Olfactory testing does not predict β-amyloid, MRI measures of neurodegeneration or vascular pathology in the British 1946 birth cohort

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Abstract

Objective To explore the value of olfactory identification deficits as a predictor of cerebral β-amyloid status and other markers of brain health in cognitively normal adults aged ~70 years.

Methods Cross-sectional observational cohort study. 389 largely healthy and cognitively normal older adults were recruited from the MRC National Survey of Health and Development (1946 British Birth cohort) and investigated for olfactory identification deficits, as measured by the University of Pennsylvania Smell Identification Test. Outcome measures were imaging markers of brain health derived from 3 T MRI scanning (cortical thickness, entorhinal cortex thickness, white matter hyperintensity volumes); 18F florbetapir amyloid-PET scanning; and cognitive testing results. Participants were assessed at a single centre between March 2015 and January 2018.

Results Mean (±SD) age was 70.6 (±0.7) years, 50.8% were female. 64.5% had hyposmia and 2.6% anosmia. Olfaction showed no association with β-amyloid status, hippocampal volume, entorhinal cortex thickness, AD signature cortical thickness, white matter hyperintensity volume, or cognition.

Conclusion and relevance In the early 70s, olfactory function is not a reliable predictor of a range of imaging and cognitive measures of preclinical AD. Olfactory identification deficits are not likely to be a useful means of identifying asymptomatic amyloidosis. Further studies are required to assess if change in olfaction may be a proximity marker for the development of cognitive impairment.

Keywords Alzheimer’s disease · Olfactory impairment · Neuroimaging

Introduction

Simple, non-invasive markers of preclinical Alzheimer’s disease (AD) are needed. Odour identification (OI) deficits have been proposed as a potential risk marker for AD. Clinically, individuals diagnosed with AD and mild cognitive impairment (MCI) have poorer OI, and OI deficits are associated with cognitive decline and conversion to MCI and AD [1]; and AD pathology affects olfactory pathways in older adults [2] and animal models [3].

