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Cross-Sectional and Longitudinal Associations Between Olfaction and White-Matter Integrity Across the Lifespan

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ABSTRACT

The loss of smell is common in older age, reducing quality of life and often precedes the onset of cognitive decline and dementia. While age-related olfactory loss has been linked to cortical thinning and volume reductions in key olfactory areas, associations between white-matter (WM) integrity and olfaction are poorly understood. Here, we studied individuals aged 25–85 years from a population-based cohort study with diffusion weighted imaging, together with self-reported olfactory impairment, odor identification and odor threshold measures at baseline ($N=248$) and follow-up 5 years later ($N=192$). Performance on the odor identification and threshold tests were lower in older adults and declined longitudinally. Older individuals also reported more olfaction complaints, and such complaints increased over time. Results from general linear models showed no cross-sectional associations between WM integrity and olfaction. However, results from non-competitive random forest models identified several tracts as significant contributors to odor identification and subjective olfactory impairment, including the fornix, cingulum and uncinate fasciculus. Moreover, longitudinal analyses showed that olfactory threshold decline was associated with decline in WM integrity in the body of corpus callosum. Taken together, the results support a link between white-matter integrity and olfaction and provide initial evidence for its interplay with age.

1 | Introduction

The sense of smell is important for regulating eating and drinking, as well as for other social and emotional behaviors. Olfactory impairment is also associated with reduced quality of life (Croy et al. 2014). Human olfaction declines with aging, such that olfactory impairment is present in almost half of the population aged between 65 and 80 years (Doty et al. 1984; Murphy et al. 2002; Rawal et al. 2016). Olfactory impairment in older adults has been associated with poorer cognitive

performance (Devanand et al. 2015; Dintica et al. 2019; Olofsson et al. 2009; Schubert et al. 2008), dementia (Motter et al. 2023; Murphy 2019; Roberts et al. 2016; Stanciu et al. 2014), and increased risk of death (Ekström et al. 2017; Pinto et al. 2014). In addition, even subjective reports of olfactory decline have been associated with future cognitive and olfactory decline (Cedres et al. 2023). Odor identification deficits may be caused by AD-related pathology accumulating in the medial temporal lobe (Diez et al. 2024). Therefore, objective and subjective changes in the sense of smell have been pointed to as risk factors and

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early detection markers for those at risk for dementia (Cedres and Olofsson 2024; Lafaille-Magnan et al. 2017).

Impaired olfactory performance has been linked to reduced volumes in the hippocampus and decreased cortical thickness in individuals with Alzheimer's disease (AD) and mild cognitive impairment (MCI; Devanand et al. 2015; Kjellvik et al. 2014; Su et al. 2021) as well as in cognitively healthy individuals (Dintica et al. 2019; Growdon et al. 2015; Menelaou et al. 2022; Vassilaki et al. 2017). The association of the olfactory system with cortical and subcortical structures, including the prefrontal cortex (Tian et al. 2023), hippocampus, and amygdala (Tian et al. 2023; Zhou et al. 2021), highlights the potential role of olfaction in executive function, memory performance, and emotion regulation. The neuroanatomical connections of the olfactory system to the rest of the brain are supported by a complex network of white matter tracts, and their functional roles are not firmly established (Fjaeldstad et al. 2021).

Age-related changes in white-matter integrity and fiber density have been commonly reported (Bilgic et al. 2012; Kelley et al. 2021). Also, a recent longitudinal study demonstrated structural connectome reorganization as indicated by decreased integration and increased segregation over 5 years (Coelho et al. 2021). Moreover, both cross-sectional and longitudinal analyses of structural network properties have demonstrated that the connections between central hubs are more strongly influenced by aging compared to connections between peripheral regions (Li et al. 2023). Age differences in structural connectivity have been associated with decline across multiple cognitive domains (Andersson et al. 2022; Kennedy and Raz 2009; Madden et al. 2012; Salami et al. 2012). To date, only a few studies have investigated the relationship between olfactory performance and white-matter integrity in relation to normal aging, with inconsistent results (Felix et al. 2021; Segura et al. 2013; Shrestha et al. 2023).

Given the significance of olfaction in human behavior and brain health, it is important to map the association between white matter integrity and olfactory function in the general population. Our aim was thus to explore the cross-sectional and longitudinal association tractography maps between white matter integrity and olfaction in a healthy adult life-span sample. A sample of individuals aged 25–85 years was scanned with diffusion weighted imaging (DWI), and olfactory function was tested using self-reported subjective olfactory impairment, odor identification, and odor threshold measures. A follow-up scanning and behavioral test session was included 5 years later, providing a basis also for longitudinal analyses.

2 | Methods

2.1 | Participants

Participants in this study belong to the Swedish Betula dataset, a longitudinal cohort study on memory, health, and aging. This project has collected seven waves of health and medical data from 1988 to 2017 (W1–W7), with a 5-year interval between each wave. Using a narrow cohort (NAC) design, the Betula project recruited participants at the age of 35–80 years, with a 5-year

interval (e.g., participants were aged 35, 40, 45, etc.). The NAC design decreases confounding effects introduced by different age cohorts, such as education and nutritional level (Rönnlund et al. 2005; Sternäng et al. 2010). Olfaction assessments started at W3 and were continued at W4, W5, and W6. The DWI neuroimaging data were first acquired for a subsample at W5, which were followed up for W6 and W7.

