also limiting the number of statistical comparisons and potential for false positive results.

A general age effect is one explanation for the gray matter associations with olfactory function, including the MTC-OFC association. That is, it was unclear whether declines in MTC-OFC structure have a direct effect on olfaction in middle-aged to older adults. It is noteworthy that the MTC-OFC regions exhibited the strongest association with age compared to the other brain regions and thus may explain why OD is common among older adults.[55] Moreover, this study appeared to characterize age-specific effects as age accounted for all of the variance in the MTC-OFC association with olfaction. In addition, there was no evidence of normative individual differences underlying the MTC-OFC and olfaction association.

5 | CONCLUSIONS

The findings of this study and extant literature suggest that olfactory and memory functions decline together when there are age-related declines in medial temporal and olfactory cortex. Mechanisms for these small to medium size effects may be found in events and accumulated damage that would affect the structural integrity of both of these regions and/or their connections. While olfactory thresholds were not related to MTC-OFC, it is possible that the olfactory discrimination and identification effects could be a consequence of peripheral olfactory losses that can affect olfactory cortex.[56] Longitudinal studies will be necessary to determine the extent to which central declines in regions supporting memory contribute to olfactory impairment and/or that the loss of central olfactory function has cascading effects on memory functions.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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REFERENCES

1. Karpa MJ, Gopinath B, Rochtchina E, et al. Prevalence and neurodegenerative or other associations with olfactory impairment in an older community. *J Aging Health*. 2010;22(2):154-168.
2. Murphy C, Schubert CR, Cruickshanks KJ, et al. Prevalence of olfactory impairment in older adults. *J Am Med Assoc*. 2002;288(18):2307-2312.
3. Swan GE, Carmelli D. Impaired olfaction predicts cognitive decline in nondemented older adults. *Neuroepidemiology*. 2002;21(2):58-67.
4. Wilson RS, Arnold SE, Tang Y, Bennett DA. Odor identification and decline in different cognitive domains in old age. *Neuroepidemiology*. 2006;26(2):61-67.
5. Carnemolla SE, Hsieh JW, Sipione R, et al. Olfactory dysfunction in frontotemporal dementia and psychiatric disorders: a systematic review. *Neurosci Biobehav Rev*. 2020;118:588-611.
6. Dan X, Wechter N, Gray S, et al. Olfactory dysfunction in aging and neurodegenerative diseases. *Ageing Res Rev*. 2021;70:101416.
7. Doty RL. Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate? *Lancet Neurol*. 2017;16(6):478-488.
8. Mi Y, Ma X, Du S, et al. Olfactory function changes and the predictive performance of the Chinese Smell Identification Test in patients with mild cognitive impairment and Alzheimer's disease. *Front Aging Neurosci*. 2023;15. https://doi.org/10.3389/fnagi.2023.1068708
9. Larsson M, Nilsson L-G, Olofsson JK, Nordin S. Demographic and cognitive predictors of cued odor identification: evidence from a population-based study. *Chem Senses*. 2004;29(6):547-554.
10. Papadatos Z, Phillips NA. Olfactory function reflects episodic memory performance and atrophy in the medial temporal lobe

