Hippocampal subfield volumes and olfactory performance: Emerging longitudinal associations over a 5-year interval

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ABSTRACT

Olfaction, the sense of smell, provides important behavioral functions in many species. The hippocampus (HC) is critical for identifying odors, and hippocampal volume is associated with odor identification ability. Impaired odor identification is often reported in old age and might provide an early marker of cognitive decline and dementia. Here, we explore cross-sectional (n = 225) and longitudinal (n = 118) associations between odor identification ability and hippocampal subfield volumes in a sample of middle-aged and older persons (25–80 years). In older participants, longitudinally decreasing volumes of the hippocampal tail, subiculum, CA4 and the dentate gyrus correlated with changes in odor identification. None of these correlations were observed in younger participants, but there was a significant correlation between longitudinal volume reduction in the tail subfield of the hippocampus and odor identification change across all participants. There were no significant cross-sectional associations between hippocampal subfields and odor identification. These exploratory results provide new information regarding precisely where and when declining HC subfield volumes might be associated with odor identification.

1. Introduction

Odor identification (OI) is the most widely used assessment of human olfaction and it involves matching common household odors to written response alternatives. Impaired OI ability is often reported in old age (see Olofsson et al., 2021, for review) and may constitute a marker of future cognitive decline, Alzheimer-type dementia, and mortality in prospective studies of aging adults (Ekström et al., 2017; Devanand et al., 2015; Stanciu et al., 2014; Schubert et al., 2008). Odor identification engages the hippocampus (HC; Aqrabawi and Kim, 2018; Aqrabawi et al., 2016; Kesner et al., 2011; Martin et al., 2007). The primary olfactory cortices show an unusually strong functional connectivity with the HC, as demonstrated by resting-state fMRI, suggesting a critical role for the HC in olfactory processing (Zhou et al., 2021). The HC displays a slow age-related decline in volume that begins in early adulthood and accelerates in old age (Raz et al., 2005, 2010). HC atrophy might be a common cause of OI decline and memory impairment in some older adults (Devanand et al., 2008), which could explain the pattern of pronounced joint episodic memory and OI decline that is observed in about 10% of older adults (Dintica et al., 2021; Olofsson et al., 2016). Below-average HC volume, in combination with OI impairment, signals an elevated risk for future dementia conversion (Lojkowska et al., 2011). However, the precise relationship between OI and the HC needs further investigation, particularly in older age where olfactory and cognitive abilities and HC volumes are most vulnerable to age-related changes, and where these variables might be used to assess the risk for future dementia (Olofsson et al., 2009; Josefsson et al., 2017; Gorbach et al., 2016).

The HC is composed of a number of subregions, each with distinct characteristics of functional specialization and vulnerability to disease (Fig. 1). While some previous studies have examined the association between HC volume and olfaction (Devanand et al., 2015), the contribution of specific HC subfields to OI ability has never been addressed before. Age-related HC atrophy is not uniform but appears to vary across individual subfields (Daugherty et al., 2016). A recent cross-sectional study reported that smaller entorhinal and parahippocampal volume was related to poorer olfactory performance in older participants (Iizuka et al., 2021). A few studies on rodents have revealed distinct contributions of HC subfields to the processing of odor stimuli (Weeden et al., 2014; Hunsaker et al., 2008; Petrusis et al., 2005). These studies suggest...
that the dentate gyrus (DG), the subiculum and CA1 subregions are involved in stimulus processing during odor memory tasks. Odor identification tasks are unique to humans and analogous tasks for rodents have only recently been developed, and not yet linked to the hippocampus (Olofsson et al., 2019). To our knowledge, no study has previously reported on how the structural integrity of the HC subfields is associated with olfactory behavioral function in aging human participants. Characterizing these relationships is an important step in tracing the changes that might lead to cognitive impairment and dementia later in life.

We explored the relationship between odor identification and subfield volumes of the HC; we hypothesized that they would be associated, given that HC integrity is crucial to perform the task (Eichenbaum et al., 1983). We first examined cross-sectional associations between Od ability and HC-subfield volume and, subsequently, we explored longitudinal associations for these variables by analyzing data from two separate measurements that were collected within a 5-year interval.

2. Methods

2.1. Participants

Participants consisted of healthy adults from the fifth (2008–2010) and sixth (2013–2015) waves of the Betula project (Nilsson et al., 1997, 2004). In the context of the current study, these two waves will be referred to as baseline (2008–2010) and follow-up (2013–2015) data collections. Betula is a population-based longitudinal study with volunteers that are randomly selected from the Umeå municipality in northern Sweden. The participants provided written consent in accordance with the Declaration of Helsinki (BMJ 1991; 302: 1194). The study was approved by the Regional Ethical Review Board in Umeå (approvals no. 870303, 97–173, 221/97, 97–173, 03–484, 01–008, 169/02, 02–164, 03–484, 05–082 M, and 08–123M).