The MRI sample included 376 participants at baseline (W5) and, of those, 220 participants were tested at follow-up (W6). Participants were excluded from the study due to the following reasons: dementia diagnosed at either baseline or follow-ups, Mini-Mental State Examination (Folstein et al. 1975) < 24, problems with visual acuity, other reported neurological disease, visible pathology in the MRI images, or lacking olfaction data. Since only one (1) participant at baseline and three (3) participants at follow-up scored below 24 on the MMSE, no further analyses on MCI/AD or neurodegeneration were performed. In addition, individuals with severe olfactory dysfunction or anosmia were excluded if they responded: “Worse than normal” to the question “How is your ability to perceive weak odors” (additional response alternatives were “normal” and “better than normal”) in combination with an identification score at chance level (< 3). Although the test does not include singular validated cut-off scores for anosmia, this procedure allowed us to remove three participants who had no functional sense of smell. The final samples consisted of 248 participants at baseline (W5). Fifty six dropped out at the 1st follow-up (W6). Compared to the dropouts, the returners had better subjective olfaction assessment ($t(102) = 2.5$, $p = 0.014$) at baseline. No difference was found for age, sex ratio, education, baseline MMSE, baseline odor identification, or baseline odor threshold test between dropouts and returners ($ps > 0.1$). The demographic information of the MRI samples was shown in Table 1. The Betula study was approved by the Regional Ethical Review Board in Umeå (dnr: 2008-08-132 and dnr: 2013-92-31M), and written consent was obtained from every participant.

2.2 | Olfactory Assessments

We used three types of olfactory tests, including two objective smell tests (odor identification and odor threshold tests), and

TABLE 1 | Demographic and olfactory measurements.

	Baseline (W5)	Follow-up (W6)
<i>n</i> (females/males)	140/108	109/83
Age (SD)	63.25 (12.24)	68.18 (11.34)
Education (SD)	12.78 (4.00)	12.88 (4.02)
MMSE (SD)	28.13 (1.57)	28.12 (1.44)
Odor identification (SD)	6.67 (2.11)	7.55 (2.15)
Odor threshold (SD)	5.83 (2.66)	5.3 (2.66)
Subjective odor assessment (SD)	3.85 (0.55)	3.81 (0.59)

Abbreviations: MMSE, mini-mental state examination; SD, standard deviation.

one subjective smell assessment. The odor identification test is a revised version of the Scandinavian Odor Identification test (SOIT; Nordin et al. 1998), which is a forced-choice test. While the original version used 16 items, the current version differed due to the removal of three odorants which had trigeminal impact and the use of more similar response alternatives to increase the task difficulty (see, Larsson et al. 2004). The 13 odorous stimuli include vanilla, lemon, apple, violet, orange, anise, tar, clove, bitter almond, cinnamon, pine-needle, lilac, and juniper berry. The stimuli are common odors that were selected to represent a wide range of odor qualities that are familiar to the Scandinavian population. The stimuli were fairly strong in intensity and represents a wide range of aromatic qualities such as floral (lilac, violet), citral (lemon, orange), non-citral fruity (apple), sweet (almond, anise, vanilla), woody (juniper berry, tar), spicy (cinnamon, clove), minty (peppermint, pine-needle), and pungent (ammonia, vinegar; Nordin et al. 1998). Participants had a 30 s rest between stimuli to avoid perceptual adaptation. Since we used a revised version of the SOIT, normative thresholds for anosmia and hyposmia were not considered in the current study. The SOIT test was available for W3–W6.

Odor detection thresholds were determined using Sniffin' Sticks (Hummel et al. 1997). In this test participants were presented with pairs of odors with decreasing concentration levels of *n*-butanol (in total 16 concentrations, where 1 represents the strongest concentration and 16 represents the weakest). The procedure begins at an intermediate concentration level (level 8). One odorous and one odorless stick were presented at each trial. Each stick was presented approximately 2 cm under the participant's nose every 15–20 s. The participant was asked to report which of the two sticks contained the odor. For participants who were able to correctly identify the stick that contained the odor four times in a row at the intermediate level, the testing procedure continues with the lowest concentration level (level 16). When incorrect responses are given at this level, the concentration of the next odor sample was increased by one step without any feedback until the participant gives correct responses at the same concentration level four times in a row. For participants who are unable to discriminate the odorous stick from the blank at the intermediate concentration-level, the odor concentration is increased by one step from the intermediate concentration level until correct responses are given four times in a row. Individual scores are based on the lowest concentration level that could be detected. Thus, a score of 16 reflects high olfactory sensitivity, whereas a score of 1 reflects low sensitivity. Note that this procedure differs from standard such that only one blank odor was presented on each trial instead of two, and that the typical "staircase" concentration procedure was simplified in order to reduce testing time. The total threshold score was 16, which indicates the number of correctly recognized odor presentations. The Odor threshold data were available for W5–W6.

In the subjective smell assessment, participants were asked "How is your ability to smell odors?" and to choose one from four options: no ability, worse than normal, normal, and better than normal. Subjective smell was assessed prior to the objective olfactory, so that the subjective reports were not confounded. The subjective odor test data were available for W3–W6.