in individuals at risk for Alzheimer's disease. *Neurobiol Aging*. 2023;128:33-42.
11. Dintica CS, Marseglia A, Rizzuto D, et al. Impaired olfaction is associated with cognitive decline and neurodegeneration in the brain. *Neurology*. 2019;92(7):e700-e709.
12. Zhong S, Wroblewski KE, Laumann EO, McClintock MK, Pinto JM. Assessing how age, sex, race, and education affect the relationships between cognitive domains and odor identification. *Alzheimer Dis Assoc Disord*. 2023;10:1097.
13. Palmquist E, Larsson M, Olofsson JK, et al. A prospective study on risk factors for olfactory dysfunction in aging. *J Gerontol A* 2020;75(3):603-610.
14. Rolls ET. The functions of the orbitofrontal cortex. *Brain Cogn*. 2004;55(1):11-29.
15. Hutton C, Draganski B, Ashburner J, Weiskopf N. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. *Neuroimage*. 2009;48(2): 371-380.
16. Callaert DV, Ribbens A, Maes F, Swinnen SP, Wenderoth N. Assessing age-related gray matter decline with voxel-based morphometry depends significantly on segmentation and normalization procedures. *Front Aging Neurosci*. 2014;6:124.
17. Stettler DD, Axel R. Representations of odor in the piriform cortex. *Neuron*. 2009;63(6):854-864.
18. Gottfried JA, Zelano C. The value of identity: olfactory notes on orbitofrontal cortex function. *Ann N Y Acad Sci*. 2011;1239(1):138-148.
19. Li AR, Schlosser RJ, Germroth M, Eckert MA. Voxel-based meta-analysis of gray matter alterations in olfactory dysfunction. *Int Forum Allergy Rhinol*. 2022;12:112-115.
20. Manan HA, Yahya N, Han P, Hummel T. A systematic review of olfactory-related brain structural changes in patients with congenital or acquired anosmia. *Brain Struct Funct*. 2022;227:177-202.
21. Bolding KA, Nagappan S, Han B-X, Wang F, Franks KM. Recurrent circuitry is required to stabilize piriform cortex odor representations across brain states. *Elife*. 2020;9:e53125.
22. You Y, Novak LR, Clancy KJ, Li W. Pattern differentiation and tuning shift in human sensory cortex underlie long-term threat memory. *Curr Biol*. 2022;32(9):2067-2075. e4.
23. Zhou G, Olofsson JK, Koubeissi MZ, et al. Human hippocampal connectivity is stronger in olfaction than other sensory systems. *Prog Neurobiol*. 2021;201:102027.
24. Linster C, Hasselmo ME. Neuromodulation and the functional dynamics of piriform cortex. *Chem Senses*. 2001;26(5):585-594.
25. Fong TG, Fearing MA, Jones RN, et al. Telephone interview for cognitive status: creating a crosswalk with the Mini-Mental State Examination. *Alzheimer's Dement*. 2009;5(6):492-497.
26. Manly JJ, Schupf N, Stern Y, et al. Telephone-based identification of mild cognitive impairment and dementia in a multicultural cohort. *Arch Neurol*. 2011;68(5):607-614.
27. Rumeau C, Nguyen D, Jankowski R. How to assess olfactory performance with the Sniffin'Sticks test®. *Eur Ann Otorhinolaryngol*. 2016;133(3):203-206.
28. Scott EP, Sorrell A, Benitez A. Psychometric properties of the NIH Toolbox Cognition Battery in healthy older adults: reliability, validity, and agreement with standard neuropsychological tests. *J Int Neuropsychol Soc*. 2019;25(8):857-867.
29. Pause BM, Zlomuzica A, Kinugawa K, Mariani J, Pietrowsky R, Dere E. Perspectives on episodic-like and episodic memory. *Front Behav Neurosci*. 2013;7:33.
30. Craik FI, Bialystok E. Cognition through the lifespan: mechanisms of change. *Trends Cogn Sci*. 2006;10(3):131-138.
31. Finkel D, Pedersen NL, Larsson M. Olfactory functioning and cognitive abilities: a twin study. *J Gerontol B*. 2001;56(4):P226-P233.
32. Salthouse TA. Selective review of cognitive aging. *J Int Neuropsychol Soc*. 2010;16(5):754-760.
33. Teubner-Rhodes S, Vaden KI, Cute SL, et al. Aging-resilient associations between the arcuate fasciculus and vocabulary knowledge: microstructure or morphology? *J Neurosci*. 2016;36(27):7210-7222.
34. Eckert MA, Keren NI, Roberts DR, Calhoun VD, Harris KC. Age-related changes in processing speed: unique contributions of cerebellar and prefrontal cortex. *Front Hum Neurosci*. 2010;4:10.
35. Li YO, Adalı T, Calhoun VD. Estimating the number of independent components for functional magnetic resonance imaging data. *Hum Brain Map*. 2007;28(11):1251-1266.
36. Diedenhofen B, Musch J. cocor: a comprehensive solution for the statistical comparison of correlations. *PLoS One*. 2015;10(4):e0121945.
37. Hittner JB, May K, Silver NC. A Monte Carlo evaluation of tests for comparing dependent correlations. *J Gen Psychol*. 2003;130(2):149-168.
38. Yang J, Pinto JM. The epidemiology of olfactory disorders. *Curr Otorhinolaryngol Rep*. 2016;4:130-141.
39. Oleszkiewicz A, Schriever V, Croy I, Hähner A, Hummel T. Updated Sniffin'Sticks normative data based on an extended sample of 9139 subjects. *Eur Arch Otorhinolaryngol*. 2019;276:719-728.
40. Crăciun IC. *Cognitive development in midlife and older age: from neuroplasticity to self-efficacy and positive views on ageing*. Fostering Development in Midlife and Older Age: A Positive Psychology Perspective. Springer; 2023:99-128.
41. Risacher SL, Tallman EF, West JD, et al. Olfactory identification in subjective cognitive decline and mild cognitive impairment: association with tau but not amyloid positron emission tomography. *Alzheimer's Dement*. 2017;9:57-66.
42. Dong J, Zhan X, Sun H, Fang F, Wei Y. Olfactory dysfunction is associated with cognitive impairment in patients with obstructive sleep apnea: a cross-sectional study. *Eur Arch Otorhinolaryngol*. 2022;279:1979-1987.
43. Klein J, Yan X, Johnson A, et al. Olfactory impairment is related to tau pathology and neuroinflammation in Alzheimer's disease. *J Alzheimer's Dis*. 2021;80(3):1051-1065.
44. Murphy C. Olfactory and other sensory impairments in Alzheimer disease. *Nat Rev Neurol*. 2019;15(1):11-24.
45. Yang S, Kuan WL, Spillantini MG. Progressive tauopathy in P301S tau transgenic mice is associated with a functional deficit of the olfactory system. *Eur J Neurosci*. 2016;44(6):2396-2403.
46. Kim B-Y, Lee SH, Kim IK, Park JY, Bae JH. Chronic intermittent hypoxia impacts the olfactory nervous system in an age-dependent manner: pilot study. *Eur Arch Otorhinolaryngol*. 2023;280(1):241-248.
47. Lee S, Kim J, Kim BJ, et al. Gray matter volume reduction in the emotional brain networks in adults with anosmia. *J Neurosci Res*. 2022;100(6):1321-1330.