The procedure for selecting participants is illustrated in Fig. 2. For the cross-sectional analysis at baseline, data from 6 older participants with mild cognitive impairment (based on MMSE scores below 25) and data from 19 participants who received a dementia diagnosis after the follow-up (2010) were not included in the analyses. Moreover, data from 68 participants with a disease of the nose at baseline (e.g., polyposis), data from 43 participants with missing volumetric data and data from one participant with missing olfactory data at baseline were excluded from all analyses. For the longitudinal analysis, 87 participants with missing volumetric data at follow-up were excluded, as well as data from 19 participants who reported disease of the nose at follow-up. Given previous demonstrations that relationships between brain function and structure are different in younger and older adults (Burzynska et al., 2012; Koen and Rugg, 2019; Rieckmann et al., 2018; Van Petten, 2004), we performed age-stratified analyses with two groups of middle-aged (MA; < 65 years; n = 108) and older participants (OA; ≥ 65 years; n = 117), in addition to whole sample analyses. Finally, we removed outliers that might risk causing false positive associations. We used a statistical measure for determining extreme values for removing outliers in baseline and follow-up data; the Mahalanobis distance D² (MD) statistic was used for identification of both univariate and multivariate outliers using the recommended threshold p < .001 threshold for the chi-square value (Tabachnick and Fidell, 2007). Two participants were excluded based on extreme baseline residual subfield volume data and one participant was excluded based on extreme follow-up subfield volume data. Two participants were also excluded based on multivariate thresholds in baseline subfield data. Follow-up analyses indicated that these outliers did not strongly affect our results. Multivariate MD distances were calculated using residual volume data for all seven ROIs. The final sample thus consisted of 225 participants for cross-sectional analyses, and 118 participants for longitudinal analyses.

Dementia status was assessed at baseline and reassessed every 5 years using a three-step procedure, which allowed us to exclude participants classified as having dementia during any part of the study. First, an overall evaluation was performed by an examining physician according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM–IV; Frances et al., 1995). Second, using a composite measure based on scores from several cognitive tests (episodic memory, working memory, processing speed, semantic memory and fluid intelligence), each participant was compared to the mean cognitive score for his/her age cohort. If an individual scored more than two standard deviations below the mean of the age cohort, he/she was flagged for further assessment of dementia by a clinical psychiatrist. Third, only participants that scored at or above the cut-off score for dementia of 24 using the mini mental state examination were included in the final sample (MMSE; Folstein et al., 1975; Tsai et al., 2016). To retain the diversity of the sample, exclusions were not made for diabetes, hypertension, mild depressive symptoms, and other moderately severe medical conditions, which are common among the elderly. The demographics of the final sample are provided in Table 1.

Table 1

| Baseline (N = 225) | Follow-up (N = 118) |
|-------------------|---------------------|
| MA (N = 108) | OA (N = 117) | MA (N = 57) | OA (N = 61) |
| Females | N = 66 | N = 62 | N = 31 | N = 30 |
| Males | N = 42 | N = 55 | N = 26 | N = 31 |
| Age average (y) | 51.0 | 70.6 | 56.5 | 74.2 |
| Age range (y) | 25–60 | 65–80 | 30–65 | 70–85 |
| Education (y) | 14.5 | 13.9 | 14.2 | 12.4 |
| MMSE score | 28.4 | 28.2 | 28.5 | 28.1 |
| Mean OI score | 7.5 | 6.7 | 8.3 | 7.2 |
2.2. Odor identification