2.3 | Image Acquisition and Preprocessing

DWI data was collected on a 3T Discovery MR750 (General Electric) scanner with a 32-channel head coil using a single-shot, spin-echo-planar, T2-weighted sequence. The spatial resolution is $0.98 \times 0.98 \times 2$ mm. The sequence parameters were: TR = 8.0 s, 64 slices with no gap in between, 256×256 matrix (FOV = 250 mm), 90-degree flip angle, TE = 84.4 ms, three repetitions of 32 independent directions, $b = 1000$ s/mm², and six $b = 0$ images. All participants were examined on the same scanner with no software or hardware update during the data-collection period.

DWI data were processed using the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) package (<http://www.fmrib.ox.ac.uk/fsl>). DTI quality control procedures were conducted by manual visual inspection, where each diffusion-weighted dataset was carefully examined gradient-by-gradient and slice-by-slice to identify and exclude scans with severe artifacts. Three sessions of diffusion acquisitions were concatenated into a 4D image for each subject. Then, the images were corrected for eddy-current distortions and head movement by full affine aligning to the first no-diffusion images ($b = 0$). The transformation matrices were used to rotate bvecs files (Jenkinson and Smith 2001). Brain extraction tool (BET) was used to generate binary brain masks on no-diffusion images, which were applied on all DWIs to remove skulls. Finally, the preprocessed DWIs were fitted to the tensor model. The tensor matrix with information in three directions (eigenvalues) was obtained for each voxel within the brain mask. Voxel-wise maps of fractional anisotropy (FA) and mean diffusivity (MD) were generated using the three eigenvalues.

2.4 | Tract-Based Spatial Statistics

First, all FA images were transformed into MNI space using the high-resolution standardized image (FMRIB158_FA) as a target. This method only applies registration once per subject and provides highly accurate realignment results. Next, the transformed FA images were averaged to produce a mean FA image for the entire group. A single 4D file was also created by merging all transformed FA images. The mean FA image was fed into the tract-skeleton generation program to produce a white matter tract skeleton, which represents the white-matter tracts common to all the subjects. Then a binary skeleton mask was created by thresholding the mean FA skeleton image with FA values larger than 0.2. Finally, each subject's FA image was projected onto the group skeleton mask. Non-FA images were processed in a method similar to the FA images. Voxel-wise statistics were then run on the skeletonized images.

2.5 | Statistical Analysis

The statistical analyses are described in detail below. In short, (1) behavioral data were analyzed using linear mixed models, (2) white matter integrity was analyzed using whole-brain voxel-wise analysis in FSL, (3) the associations between olfactory

assessment and FA were analyzed using the general linear model (GLM), (4) the associations between all white matter tracts, age, and olfaction were additionally analyzed using a non-competitive model random forest (RF) model, and (5) moderation/mediation effects were tested using Bayesian mediation and moderation models. Results were considered significant if the probability of a Type 1 error (α -level) was below 0.05.

2.5.1 | Behavioral Analysis

For both odor identification and subjective olfaction assessment, we used linear mixed models to estimate how the objective/subjective olfaction changes with time, taking into account the effects of random intercept and random slope. Subjective olfaction assessment was treated as a continuous variable. The interaction term of age and wave (i.e., W1–W4) was included in the model if the model fit was significantly improved when compared to the maximum likelihood (ML). The coefficient of the fixed effect of wave represents the average change over 5 years in olfaction. Sex was controlled for as the covariate of all the models. For the odor threshold test, we subtracted the test scores of the 1st follow-up from the baseline to index the 5-year change of olfaction threshold. We then extracted the random slope of how olfaction changes across four waves for each subject. The associations among the three tests were estimated using Pearson's correlation and Kendall rank correlation when the variable is not normally distributed.

2.5.2 | DTI Analysis

Whole-brain voxel-wise analysis was conducted on the skeletonized images using the randomize tool (part of FSL). GLMs were used to investigate the association between olfactory assessment and FA, controlling for age. The threshold-free cluster enhancement (TFCE) algorithm uses sensitive cluster-based inference without the need for an initial cluster-forming hard threshold. The permutation test was used to generate corrected p -values for each voxel. Five thousand permutations were performed for each contrast, resulting in a minimum possible p -value of 0.0002 ($1/P$).

2.5.3 | Cross-Sectional DTI Analysis

We examined the association between white-matter FA and olfaction collected at the same time point. The olfactory assessments were analyzed separately for odor identification, odor threshold, and subjective olfaction. In addition to GLM analysis, we included Random Forest (RF) models to explore the relative contribution of tract-specific white matter to olfactory function, while accounting for age. RF analyses are robust to multicollinearity problems and suppression effects, which are especially relevant in the study of aging and white matter integrity (i.e., highly correlated predictors). In the current study, the RF approach is used as complementary to the GLM approach since RF enables variable importance estimation in non-competitive models aside from shared variance nuisance.