48. Kashibayashi T, Takahashi R, Fujita J, et al. Correlation between regional brain volume and olfactory function in very mild amnestic patients. *J Neurol Sci*. 2020;411:116686.
49. James J, Palte IC, Vilarello BJ, et al. Beyond aroma: a scoping review on the impact of chronic rhinosinusitis on retronasal olfaction. *Front Allergy*. 2022;3:969368.
50. Yan X, Whitcroft KL, Hummel T. Olfaction: sensitive indicator of inflammatory burden in chronic rhinosinusitis. *Laryngoscope Investig Otolaryngol*. 2020;5(6):992-1002.
51. Fitzek M, Patel PK, Solomon PD, et al. Integrated age-related immunohistological changes occur in human olfactory epithelium and olfactory bulb. *J Comp Neurol*. 2022;530(12):2154-2175.
52. Mattos JL, Schlosser RJ, Storck KA, Soler ZM. Understanding the relationship between olfactory-specific quality of life, objective olfactory loss, and patient factors in chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2017;7:734-740.
53. Sorokowska A, Albrecht E, Haehner A, Hummel T. Extended version of the "Sniffin'Sticks" identification test: test–retest reliability and validity. *J Neurosci Methods*. 2015;243:111-114.
54. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18(7):684-696.
55. Schlosser RJ, Desiato VM, Storck KA, et al. A community-based study on the prevalence of olfactory dysfunction. *Am J Rhinol Allergy*. 2020;34(5):661-670.
56. Han P, Whitcroft KL, Fischer J, et al. *Olfactory brain gray matter volume reduction in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol*. 2017;7:551-556.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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