The current study included the Scandinavian Odor Identification Test (SOIT), which was used to assess olfactory identification ability in the Betula study (Nordin et al., 1998; Larsson et al., 2004). The following odorous stimuli were used: almond (bitter), anise, apple, cinnamon, clove, juniper berry, lilac, lemon, orange, pineapple, tar, vanilla and violet. These stimuli are perceptually fairly strong in intensity, and can be considered to represent a wide range of qualities, such as floral, citrus, non-citrus fruity, sweet, woody, spicy and minty. Tar was an off-the-shelf product, whereas the remaining stimuli were natural etheric oils (Stockholm Ether and Essence Manufactory, Stockholm, Sweden). The liquid odorant was injected into a cotton roll filled to saturation and placed in an opaque, 80 ml glass jar. For each stimulus, the participant was provided with a written list of the four response alternatives from which they were asked to indicate the most appropriate item for identification. The stimuli were presented birlarily 1–2 cm under the participant’s nose for as long as required to accomplish the task. The SOIT version used in the Betula study (e.g. Larsson et al., 2004), differs from the original version of the SOIT (Nordin et al., 1998), in that three odors with a strong trigeminal impact (i.e. ammonia, vinegar and peppermint) were removed when the SOIT was adapted for the Betula study, reducing the number of odor items from 16 to 13. The version of the SOIT that is used in the Betula study also differs from the original version in that the response alternatives are perceptually similar to the corresponding test odorant, making the test more difficult such that ceiling effects are avoided (Larsson et al., 2004). The stimulus order was randomized between subjects by randomly assigning one out of ten different stimulus orders to each subject. There was a 30 s interstimulus interval between stimuli to limit the effects of adaptation. Odors were replaced every 6 months when the SOIT was used in Betula testing.

2.3. MRI data acquisition and hippocampal subfield segmentation

Anatomical MRI data were collected on a 3T General Electric scanner (equipped with a 32-channel head coil). T1-weighted data were acquired in axial orientation using a 3D fast spoiled gradient echo sequence (180 slices with 1 mm thickness, TR: 8.2 ms, TE: 3.2 ms, TI: 450 ms, flip angle: 12, field of view 25 × 25 cm, matrix: 256 × 256, reconstructed to 512 × 512). FreeSurfer v.6.0 (https://surfer.nmr.mgh.harvard.edu/swiki/HippocampalSubfields) was used for the hippocampal subfield segmentation. This pipeline contains motion correction and normalization of the structural T1-weighted images. A hybrid surface deformation procedure removes non-brain tissue and transforms images to Talairach space. Maximal shifts in signal intensity are used to define gray/white matter and gray matter/cerebrospinal fluid boundaries (for more details see Dale et al., 1999). Images were automatically processed with the longitudinal stream in FreeSurfer (Reuter et al., 2012).

2.4. Statistical analysis

Standardized regression residuals were computed for hippocampal volumes and olfactory data by regressing out the effects of age, sex and education. Hippocampal volumes were additionally controlled for total intracranial volume (TIV) as measured at baseline or follow-up. Although the method used here involved a linear regression approach to account for differences in total brain volume, we were able to replicate all main findings using a method where subfield volumes were instead proportionally scaled to total brain volume. Separate residuals were computed for baseline and follow-up data. A residual change value, obtained by subtracting follow-up from baseline residual value for each variable of interest, was also established for each participant. These standardized change scores were used to correlate volumetric HC subfield changes with behavioral OI changes. Pearson correlations were then obtained using the resulting residuals to estimate the relationship between the cortical volume of each HC subfield of interest and the olfactory test scores. Furthermore, we visually inspected potential outliers in our correlation plots. In the case of one MA participant, we encountered a seemingly deviating value in the standardized volume change value for the HC tail subfield (as presented in Fig. 4). This case appeared very close to the regression line and its inclusion or exclusion had no influence on the correlations reported. We thus opted to include this case in our results.

3. Results

A repeated-measures ANOVA was used to examine how odor identification changed from the baseline to follow-up time points. For MA participants, there was a small, but significant increase in OI scores over time (F(55) = 16.8, p < .001), a surprising increase that was not observed in OA participants (F(60) = 2.34, p = .13). There was also no significant interaction between the change in OI scores and age groups (F(1, 117) = 2.54, p = .11). We conducted supplementary analyses where baseline SOIT score was used as a predictor of SOIT score at follow-up. Results showed that SOIT scores at baseline and follow-up were moderately correlated (Pearson’s r = .56; p < .001) such that 31% of the variance of the follow-up assessment could be predicted from the baseline scores. A hierarchical regression analysis showed that even after adjusting for participant age, sex, and education, three demographic variables known to influence odor identification scores (Larsson et al., 2004), baseline SOIT scores remained a strong predictor of SOIT scores 5 years later (explaining additionally 22% of the variance of SOIT at follow-up; p < .001). Since the current study was not intended to study normative olfactory impairment, only individual differences in olfaction, we proceeded with the correlations of subfield volume changes and OI scores even if there was no overall decrease in OI scores for OA participants over time. We thus examined whether individual differences in HC subfield volumes coincided with differences in olfactory abilities, cross-sectionally as well as longitudinally. Given the exploratory approach of the study, we did not adjust our statistical threshold for multiple comparisons.

