LETTER

Olfactory impairment in posterior cortical atrophy

INTRODUCTION

Olfactory dysfunction develops in many neurodegenerative diseases, and is an early feature of the most common neurodegenerative disorder, Alzheimer's disease (AD).[1–5] Anatomically, the central olfactory pathways traverse brain regions implicated in the common neurodegenerative diseases, including the mesial temporal and inferior frontal lobes.[6–10] Phenotypically, AD shows substantial diversity with several important variant syndromes, notably posterior cortical atrophy (PCA),[11] which is underpinned by AD pathology in over 70% of cases across series. Olfactory impairment in PCA might act as an early signal of underlying AD pathology in these clinically atypical cases; while if olfactory processing were spared in PCA, this would imply that olfaction depends chiefly on disease topography. However, there is presently very little information concerning olfaction in PCA.

Here we compared olfactory function prospectively in cohorts of patents with PCA and typical AD (tAD). Neuroanatomical associations of odour identification were assessed using voxel-based morphometry (VBM). We hypothesised that PCA would be associated with olfactory impairment qualitatively similar to tAD, but less severe (reflecting differential involvement of olfactory cortex); and that deficits of odour identification in both syndromes correlate with grey matter loss in anteromedial temporal and inferior frontal lobes.[2 6–10]

METHODS

Fifteen patients fulfilling consensus criteria for PCA,[11] 10 patients fulfilling The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for tAD and 32 healthy control (HC) subjects participated. Cerebrospinal fluid (CSF) measurements, available for four patients with PCA, revealed a raised total-τ:β-amyloid ratio (>1) in each case, consistent with underlying AD. Informed consent was obtained from all subjects and the study had local ethics committee approval.

All subjects had a comprehensive general neuropsychological assessment which corroborated the clinical impression in both disease groups (see online supplementary table S1). Further details about the behavioural assessments are in online supplementary material.

Olfactory processing was assessed using the 40-item, four-alternative-forced-choice University of Pennsylvania Smell Identification Test (UPSIT: British version).[12] We modified the standard UPSIT in two ways: on each trial, the subject was asked to categorise the source of the odour as edible or inedible (see online supplementary table S2) before identifying it; and target-foil choices were name-picture combinations rather than odour names alone, to maximise available response cues. Group differences were assessed using analysis of variance (ANOVA) or χ^2 tests (Stata V.12.1), adjusting for cognitive severity, verbal processing measures, age and gender.

Twelve patients with PCA and eight patients with tAD had T1-weighted volumetric magnetic resonance (MR) brain images acquired on a 3.0T Siemens Trio scanner. VBM was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) following previously described procedures (see online supplementary material). Linear regression was used to examine voxel-wise associations between regional grey matter volume and odour identification performance (age-normed and gender-normed percentile score) across the combined patient cohort, within the PCA subgroup, and between syndromic subgroups, incorporating syndromic group, mini-mental state examination (MMSE) score and total intracranial volume as covariates. Statistical parametric maps were assessed thresholded over the whole brain volume and after multiple-comparisons correction over small volumes of interest (right and left anteromedial temporal lobes and orbitofrontal cortex) specified in our prior anatomical hypotheses.

RESULTS

For both patient groups, mean odour categorisation and identification raw scores were significantly lower than the HC group ($p<0.001$; figure 1A, online supplementary table S1; individual data in online supplementary figure S1). Based on published UPSIT norms,[12] four patients with PCA (26%) and three patients with tAD (30%) scored <5th percentile. Mean raw or percentile scores did not differ significantly ($p>0.1$) between the PCA and tAD groups. After correction for guessing, mean odour identification scores were higher than mean categorisation scores for PCA patients as well as HC subjects (see online supplementary table S1). An error analysis of individual odour items in the identification test revealed a qualitatively similar profile of errors across all groups (see online supplementary figure S2).