While the evidence for these associations in clinically defined groups is strong, the evidence regarding imaging biomarkers is more mixed. Table 1 summarises the previous literature investigating associations between OI and imaging markers of preclinical AD. Considering the two largest cohorts, Vassilaki et al. [4] and Growdon et al. [5] each found associations between poorer OI and imaging markers of neurodegeneration. Amyloid status was positively associated with poorer OI in the former, and at trend level in the latter study. In smaller studies, associations were not found...
| Study                  | Year | Region   | Outcome measures                  | Olfactory test | Design                | n       | Mean age, years (SD, if available) | % female | Key findings                                                                 |
|------------------------|------|----------|-----------------------------------|----------------|-----------------------|---------|-----------------------------------|-----------|----------------------------------------------------------------------------|
| Devanand et al. [10]   | 2010 | USA      | sMRI, cognitive tests             | UPSIT          | Cross-sectional       | 1092 (802 CN, 120 naMCI, 170 aMCI) | 80.5 (5.8) | 70                            | Lower OI associated with lower hippocampal volumes and cognitive test results, but not WMH or entorhinal cortex volumes |
| Bahar-Fuchs et al. [9] | 2010 | Australia| Amyloid-PET (PiB)                 | 6 items from the UPSIT | Cross-sectional       | 63 (19 CN, 24 aMCI, 20 AD)     | 73.6     | 57                            | Higher PiB-PET SUVR associated with lower OI in pooled analyses; however, no relationship found within each cognitive group |
| Growdon et al. [5]     | 2015 | USA      | Amyloid-PET (PiB), sMRI, Cognitive tests (composite) | UPSIT          | Cross-sectional       | 215 (all CN)                       | 73.9 (5.9) | 59.1                          | Poorer OI associated with lower hippocampal and entorhinal cortex volumes, and cognitive scores. Association with amyloid status at trend level |
| Dhilla Albers et al. [6]| 2016 | USA      | Amyloid-PET (PiB) ($n=41$), sMRI ($n=49$) cognitive tests | Two novel olfactory tests | Longitudinal follow-up of cognition | 183 (70 CN, 74 SCD, 29 MCI, 10 AD) | 76.7 | 60.8                          | Poor performance associated with lower hippocampal and entorhinal cortex volumes (pooling all cognitive groups) but not with amyloid status; also associated with longitudinal cognitive decline in CN group |
| Vassilaki et al. [4]   | 2017 | USA      | Amyloid-PET (PiB) ($n=306$), FDG-PET ($n=305$), sMRI ($n=829$) | B-SIT          | Cross-sectional       | 829 (all CN)                       | 79.2    | 48.5                          | Anosmia (B-SIT < 6) (but not hyposmia) associated with abnormal PiB-PET and sMRI measures (hippocampal volume, AD signature CT). Continuous B-SIT scores also associated with sMRI measures |
| Study                        | Year | Region | Outcome measures | Olfactory test | Design             | n            | Mean age, years (SD, if available) | % female | Key findings                                                                                                                                                                                                 |
|------------------------------|------|--------|------------------|----------------|--------------------|--------------|------------------------------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risacher et al. [7]          | 2017 | USA    | Amyloid-PET (florbetapir/ florbeta-ben); Tau-PET (flortaucipir), sMRI | UPSIT          | Cross-sectional    | 34 (19 CN, 10 SCD, 5 MCI) | 70.8 | 64.7 | Olf not associated with amyloid-PET across sample or any subgroup. Poorer Olf associated with tau deposition in the temporal lobe across pooled sample, and in CN plus SCD group. Lower temporal, hippocampal and entorhinal GM volumes across pooled sample |
| Heinrich et al. [11]         | 2018 | France | sMRI, cognitive tests | B-SIT          | Cross-sectional    | 75 MCI       | 77.1 (6.2) | 74.7 | B-SIT < 8 associated with lower hippocampal volume, higher WMH rating, lower MMSE and FCSRT                                                                                                               |
| Kriesl et al. [8]            | 2018 | USA    | Amyloid-PET (PiB), Cognitive tests (composite) | UPSIT          | Longitudinal follow-up of cognition | 71 (25 CN, 46 MCI) | 68.5 (7.5) | 58 | UPSIT < 35 had NPV 100%, PPV 41% for binary amyloid status. UPSIT < 35 predicted memory decline in MCI but not CN participants |

sMRI structural MRI, UPSIT University of Pennsylvania Smell Identification Test, CN cognitively normal, MCI mild cognitive impairment, aMCI amnestic MCI, naMCI non-amnestic MCI, Olf odour identification, WMH white matter hyperintensity, PET positron emission tomography, PiB Pittsburgh compound B tracer, AD Alzheimer’s Disease, CT cortical thickness, SUVR standard uptake value ratio, FDG fluorodeoxyglucose, B-SIT Brief Smell Identification Test (a validated 12 item selection from the UPSIT), PPV positive predictive value, NPV negative predictive value, SCD subjective cognitive decline, MMSE mini-mental status examination, FCSRT Free and Cued Selective Reminding Test, GM grey matter
[6, 7], or only seen when individuals with MCI or AD were included in pooled analyses [8, 9]. Associations between poorer OI and AD signature cortical thickness, and lower hippocampal volumes have been described [4, 7, 10, 11]. Associations with entorhinal cortex thickness or white matter hyperintensity volume have been present or absent in various studies [4–6, 10, 11].

A useful marker for preclinical AD would be positive early in the disease course, allowing a window for treatment. As the prevalence of AD pathology increases steeply with age, younger cohorts may be useful to investigate the earlier stages of disease.

In the current study, we explored associations between OI and markers of cerebral β-amyloid deposition (using 18F-florbetapir PET scanning), neurodegeneration, and cognition in a uniquely well-characterised cohort of near identical age drawn from the MRC National Survey of Health and Development (NSHD; the British 1946 birth cohort).