We correlated HC subfield volumes with OI at baseline. No significant associations were obtained across the whole sample (all p values > .13; Fig. 3). Separate follow-up analyses were conducted for MA and OA groups, since we had reasons to believe that effects are more likely to be found in older cohorts (Josefsson et al., 2017; Daugherty et al., 2016; Gorbach et al., 2016; Olofsson et al., 2009). These cross-sectional analyses yielded no significant correlations between OI and HC-subfield volume in either younger or older adults (all p values < .21; see supplementary Figs. 8 and 9 in the appendix for individual group results).

We then analyzed longitudinal changes across the 5-year follow-up period. Longitudinal analyses across all participants revealed significant correlations between OI and volume changes in the tail of the HC (r = .21, p = .002) (Fig. 4). A non-significant trend was also observed between longitudinal changes in OI ability and subiculum volume (r = .17, p = .074). In the OA group (Fig. 5), change in OI ability was correlated with volume changes in CA4 (r = .30, p = .017), DG (r = .27, p = .036), tail (r = .27, p = .037) and subiculum subfields (r = .28, p = .032). No corresponding significant correlations were observed in the MA group (Fig. 6). Finally, we examined whether the OI and subfield correlations differed between the two age groups, using r-to-Fisher z transformations. Significant age differences were observed in the correlations between longitudinal OI and volume changes in the DG (Z = 2.81, p = .005) and CA4 (Z = 2.82, p = .005) subregions. This indicates that, for these two adjacent regions, the longitudinal association between OI and HC subregions were significantly greater in older adults than in middle-aged adults.

4. Discussion

The association between age-related changes in olfactory abilities

and hippocampus (HC) volume is poorly understood in humans, even though olfaction is a key behavioral function of the mammalian HC, and implicated in cognitive aging and dementia. Here, we explored both cross-sectional and longitudinal associations between HC-subfield volumes and OI performance in a population-based sample spanning 5 years. No significant correlations were observed in the cross-sectional analyses, but they emerged longitudinally. Specifically, 5-year change in OI performance was related to volume change in the HC tail across all participants, while a similar albeit non-significant trend was observed for the subiculum subregion. Age-stratified analyses demonstrated that these associations were generally restricted to older participants, and not present in middle-aged individuals. In older participants, OI performance changes were correlated with HC tail, CA4, DG, and subiculum volume loss. These results suggest that olfactory abilities in old age appear directly dependent on the integrity of some HC subfields.

The current results are in line with previous findings showing that the HC is engaged in memory-based odor tasks, such as odor identification (Eichenbaum et al., 1983) and retrieval (Cerf-Ducastel and Murphy, 2006; Gottfried et al., 2004; Lehn et al., 2013). The HC is highly connected with the primary olfactory cortex, that includes the piriform cortex and the primary olfactory nucleus, presumably enabling memory associations to establish between representations of odors and their contexts (Zhou et al., 2021). A decline in the volume of these early olfactory structures has also been reported to occur in parallel with a decline in OI functions in healthy older adults (Wang et al., 2005) and it has been observed in MCI and dementia (Jobin et al., 2021; Kjelvik et al., 2021; Vasavada et al., 2015). Importantly, OI impairment is associated with general cognitive decline, dementia and hippocampal atrophy in older adults (see e.g., Murphy, 2019 and Olofsson et al., 2021, for reviews).

Our findings indicate, for the first time, an age-specific relationship between changes in the morphology of individual HC subfields and
changes in OI performance. Although the coarse nature of in vivo volumetric measurements prevents us from making strict mechanistic interpretations, we note that our results are broadly congruent with previous results in non-human animals as well as the relative age-sensitivity of some HC subregions. It is notable that changes in HC input regions (e.g., DG) as well as HC output regions (e.g., subiculum) were found to be important for retaining olfactory abilities. Input regions such as the DG could be involved in the disambiguation of odor signals received by primary olfactory areas and subsequent broadcasting of decorrelated responses to the downstream CA1 subregion (Wiebe and Staubli, 1999; Woods et al., 2020). Recognition functions become increasingly more stimulus-invariant along the input-to-output gradient, with neuronal responses in CA1 being insensitive to the identities of sensory stimuli (Otto and Eichenbaum, 1992). However, regions such as the subiculum, which channels information from the CA1 to extra-hippocampal regions, also appear to be involved in higher odor representation and recognition functions (e.g., for social odors; Petrulis et al., 2005). Interestingly, DG volume appears to be particularly affected by age (Daugherty et al., 2016), and, in our data, this OI-DG effect was only present in older, and not middle-aged participants. In contrast, previous reports do not demonstrate a consistent link between subiculum volume changes and aging (Daugherty et al., 2016; La Joie et al., 2010). The subiculum may be affected at an early, pre-clinical stage of Alzheimer’s disease (Mueller and Weiner, 2009) and lower subicular volumes have been associated with poor cognitive performance and later MCI and dementia conversion (Evans et al., 2018; Kwak et al., 2022). For this reason, subicular atrophy might provide a biological basis for the olfactory deficit appearing in individuals with dementia (Stanciu et al., 2014; Devanand et al., 2008). The exact timeline and profile of preclinical changes of this process needs confirmation in future studies.