Statistical parametric maps of significant regional grey matter associations of odour identification performance are displayed in figure 1B (quantitative data summarised in online supplementary table S3). Across the combined patient cohort, performance on the odour identification task was positively associated with regional grey matter volume in right entorhinal cortex and parahippocampal gyrus ($p<0.05$ FWE-corrected over the temporal lobe volume of interest). At a more lenient threshold ($p<0.001$ uncorrected over the whole brain volume), additional associations were present in more distributed, predominantly right-sided cerebral areas, including hippocampus, posterior inferior temporal gyrus/sulcus, temporo-parieto-occipital junction and premotor cortex (see online supplementary table S3). Similar grey matter associations of odour identification performance were identified for the PCA subgroup alone ($p<0.001$ uncorrected over the whole brain volume; online supplementary table S3). Direct comparison between the PCA and tAD subgroups revealed no significant between-group differences in regional grey matter correlations of olfactory performance.

DISCUSSION

Here we have demonstrated deficits of odour identification and categorisation in patients with PCA relative to HCs. A similar proportion (around 30%) of patients with PCA and tAD in this study had an absolute deficit of odour identification referenced to published age and gender norms and taking account of associated cognitive impairment. Olfactory impairment was similar quantitatively and qualitatively in the PCA and tAD groups. To the extent that PCA manifests underlying AD, the findings imply that olfactory impairment is a hallmark of AD pathology. It is noteworthy that only a minority of patients in both phenotypical groups here reported olfactory symptoms, suggesting that in many cases olfactory impairment is 'subclinical'. Mean corrected odour identification scores were higher than categorisation scores in the HC and PCA groups: this unexpected finding might hold clues to the cognitive organisation of olfactory knowledge or the cognitive strategies engaged by these tests, and would warrant further study in larger populations. Odour identification tasks tend to be cognitively demanding and therefore potentially susceptible to executive and attentional deficits that accompany AD.[3 13]