Methods

Participants

The Insight 46 study included 502 older adults recruited from the NSHD [12], a representative sample of singleton births in one week in March 1946 originally comprising 5326 individuals who have been followed prospectively throughout their lives [13]. Ethical approval was granted by the National Research Ethics Service Committee London (reference 14/LO/1173); participants provided written informed consent.

Participants attended a one-day visit at University College London between May 2016 and January 2018 (age 69–71 years). The cohort profile and recruitment information has been published [14]. We excluded participants without high-quality imaging (T1-weighted MRI and amyloid-PET), and those with mild cognitive impairment (MCI), neurodegenerative conditions, or conditions likely to affect olfactory function including previous sinus surgery or upper respiratory tract infection (Supplementary data).

Olfactory testing

The University of Pennsylvania Smell Identification Test (UPSIT) is a validated “scratch-and-sniff” test comprising 40 micro-encapsulated odorants, with four-option forced-choice answers [15]. Participants completed the “British” version at the study visit or soon thereafter. Where there was missing data for four or fewer items, a correction factor of 0.25 per missing item was applied, in line with other studies [16].

For categorical analyses, hyposmia was defined as UPSIT score ≤ 33 for males, ≤ 34 for females, and anosmia as UPSIT score ≤ 18 [15]. Normative data for the UPSIT British version have not been published; a comparison to norms for the UPSIT American version is shown in Table 1.

Neuropsychological testing

The cognitive battery included the Mini-Mental Status Examination (MMSE), Logical Memory, Digit-Symbol Substitution Test, and the Face-Name test [12]. These tests were combined into a modified version of the Preclinical Alzheimer Clinical Composite (PACC) score as described in Lu et al. [17].

Imaging

Participants underwent PET-MRI scanning on the same 3-T Siemens Biograph mMR scanner [12]. β-amyloid deposition was assessed over a 10-min period, 50 min after injection of 18F-florbetapir (370 mBq). A standardised uptake value ratio (SUVR) was generated from a grey matter cortical composite, with eroded white matter as the reference region. Gaussian mixture models determined a SUVR cut-point of 0.6104 to categorise binary amyloid status.

Hippocampal volume, entorhinal cortex thickness and AD signature cortical thickness were used as markers of neurodegeneration [4, 5]. Hippocampal volumes were determined using STEPS [18] with manual edits where appropriate. AD signature cortical thickness (a composite of temporal cortex regions as described in [19]) and entorhinal cortex measurements were determined using Freesurfer 6.0. Total intracranial volume was calculated using SPM12 (Statistical Parametric Mapping, https://www.fil.ion.ucl.ac.uk/spm/) [20]. White matter hyperintensity volume (WMHV) was derived using Bayesian Model Selection (BaMoS) [21].

Statistical methods

Data were analysed using Stata 14.1 (StataCorp LP). Chi-squared or Wilcoxon rank-sum tests were used for unadjusted analyses comparing OI category with binary or continuous demographic variables, respectively. Logistic regression was used for adjusted analysis of (binary) amyloid status, linear regression for hippocampal volumes, AD signature cortical thickness, entorhinal cortex thickness and PACC score. As WMHV was non-normally distributed, we used a general linear model with gamma log link. For each of these outcomes, we fitted models with continuous UPSIT score or OI impairment category as the predictor variable, and age, sex, and (where appropriate) TIV as covariates.
Results

Full data on 389 individuals were available for analysis: mean age at visit was 70.6 (SD 0.68) years, and 50.8% were female. Table 1 compares the distribution of UPSIT scores in this cohort with those of a large cohort of similar age assessed using the UPSIT (American version); the distribution of scores is similar.

Demographic and background features of the normosmic (32.9%), hyposmic (64.5%) and anosmic (2.6%) groups are shown in Table 1. There were no significant differences in sex, age, socio-economic position, smoking, history of head injury, ApoE4 status, or MMSE score between groups.