Even though our observations support the possible role of specific HC

Fig. 4. Longitudinal correlations between HC subfields and OI scores in the entire sample.
subregions in OI processing, rodent work suggests that the entire ventral HC is likely important for the processing of odors (Weeden et al., 2014; Petrulis et al., 2005). Although much more emphasis has been given to the spatial cognitive functions of the dorsal HC, a separate line of evidence suggests that the ventral HC is especially concerned with the processing of odor information (Aqrabawi et al., 2016; Weeden et al., 2014; Kesner et al., 2011; Pentkowski et al., 2006; Petrulis et al., 2005). Similarly, the functional connectivity with olfactory cortices is greater for ventral/anterior HC than for dorsal/posterior HC (Zhou et al., 2021). It will therefore be important to evaluate our findings using MRI data of higher resolution so as to further examine how morphological changes along the dorsoventral HC axis influence OI functions. This could provide a more definitive profile of subregional changes and their relationship with changes in odor perception in older age. Another pressing issue is to investigate how dementia status moderates HC-subfield morphology and thereby olfactory abilities in order to distinguish between OI decline-HC atrophy relationships that pertain to normal and pathological aging. Finally, it is important for future studies to examine cortical and HC regional brain activation and connectivity during OI using fMRI (e.g. Kollindorfer et al., 2015).

The current study has several strengths, including a relatively large sample size with a wide age-range, and the availability of both cross-sectional and longitudinal data on HC subfields volume and OI, but a few limitations should also be highlighted. First, only one test was used to assess olfactory ability, and trigeminal perception was not assessed, limiting the scope of our study. Second, instead of an overall decline in olfactory scores, we observed a small increase in the OI scores in middle-aged adults from baseline to follow up. It is possible that test-retest and/or instrument effects were present in the longitudinal olfactory test results, thus overshadowing the typical age-associated decline which was expected, especially in older adults. However, the fact that baseline OI predicted OI at the 5-year follow-up suggests that the SOIT test is...
nevertheless a valid test of individual differences in OI. Third, only data from one region (HC) were used. As olfactory function is determined by many interacting brain processes and functions (WM integrity, brain activation, molecular functioning), relevant changes should be profiled using several brain regions, and various olfactory and trigeminal ability assessments that were not included in the current study (see e.g. Seubert et al., 2020; Frasnelli et al., 2010). Fourth, we used a single-sample study design with only two measurement points. We were therefore not able to examine curvilinear trajectories of change and this design also did not permit independent estimations of retest effects, which might influence longitudinal data (Ghisletta et al., 2012; Salthouse, 2013, 2014). Future work with three or more time points could provide more detail in terms of long-term trajectories in OI and HC subfield data that we are unable to track in the current study, and may also help in estimating the influence of possible retest and/or instrument effects.

As this is the first study of its kind in human participants, we did not have any strong a-priori hypotheses about HC sub-regional specificity and the associations with OI performance. We therefore decided not to adjust our analyses using correction for multiple comparisons in order to minimize the risk of type-2 errors (Althouse, 2016; Lieberman and Cunningham, 2009). Because of our exploratory approach and lack of correction, our empirical results need independent replication in future studies. The effect sizes were relatively small; this might be expected in brain-behavior association studies in non-clinical samples, where the size of particular brain regions are determined by several factors and where complex behavioral tasks engage several brain regions. In particular, longitudinal studies often report results with small effect-sizes, but they are nevertheless meaningful (Adachi & Willoughby, 2014).

We can conclude that longitudinal changes in OI in aging may be explained by a concurrent atrophy in specific HC subregions. Although olfactory processing engages also fronto-temporal structures (Olofsson and Freiherr, 2019 for review), the HC is a central node in this network, and concurrent aging-related changes in the HC may parsimoniously explain parts of the OI decline often observed in aging. Furthermore, our findings may explain the observation that, in some older individuals, there is an accelerated common decline in odor identification and episodic memory abilities given that both functions depend on HC circuit integrity (Dintica et al., 2021; Olofsson et al., 2016). The overlap and divergence of subregional changes within the HC that are implicated

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**Fig. 6.** Longitudinal correlations between HC subfields and OI scores in middle-aged participants.
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