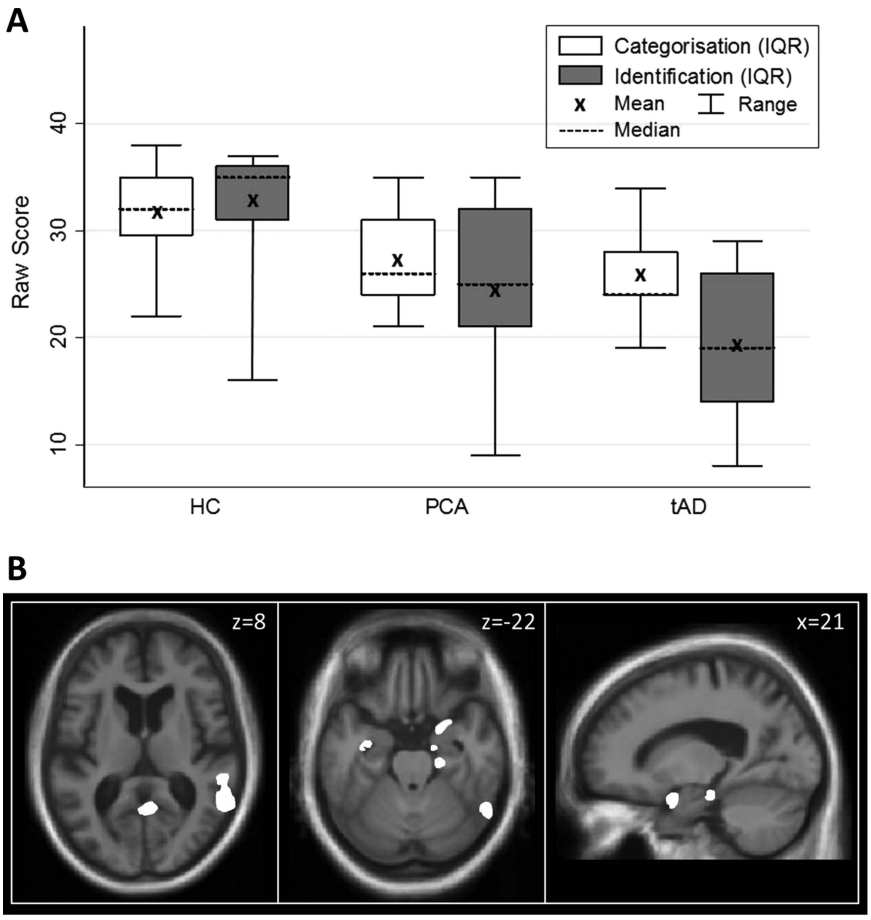

Figure 1 Summary of behavioural and neuroanatomical findings. (A) Distribution plots of olfactory performance comparing mean, median, IQR and full range of odour categorisation and identification of raw scores of subjects in the healthy control (HC), posterior cortical atrophy (PCA) and typical Alzheimer's disease (tAD) groups. (B) Statistical parametric maps (SPMs) of regional grey matter atrophy associated with odour identification performance across the combined PCA and tAD cohorts. SPMs are shown rendered on axial (left, middle panels) and sagittal (right panel) sections of the mean normalised structural T1-weighted brain MR image. The axial sections show the right hemisphere on the right; the sagittal section is through the right hemisphere. For display purposes, SPMs have been thresholded at $p<0.001$ uncorrected over the whole brain volume; see online supplementary table S3 for associations attaining significance after multiple-comparisons correction. The plane of each section is shown in Montreal Neurological Institute (MNI) coordinates in millimetres (mm).

The deficit of odour identification identified here was associated with regional grey matter volume in a cerebral network focussed on the right anteromedial temporal lobe. The most robust neuroanatomical associations occurred in parahippocampal gyrus and entorhinal cortex: areas linked to odour identification in healthy human subjects.[6 7] Right temporal lobe degeneration has been associated previously with clinical deficits of odour recognition.[2] Additional, less robust anatomical associations here included more posterior superior temporal and adjacent parietal areas, and premotor cortex: similar areas have been shown previously to be engaged in odour analysis,[14] olfactory working memory[15] and sniffing.[16] An overlapping cerebral network has been implicated in the pathogenesis of tAD and PCA.[11] Olfactory dysfunction may have a characteristic network signature that transcends conventional phenotypic boundaries and could potentially be used to predict AD pathology in the face of phenotypical variation. However, any claim to pathological specificity carries the important caveat that olfactory impairments have been defined for a range of non-Alzheimer neurodegenerative pathologies (notably, parkinsonian and other disorders in the frontotemporal lobar degeneration spectrum.[3–5 10] Rather than olfactory impairment per se, the signature of the impairment may be more likely to predict underlying pathology.[3] In addition, the present study was underpowered to detect subtle behavioural or neuroanatomical differences between the syndromic groups.

This study has several limitations that suggest directions for future work. We did not assess perceptual encoding of odours: it will be important to compare associative and perceptual olfactory functions directly, to assess the extent to which these different factors contribute to olfactory impairment in AD. The patient groups studied here were relatively small: there is a need to extend the work to larger patient cohorts spanning other AD phenotypes (eg, logopenic aphasia) and in direct comparison with other neurodegenerative pathologies.[3] Although PCA is usually attributable to AD pathology, neuropathological substrates in the present PCA cohort remain to be determined. Future longitudinal studies in different AD phenotypes (ideally, including presymptomatic carriers of AD-causing genetic mutations) will be required to assess onset and evolution of olfactory deficits.

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Contributors PW was involved in study planning, design and coordination, acquisition and analysis of

experimental behavioural and neuroimaging data, and in drafting and critically revising the paper. TJS and KXY were involved in acquisition of behavioural data and drafting and critically revising the paper. JMN was involved in study design, in the statistical analysis of experimental data and in drafting the paper. RO was involved in study design, preparation of experimental behavioural tests, and in drafting the paper. DMC was involved in study design, analysis of neuroimaging data and in drafting the paper. SJC and MNR were involved in planning the study and in critically revising the paper. JDW obtained funding for and supervised the study, and was involved in study planning and design and in drafting and critically revising the paper.

Competing interests None.

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SUPPLEMENTARY MATERIAL

Details of behavioural assessments

Olfactory questionnaire. Prior to recruitment, all subjects completed a questionnaire (described previously)[1] detailing current olfactory symptoms and factors in their previous medical history that might impact on peripheral olfactory function (including any history of significant head injury, active disorders or surgery of upper respiratory tract, or smoking).

Olfactory assessments. Olfactory processing was assessed in all subjects using the British version of the University of Pennsylvania Smell Identification Test (UPSIT), the most widely used, quantitative assessment of olfaction.[2] The test comprises 40 odourants implanted individually on microencapsulated scratch and sniff crystals. In the standard version of the test, the subject is asked to decide on each of the 40 trials which one of four alternative written names best describes the binasally presented odour (or to guess, if no odour is perceived).