Two separate RF regression models were fitted for the prediction of odor identification and odor threshold, respectively, including

mean FA of the tractography maps and age. A third RF was fitted to separate participants with and without subjective olfactory impairment based on their mean FA in the tractography maps and age. Given the small number of participants with subjective olfactory impairment, an automatic method combining both random over-sampling and down-sampling was performed for unbalanced groups. Briefly, RF is a machine learning method based on multiple decision trees via bootstrap aggregation. A conditional value of importance is computed based on the multiple decision trees in the RF analysis. This importance denotes the contribution of each predictor to the final model-based change in the mean increase in the prediction error (MSE) for RF regression or the mean decrease in classification accuracy (mdGini) for the RF classification models. Importance values below or equal to zero show no contribution. Each RF comprised 1,000 conditional inference trees. R^2 is computed to assess the quality of the RF regression and out-of-bag (OOB) error is computed to assess the quality of the RF classification models. Mean decrease in classification capacity (Gini) was used to assess the importance of each variable. The randomForest (Liaw and Wiener 2003) and Party (Hothorn et al. 2015) packages were used for the RF analysis. Since the sample size is largest at W5, these analyses were conducted at W5.

2.5.4 | Longitudinal Analysis

The longitudinal changes of olfaction were associated with FA changes. Change scores were calculated as follow-up minus baseline (i.e., W5–W6), which is a standard measure in longitudinal studies. It accounts for baseline values and avoids problems with infinite values that can occur when percent change is used with zero baselines. This was conducted using three GLMs separately for odor identification slopes, subjective olfaction slopes, and olfaction threshold changes. Age was included as the covariate for all the analyses.

2.5.5 | Mediation and Moderation Analyses

We further investigated the relation among age, white matter, and olfaction using mediation and moderation. The mean FA of the tracts that demonstrated significant results from the previous analysis was extracted based on the JHU-ICBM-DTI-81 white-matter atlas. The extracted values were fed into Bayesian mediation and moderation models. For both models, four chains of samplings with 1000 tuning and 1000 of each were used to generate the posterior distribution of the parameters.

For the mediation mode:

$$FA \sim \text{Normal}(i_{fa} + a \cdot \text{Age}, \sigma_{fa})$$

$$\text{Olfaction} \sim \text{Normal}(i_o + c \cdot \text{Age} + b \cdot FA, \sigma_o)$$

where a , b , and c are the model parameters. c is the direct effect, $a \cdot b$ is the indirect effect (mediation effect), and $c + a \cdot b$ is the total effect. i is the intercept, and σ^2 is the standard deviation of the observation noise.

$$\text{Olfaction} \sim \text{Normal}(\beta_0 + \beta_1 \cdot FA + \beta_2 \cdot \text{Age} \cdot FA + \beta_3 \cdot \text{Age}, \sigma^2)$$

where β_2 , β_2 , and β_3 are the model parameters. B_0 is the intercept, and σ^2 is the standard deviation of the observation noise.

3 | Results

3.1 | Behavioral Results

For the odor identification test, adding an age $\times$ wave interaction significantly improved the model fit ($p=0.004$). After adding the interaction term, the model showed a negative main effect of age ($t=-14.75$, $p<0.001$) and time (i.e., wave) on performance (Figure 1A; $t=-13.1$, $p<0.001$) suggesting olfaction decline over four waves (20 years). The interaction between age and wave was significant ($t=-3.5$, $p=0.003$), suggesting that older age is associated with a greater decline in odor identification. There were

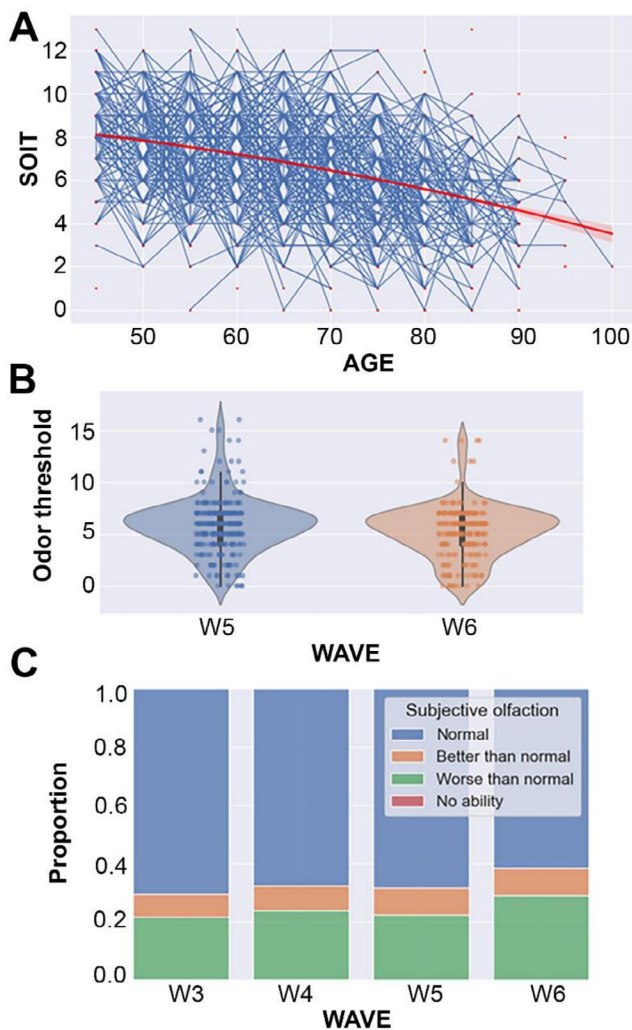


FIGURE 1 | (A) Age trajectory of odor identification across adults' life span. For visualization purposes, generalized additive mixed models were used to fit a smooth spline (bold line) of odor identification in relation to time-varying age. Confidence intervals (shaded area) are $1 \times$ std. error. (B) Changes of odor threshold across time points, and (C) changes of subjective olfaction over time. Note that participants were excluded if they had self-reported anosmia (no ability to perceive smells) in combination with a chance-level odor identification score.