There was no significant relationship between continuous UPSIT score and binary amyloid status, adjusting for age and sex (OR 1.04, 95% CI 0.98–1.10, \( p = 0.24 \)).

There was no evidence that adding UPSIT score to a base model of age and sex improved prediction of amyloid status (Fig. 1).

Hippocampal volume, entorhinal cortex thickness, cortical thickness, PACC, or WMHV was not associated with continuous UPSIT scores, or when comparing groups categorically (Table 2) after adjusting for age and sex. There was similarly no relationship between UPSIT score and any of the components of the PACC (data not shown).

Discussion

In this study of 389 cognitively normal individuals around the age of 70 years, our main findings were (1) ~2/3 of individuals fulfil criteria for hyposmia, and (2) that there were no associations between low scores on olfactory identification testing and imaging evidence of \( \beta \)-amyloid pathology.

![Fig. 1](image-url) **Fig. 1** Receiver operating characteristic curve illustrating the predictive value of age, sex and UPSIT score for amyloid status. Area under the curve for age and sex alone, 0.517 (95% confidence interval: 0.444–0.590), versus 0.545 (95% confidence interval 0.465–0.624) when UPSIT score is added to the model \( p = 0.466 \). This indicates that the addition of UPSIT score has very limited additional discriminatory value to predict amyloid status.

| Percentile | UPSIT score |
|------------|-------------|
| Males      |             |
| UPSIT: American, age 70–74 (n = 77) | UPSIT: British, age 69–71 (n = 191) |
| 99         | 39          | 39          |
| 75         | 34–35       | 35          |
| 50         | 29–30       | 32          |
| 25         | 24          | 28          |
| Females    |             |
| UPSIT: American, age 70–74 (n = 87) | UPSIT: British, age 69–71 (n = 198) |
| 99         | 40          | 38          |
| 75         | 35–36       | 35          |
| 50         | 32–33       | 33          |
| 25         | 27–28       | 31          |
neurodegeneration or cerebrovascular disease, or cognitive performance.

The strongest associations between olfaction and imaging metrics relevant to AD were reported in the Mayo Clinic cohort [4], which also has the highest average age (79 years). The Harvard cohort (mean age 74 years) [5] found a trend level association with amyloid status, and significant associations with imaging markers of neurodegeneration. Noting that our cohort was ~ 10 and 5 years younger than these, respectively, and as older individuals would be expected to have a shorter time to AD onset, this suggests that if OI impairment is not a useful screening tool for asymptomatic pathology, it may however be useful as a proximity marker for the emergence of cognitive impairment. The finding in smaller studies that associations between OI and imaging markers were strengthened by the inclusion of individuals with MCI (who are closer to disease onset) may also indicate this [8, 9].

Limitations of this study include its cross-sectional design and lack of a marker of tau pathology, as there is evidence from pathological [2] and biomarker [7, 22] studies that tau deposition may be more closely linked to olfactory changes. Longer term follow-up of this cohort and the addition of markers of tau pathology will be able to address the latter and the potential proximal relationship of OI to the development of cognitive impairment. Whether or not olfactory loss than can be seen in patients infected with Covid-19 relates to damage to olfactory epithelium or neuronal injury is the subject of ongoing debate, but at the current time, there is no evidence that this is related to Alzheimer pathology [23].