In the present study, we modified the standard UPSIT testing procedure in two ways. Firstly, on each trial prior to being presented odour names, the subject was asked to classify the source of the odour as edible or inedible (odour categorisation); the breakdown of individual UPSIT items by edibility classification (24 edible, 16 inedible) is presented in Supplementary Table S2. This odour categorisation task was motivated by evidence concerning the organisation of object processing in the visual and auditory modalities, indicating that superordinate knowledge about sensory objects can be retained even though perceptual or semantic deficits preclude explicit identification of the object. Here, we hypothesised specifically that the ability to classify odours into superordinate categories might be retained even despite degraded odour identification; and that this superordinate processing might provide an additional relevant index of central olfactory function in the target disease groups. Secondly, in order to assess odour identification, word-picture combinations were presented, and name choices were spoken by the examiner as well as presented visually: this modification was designed to reduce reliance on specific, non-olfactory (e.g., written) response cues, in order to facilitate a more accurate measure of odour processing capacity in cognitively impaired patients, as previously described.[1, 3]

Subject responses were recorded for offline analysis, and odour identification and odour categorisation performance were scored separately. No feedback was given about performance, and no time limit was imposed.

Analysis of behavioural data. Group differences in general demographic and neuropsychological characteristics were assessed using t-tests or chi-square tests. Differences between groups (PCA, tAD, HC) in olfactory performance were assessed using ANOVA. In addition to unadjusted group comparisons two adjusted analyses were conducted. The first model related raw scores on the odour identification or categorisation test to group membership (PCA, tAD, HC) with adjustment for

relevant cognitive severity measures (MMSE, executive [WASI Matrices] and verbal processing [GNT] scores), subject age and gender as covariates of no interest which could potentially influence performance on the experimental tests. The second model related odour identification scores for individual subjects after transformation to percentile scores based on published norms,[2] in order to take account of age and gender effects, to covariates of group membership and cognitive severity measures.

Raw scores on the odour identification and categorisation tasks were not directly comparable because the chance of answering correctly by guessing was higher for the categorisation test (50%) than the identification test (25%). In order to compare performance on these tasks within each group, the raw scores on each test were therefore transformed to corrected scores using a formula for scoring of multiple-choice tests[4] and differences between the test scores were then assessed using paired t-tests. The threshold for statistical significance was set at $p<0.05$. All analyses were conducted using STATA version 12.1.

Brain image acquisition and analysis

Twelve patients with PCA and eight patients with tAD had T1-weighted (MP-RAGE) volumetric MR images acquired on a 3.0T Siemens Trio scanner (Siemens) (FOV of 282 mm, 256 x 256 matrix with 208 slices; 1.1 cm isotropic resolution, with TE=2.9ms, TR=2200ms, TI=900ms) at the time of the behavioural assessments.

Voxel-based morphometry (VBM) was performed on the MR images using SPM8® (http://www.fil.ion.ucl.ac.uk/spm) following previously described procedures.[5] Briefly, native space study images were roughly aligned visually to the standard SPM8 T1 template. Then the images were segmented in to grey matter, white matter, and cerebrospinal fluid using the unified segmentation algorithm.[6] Images were then spatially normalized onto the SPM8 templates using DARTEL.[7] A study specific template was created from the MR images by creating an iteratively updated group-wise average of the grey and white matter values.[8] The grey matter and white matter segmentations were then normalised using the final transformations to the group-wise atlas and modulated to account for volume changes. The images were then smoothed with an 8 mm isotropic Gaussian kernel. Before performing statistical analysis, all images were affine-registered to Montreal Neurological Institute (MNI) stereotactic space to provide standardized coordinates for reporting of significant findings.

Linear regression was used to examine voxel-wise associations between regional grey matter volume and performance on the odour identification task across the combined patient cohort. Voxel intensity was modelled as a function of normalised odour identification scores (percentile scores), incorporating disease group (PCA and tAD), MMSE score (a measure of overall cognitive function) and total intracranial volume (calculated using a previously described procedure)[9] as covariates. A separate analysis restricted to the PCA group with the same covariates was also performed in order to assess neuroanatomical associations of odour identification performance in this target syndromic group alone. Analysis masks were created by

thresholding the group-wise average grey matter image at 0.2, so as to exclude areas with very low signal from the voxel-wise statistical analysis.