significant age effects on the performance on odor threshold ($t=3.91$, $p<0.001$). The odor threshold significantly declines from baseline to the 1st follow-up (Figure 1B; $t=2.79$, $p=0.005$). The changes in odor threshold were not associated with age ($t=0.56$, $p>0.1$), indicating that 5-year decline was similar irrespective of participant age. For subjective olfaction assessment, there was a negative age effect on the subjective assessment ($t=-6$, $p<0.001$), suggesting that older age was associated with more olfaction complaints. Moreover, there was a negative effect of time (i.e., wave) on the subjective olfactory assessment (Figure 1C; $t=-5.25$, $p<0.001$) indicating an age-related increase in olfaction complaints over the testing period (i.e., W3–W6, spanning 20 years). The individual slopes of subjective olfaction assessment were not related to age ($t=-1.01$, $p>0.1$). Adding the interaction of age and wave did not improve the model fit ($p>0.1$).

The associations among the three olfaction tests for all time points are shown in Figure S1. The results show that the three different tests of olfaction were weakly, but positively, correlated at each specific time point. The tests of odor identification and subjective olfaction assessments were significantly correlated across time (i.e., significant test–retest correlations), while the olfaction threshold test shows a weak correlation between wave 5 and wave 6.

We then examined the relation of the changes among the three olfaction tests. Results show that there was a significant association between individual slopes of odor identification and slopes of subjective olfaction assessment after controlling for age ($t(248)=2.641$, $p=0.009$), and a trend towards an association between the threshold changes and the slopes of the subjective olfaction assessment ($t(187)=-1.707$, $p=0.089$). No association was found between the threshold changes and odor identification changes ($t(187)=-0.104$, $p>0.1$). These results suggest that olfaction identification and olfaction threshold might reflect different aspects of human olfactory changes over time, and changes in subjective olfactory ability might be related to general olfactory changes that is reflected in performance declines in both objective odor tests.

3.2 | Effects of Age and Sex on White Matter Integrity

In the current sample global FA across the whole white-matter skeleton was strongly, and negatively, associated with age, both at W5 ($r=-0.517$, $p<0.001$) and W6 ($r=-0.605$, $p<0.001$). FA also significantly decreased across 5 years from W5 to W6 ($F=21.4$, $p<0.001$, $\eta^2=0.123$). Males had significantly higher FA across the whole white matter skeleton compared to females both at W5 ($F=4.22$, $p=0.041$, $\eta^2=0.016$) and W6 ($F=12.2$, $p=0.001$, $\eta^2=0.060$).

3.3 | Cross-Sectional Association Between White Matter Integrity and Olfaction

For the cross-sectional analysis, there were no significant associations between FA and olfaction at W5 for any of the three olfaction tests when including age as a covariate in the GLM models.

The RF regression model predicting odor identification ($MSE = 3.92$; $R^2 = 6.68\%$) showed that age was the most important predictor for odor identification (increase in $MSE = 45.1\%$), followed by white matter integrity of the fornix (incMSE = 19.7%), superior longitudinal fasciculus tract (incMSE = 17.4%), splenium (incMSE = 15.0%), and genu (incMSE = 16.23%) of corpus callosum (Figure 2A). The RF classification model with the SOI group as dichotomous outcome showed an OOB estimate error rate of 10%. The cingulum-hippocampus (mdGini = 5.29) and the anterior limb of the internal capsule (mdGini = 5.38) tracts were the most important variables in the classification followed by the tapetum (mdGini = 4.43). These results are shown in Figure 2B.

3.4 | Longitudinal Association Between White Matter Integrity and Olfaction

For the longitudinal analysis, decrease in odor threshold test performance was significantly associated with degradation in WM FA from baseline to follow-up. The change-change associations were observed in the body of corpus callosum (Figure 3). No association was found for odor identification test or subjective olfaction assessments on FA changes when including age as a covariate.

3.5 | Moderation and Mediation Analyses

We further explored possible relationships among white-matter integrity, age, and olfaction variables using mediation and moderation. No mediation effect of FA was found for the age effects on either odor identification, odor threshold, or subjective olfaction at baseline. However, we found that age was a significant moderator of the relationship between FA in uncinate fasciculus and odor threshold (Table 2). The age moderation effects indicated different directions of the associations between younger and older adults, and that the association between FA in uncinate fasciculus was most pronounced in younger adults and non-significant in older adults (Figure 4). Results are consistent with the notion that in younger participants, integrity of the uncinate fasciculus is associated with odor threshold performance.

4 | Discussion

Although both white matter integrity and olfactory functions are compromised in older age and constitute early markers of dementia (Audronyte et al. 2023; Chen et al. 2023; Walker et al. 2021), their relationship is not well understood. The main aim of the current study was to establish the cross-sectional and longitudinal associations between white matter integrity and olfaction in an adult life span sample. Furthermore, we explored such associations using three complementary assessments of olfactory function, including self-reported subjective olfactory impairment, odor identification and odor threshold. We found an age-related decrease in the performance of the odor identification task over 20 years and odor threshold over 5 years, along with an increase in the frequency of subjective olfactory complaints across 20 years. The partial association between white-matter integrity and olfaction was generally weak when

controlling for age, indicating that FA may not be critical to olfaction functioning independently of age. However, a contribution of interhemispheric tracts, such as fornix, which is the main output tract from the hippocampus, and corpus callosum, which is the main tract subserving interhemispheric communication, was found in non-competitive models for the association with odor identification.