In summary, the high prevalence of OI impairment in populations at this age and lack of relationship between OI

### Table 3: Associations between demographic factors and olfactory identification impairment

|                   | Normosmia (n = 128) | Hyposmia (n = 251) | p²  | Anosmia (n = 10) | p²  |
|-------------------|---------------------|-------------------|-----|-----------------|-----|
| Sex, female       | 62 (48.4)           | 134 (53.4)        | 0.362 | 2 (20.9)        | 0.082 |
| Age, years        | 70.7 (0.62)         | 70.6 (0.70)       | 0.181 | 70.6 (0.95)     | 0.790 |
| SEP, manual occupations | 22 (17.2)   | 34 (13.6)         | 0.345 | 2 (20.0)        | 0.821 |
| Current or former smoking | 80 (62.5) | 166 (66.1)        | 0.483 | 6 (60.0)        | 0.875 |
| Head injury prior to age 69–71 | 22 (17.2) | 28 (11.2)        | 0.101 | 2 (20.0)        | 0.821 |
| ApoE 4 carrier     | 39 (29.7)           | 72 (28.9)         | 0.472 | 4 (40)          | 0.495 |
| MMSE score         | 30 (29–30)          | 30 (29–30)        | 0.973 | 29.5 (29–30)    | 0.565 |

SEP socio-economic position, MMSE mini-mental status examination
*a* p value compared to normosmia, determined by chi-square test (categorical variables) or Wilcoxon rank-sum test (continuous variables)

### Table 4: Associations between continuous and categorical UPSIT scores and imaging outcomes in 389 cognitively normal individuals at age 69–71

|                               | Continuous analyses | Categorical analyses |
|-------------------------------|---------------------|---------------------|
|                               | β   | 95% CI      | p   | β   | 95% CI      | p   | β   | 95% CI      | p   |
| Associations by linear regression (β coefficient) |                  |                      |     |     |                      |     |     |                      |     |
| Hippocampal volume (mL)       | −0.002 | −0.004, 0.011 | 0.805 | −0.075 | −0.200, 0.050 | 0.239 | −0.162 | −0.540, 0.217 | 0.401 |
| Entorhinal cortex thickness (mm) | 0.001 | −0.004, 0.006 | 0.671 | 0.010 | −0.039, 0.059 | 0.693 | −0.041 | −0.191, 0.108 | 0.587 |
| Cortical thickness (mm)       | 0.001 | −0.001, 0.003 | 0.156 | −0.003 | −0.022, 0.017 | 0.771 | 0.001 | −0.058, 0.059 | 0.986 |
| Global cognitive score (modified PACC) | −0.003 | −0.017, 0.011 | 0.657 | 0.001 | −0.141, 0.140 | 0.992 | 0.252 | −0.172, 0.677 | 0.244 |
| Associations by generalised linear model (exponentiated β coefficient) |                  |                      |     |     |                      |     |     |                      |     |
| White matter hyperintensity volume (mL) | 0.992 | 0.967, 1.016 | 0.609 | 1.153 | 0.906, 1.468 | 0.247 | 1.280 | 0.624, 2.628 | 0.501 |

*a* Adjusted for age and sex

*b* Adjusted for age, sex and total intracranial volume

*c* Expressed as the mean of right and left

*d* n = 377 for this outcome

*e* Expressed as exponentiated β coefficient; value represents the ratio change in WMHV per 1 point increase in UPSIT score, or between groups
and markers of β-amyloid and neurodegeneration we find, indicate that the UPSIT is unlikely to be a reliable predictor of preclinical AD in its very earliest stages (Tables 3, 4).

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**Availability of data and material** A data-sharing policy is available on the NSHD Data Sharing website https://www.nshd.mrc.ac.uk/data.

**Compliance with ethical standards**

**Conflicts of interest** Dr Fox’s research group has received payment for consultancy or for conducting studies from Avid Radiopharmaceuticals, Biogen, Eli Lilly Research Laboratories, General Electric Healthcare, and Roche; Dr Fox receives no personal compensation for these activities. Dr Schott reports grants from Weston Brain Foundation during the conduct of the study and personal fees from Axon Neuroscience, Roche, Eli Lilly, General Electric Healthcare, Merck Sharp & Dohme, Oxford University Press, Biogen, and EU Horizon 2020 outside the submitted work.

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**Consent to participate** Participants provided written informed consent.

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