Statistical parametric maps were assessed at three voxel-wise significance thresholds: at $p<0.05$ after family-wise error (FWE) correction for multiple comparisons over the whole brain volume; at $p<0.001$ uncorrected for multiple comparisons over the whole brain volume for the purposes of characterizing the patterns observed that do not reach significance; and at $p<0.05$ after FWE correction for multiple comparisons over the anatomical small volumes of interest specified in our prior anatomical hypotheses. These anatomical small volumes were derived by manual tracing from the template brain image using MRIcron® (http://www.mccauslandcenter.sc.edu/mricro/mricron/) and comprised bilateral orbitofrontal cortices (including the orbital surface of frontal lobes and the lateral orbital gyri below the inferior frontal sulcus bilaterally), and right and left antero-medial temporal lobes anterior to Heschl's gyrus.

Supplementary results

Subject characteristics. General demographic and neuropsychological data for patients and HC subjects are summarised in Supplementary Table S1. The mean age of PCA group was significantly lower than each of the other groups; the mean age of the tAD and HC groups did not differ significantly. Subject groups did not differ significantly in gender distribution though females were relatively under-represented in the tAD group. Age and gender were included as covariates of no interest in subsequent analyses. Educational background (years of education) did not differ significantly among the groups. The patient groups did not differ in mean symptom duration or proportion of patients taking cholinesterase inhibitors at the time of testing. General neuropsychological profiles corroborated the clinical syndromic diagnosis in each of the disease groups. Both the PCA and tAD groups performed significantly worse than the HC group across cognitive domains. The PCA group performed significantly worse than the tAD group on the VOSP Objection Decision task and WASI Matrices; the tAD group performed significantly worse than the PCA group on the SRMT for words.

Olfactory symptoms. One patient in the PCA group and two patients in the tAD group reported olfactory symptoms. The PCA patient had olfactory hallucinations prior to onset of other cognitive deficits and subsequently less ability to detect odours while the two tAD patients reported loss of ability to detect odours before the onset of disease. None of the healthy control subjects reported any symptoms to suggest altered olfactory function. No subject gave a history of factors likely to have affected peripheral olfactory function.

Odour identification and categorisation. Group performance profiles on olfactory tests are summarised in Supplementary Table S1 and individual raw data are presented in Supplementary Figure S1. Although the mean identification and categorisation raw scores of PCA patients tended to be higher than those of tAD patients, there was no significant difference in scores between the syndromic groups

either before or after adjusting for age, gender and potentially relevant cognitive severity measures.

Comparing performance on odour identification and categorisation tasks within each group after correcting for guessing, mean corrected identification scores were significantly higher than mean corrected categorisation scores in the HC and PCA groups ($p<0.001$ and 0.028 respectively); no performance difference between tasks was found in the tAD group ($p=0.969$), though this is likely at least in part to have reflected the low mean scores on both tests achieved by tAD patients.

An error analysis of individual odour items in the identification test is shown in Supplementary Figure S2. The profile of odour identification errors across the set of items (expressed as the proportion of subjects making errors on each item) was qualitatively similar across the PCA, tAD and HC groups.

Neuroanatomical data. Anatomical data associated with performance on the odour identification test for the combined PCA and tAD group and for the PCA subgroup alone are summarised in Supplementary Table S3.

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Figure S1. Individual olfactory performance data
The figure shows raw scores on the odour identification test (A) and the odour categorisation test (B) of individual subjects in the healthy control (HC), posterior cortical atrophy (PCA) and typical Alzheimer's disease (tAD) groups.