We also observed a longitudinal change–change association between white-matter integrity in the body of the corpus callosum and olfactory sensitivity threshold scores. These novel findings suggest links between age-related alterations in cross-hemispheric and hippocampal connectivity and olfaction. This finding suggests that interhemispheric communication might play a role in olfactory processing and that white matter degradation might impair the ability to detect odors. Olfactory cortical processing is sometimes regarded as mostly occurring in the hemisphere ipsilateral to the stimulated nostril. Because AD-related neuropathology might accumulate in an asymmetric pattern in the olfactory system, unirhinal odor assessments (i.e., testing each nostril separately) may establish olfactory impairment differences between nostrils, which might reflect ipsilateral neuropathology (Bahar-Fuchs et al. 2010; Huart et al. 2015). However, contralateral processing of odors is observed at a 480 ms delay, and a naturalistic, birhinal olfactory stimulation (i.e., testing both nostrils simultaneously, as in the present study) facilitates a more rapid cortical response and superior odor identification performance (Dikeçilgil et al. 2023). The olfactory system is thus largely bilateral and might require effective interhemispheric communication for successful cortical processing, even in sensory tasks. While the anterior commissure is that main pathway connecting the left and right olfactory cortex (Dalal et al. 2020), interhemispheric communication through the corpus callosum might also be critical in integrating olfactory input from the two nostrils and their targets in the olfactory cortex. Such interhemispheric communication enables sensory input from one olfactory bulb to be processed and integrated across both hemispheres, contributing to a unified olfactory percept. A key question for future studies is to study whether this contralateral integration is accomplished via the pathways suggested in our present work, and how they are affected in neurodegenerative disorders.

We observed declined olfaction with increasing age across all three olfactory tests, which is in line with previous findings (Attems et al. 2015; Cedres et al. 2023; Sabiniewicz et al. 2023). Changes in the different olfactory tests were not highly correlated, suggesting that they might reflect different aspects of human olfaction. Odor identification tasks require participants to identify the odorants and rely on both perceptual processing and semantic knowledge to retrieve the names of the smells. On the other hand, odor threshold measures perceptual sensitivity, and subjective olfactory complaints reflect self-evaluation of general olfactory ability. Change in subjective olfactory impairment was associated with changes in both objective olfactory measures. Thus, it might reflect both cognitive and sensory aspects of the olfactory tests. Older age was associated with greater decline in odor identification and older adults also had more olfactory complaints, while change in odor threshold was non-significant, suggesting different trajectories of decline in these three aspects of olfaction, although the abbreviated

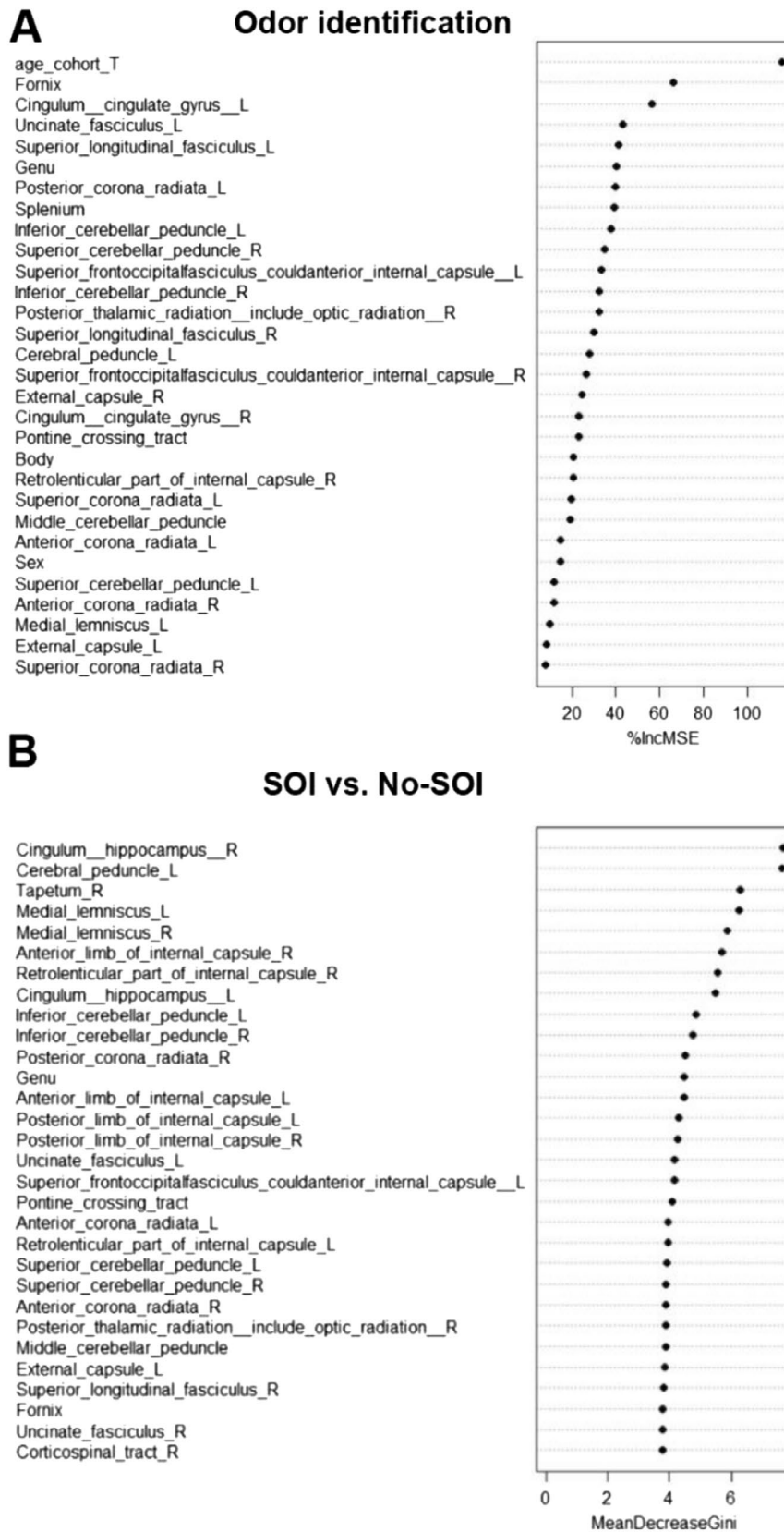


FIGURE 2 | (A) Prediction of odor identification performance. IncMSE on the x axis represents the percentage of increase in the prediction error when removing each predictor (y axis) from the random forest model predicting odor identification performance. (B) Prediction of subjective olfactory impairment (SOI). mdGini parameter on the x axis represents the decrease in the mean of the model's discriminative classification capacity each predictor (y axis) is excluded from the model classifying SOI versus no SOI individuals. Abbreviations: L, Left; R, Right.

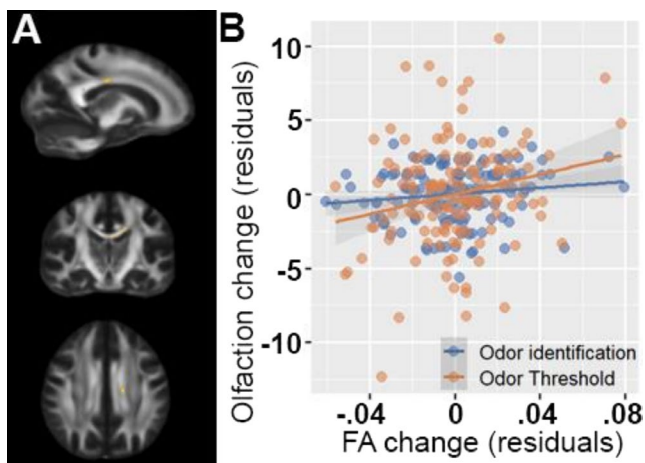


FIGURE 3 | Threshold decline was associated with FA decline in the body of corpus callosum (W5–W6). Significant voxels ($p < 0.05$, corrected for multiple comparisons across the whole skeleton) are overlaid on a T1-weighted image (coordinates according to MNI152 template), with yellow indicating smaller p -values.

TABLE 2 | Significance of the moderation effects of age on the relation between white matter and olfaction threshold test performance.

	p	FDR-corrected p
Genu	0.160	0.642
Body	0.527	0.905
Splenium	0.908	0.946
Fornix	0.754	0.905
Corticospinal tract	0.607	0.905
Sagittal stratum	0.744	0.905
Corona radiata	0.946	0.946
Internal capsule	0.153	0.642
External capsule	0.335	0.905
Superior longitudinal fasciculus	0.403	0.905
Superior fronto-occipital	0.579	0.905
Uncinate fasciculus	0.004	0.046

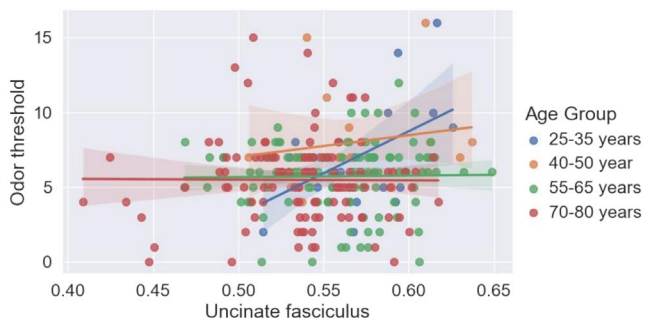


FIGURE 4 | The relation between mean FA in the uncinate fasciculus and odor threshold was moderated by age.

nature of the threshold test should warrant caution in interpreting this absence of effect as evidence of absence. Males had generally lower olfactory performance and also reported more olfactory complaints than females, which has been previously reported in the Betula sample (Larsson et al. 2004) and is in line with previous studies (Brand and Millot 2001; Doty and Cameron 2009; Solla et al. 2020). It should also be noted that while olfaction identification declined over 20 years, performance on this test was slightly higher at follow-up (W6) compared to baseline (W5). It is possible that selective dropout, test-retest, and/or instrument effects contributed to this unexpected increase in performance on the olfactory identification test during this time period.

After controlling for age, cross-sectional associations between odor identification and odor threshold and white-matter integrity were all non-significant, suggesting that tensor-based measures of white-matter integrity, such as FA might not be related to individual differences in olfactory function. The relationship between white-matter integrity and olfactory function has been very sparsely investigated previously. One previous study (Woodward et al. 2017) found no significant associations between odor identification and white-matter integrity in healthy aging individuals. Similarly, it has been demonstrated that FA did not differ between patients with anosmia and healthy controls (Chen et al. 2020), while those with anosmia showed white-matter network dysfunction using graph-theoretical and network based analyses. Possibly, network-based analyses of structural connectivity might be more sensitive for investigating the associations between white-matter and olfactory function. However, a recent large population-based study that included 1,418 older adults (Shrestha et al. 2023) found a significant relationship between odor identification and white-matter integrity (FA and MD) in several tracts, including tracts within the occipital and temporal lobe and the corpus callosum. While these results show a somewhat different pattern compared to the current results, it could possibly be attributed to that particular sample being older (mean age 76 years), included participants with MCI and dementia, and also included mean diffusivity as a measure of microstructural integrity.

In our study, when including age and white matter integrity in a non-competitive model, several tracts were identified as significant contributors to odor identification and subjective olfactory impairment. As expected, age resulted in the most important predictor for odor identification performance. However, in line with previous findings (Shrestha et al. 2023), the fornix was identified as the second most important contributor. The fornix is a crucial bundle of fibers with intra- and interhemispheric connections of hippocampus and the limbic system (Amaral and Lavenex 2007). Previous studies have linked fornix integrity with hippocampal-based spatial memory strategies and odor identification, suggesting shared networks and structures for spatial memory and olfaction (Dahmani et al. 2020). In addition to the fornix, left cingulum and uncinate fasciculus were also identified as strong contributors. These tracts may have a role in the networks associated with odor perception, decision making, retrieval, and naming of odors, again highlighting the implications of hippocampal and limbic structures. Using task-based functional MRI approach, it has been demonstrated that olfactory error (i.e., odor vs. picture incongruence) activates

transmodal cortical networks from primary olfactory and visual cortex to cingulate regions (Pierzchajlo et al. 2024). These findings point to the integrity of limbic and frontotemporal white matter tracts, especially on the left hemisphere, as a contributor for odor identification, possibly through their implications in memory retrieval, language and semantic processing of odors. Furthermore, the integrity of these tracts is critical for a normal cognitive performance and their neurodegeneration is associated to increased risk of neurodegenerative diseases (Douet and Chang 2015). Future studies should explore the role decline in odor identification as a potential symptom of underlying white matter neurodegeneration of these structures.

However, we also found age dependent associations between white matter integrity of interhemispheric structures and odor identification, suggesting that neural white matter correlates of olfaction might change across the lifespan. Thus, our results indicate that interhemispheric communication might be involved in olfactory processing and that its disruption might affect the ability to detect odors. In older participants, cumulative damage from viral infections in combination with typical aging effects may affect the olfactory epithelium such that individual variability in olfactory thresholds is largely dependent on the integrity of the peripheral nervous system, whereas in younger adults where there is little peripheral damage, central fiber tracts may play a bigger role.

The current study has some limitations. First, the analysis is based on tensor-based DTI measurement. The tensor estimation is problematic in estimating the integrity of crossing fibers within a voxel. Thus, TBSS may not be sensitive enough to capture the potential link between olfaction and crossing fiber regions. While the use of FA is often regarded as a gold standard for estimating white matter integrity, the model has difficulties in determining anatomical specificity in regions where pathways of different structures merge. Without directional tract information about orientation, it is therefore challenging to assign FA values of the same voxel to different tracts. Moreover, a key question has also been the source of anisotropy and whether it relates to a specific microstructural component. Although FA is a sensitive measure, it is inherently non-specific (Timmers et al. 2016). For example, a reduction in FA could be caused by reduced neurite density, increased dispersion of orientation, and several other factors. Second, while the wide age range in our study sample provides an advantage for examining how olfaction changes across different age groups, it poses a challenge in the context of investigating the neural mechanisms underlying cognitive functions. The wide age span, coupled with limited sample size within each age group, may result in insufficient variance of the olfaction variable, leading to a lack of significant correlations between olfaction and white matter. The brief nature of our tests, especially olfactory thresholds and SOI, might yield noisier data relative to more extensive assessments and might not capture all true effects.

This present study is one of the first to examine cross-sectional and longitudinal associations between white matter integrity and olfaction in an adult life span sample and offers new insights into the relationship between structural connectivity and age-related olfactory decline. Future studies might consider using more sensitive approaches, such as tractography and

multivariate analysis, to investigate white-matter properties in olfaction and aging.

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Ethics Statement

The Betula study was approved by the Regional Ethical Review Board in Umeå (dnr: 2008-08-132 and dnr: 2013-92-31M), and written consent was obtained from every participant.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Associations among the three olfaction tests for all time points, controlling for age. Numbers represent the un-corrected *p*-values of Pearson's correlation coefficients. Abbreviations: OI, odor identification; Sub, subjective olfaction assessment; Threshold, odor threshold test; w3, 3rd wave; w4, 4th wave; w5, 5th wave; w6, 6th wave.