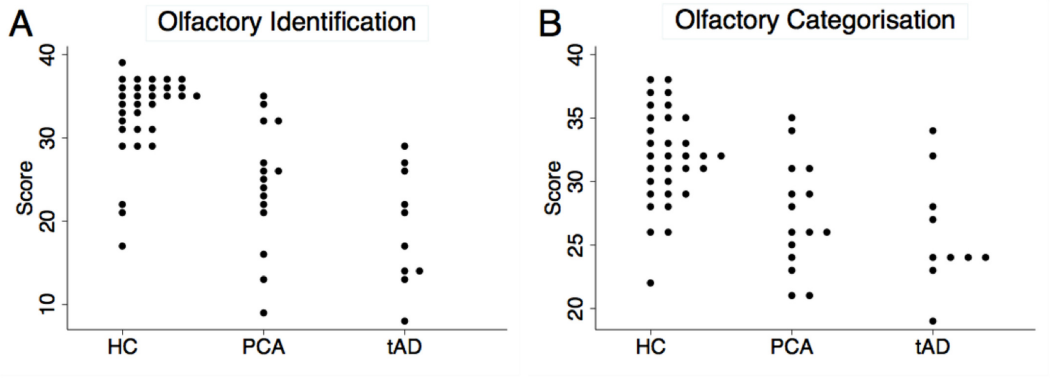
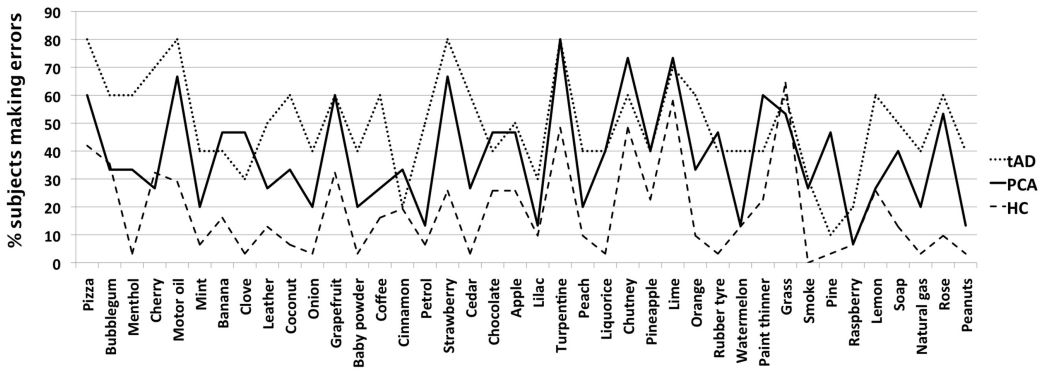


Figure S2. Error analysis profiles for individual items on the odour identification test for all groups



SUPPLEMENTARY TABLES

Table S1. Clinical, general cognitive and olfactory function data for all groups

	HC n = 32	**PCA** n = 15	**tAD** n = 10	**P value** (tAD vs PCA)
Demographic data				
Gender (F:M)	19:13	10:5	3:7	0.082
Age (years)	68.2 (7.3)	62.6 (6.6)	69.6 (6.3)	**0.014**
Education (years)	14.2 (2.7)	12.1 (2.2)	12.6 (2.4)	0.951
Symptom duration (years)	N/A	5.84 (2.39)	7.5 (3.74)	0.187
General cognitive functions				
MMSE (/30)	29.88 (0.34)	19.07 (4.48)	22.9 (5.86)	0.077
SRMT (words) (/25)	24 (1.05)	20.27 (3.67)	16.8 (3.55)	**0.028**
SRMT (faces) (/25)	21.41 (2.60)	18.87 (4.53)	17.75 (3.66)	0.521
GNT (/30)	25.07 (3.45)	16.36 (6.15)	16.6 (7.99)	0.939
VOSP Object decision (/20)	18.07 (3.25)	10.6 (4.64)	16.9 (1.73)	**<0.001**
WASI Vocabulary (/80)	70.25 (5.29)	47.36 (17.04)	55.6 (16.63)	0.277
WASI matrices (/32)	24.54 (2.82)	7.64 (8.12)	19.5 (8.17)	**0.003**
Olfactory functions				
Identification score: raw (/40)	32.94 (4.98)	24.33 (7.51)	19.10 (6.97)	0.093
Identification score: percentile	51.81 (23.71)	14.47 (9.56)	12.3 (10.87)	0.604
Identification score: corrected* (/40)	30.58 (6.64)	19.11 (10.01)	12.13 (9.29)	0.093
Categorisation score: raw (/40)	31.91 (3.73)	27.27 (4.28)	25.9 (4.46)	0.450
Categorisation score: corrected* (/40)	23.81 (7.45)	14.53 (8.57)	11.8 (8.92)	0.450

Mean (standard deviation) values are shown. Significant differences ($p<0.05$) between patient groups are shown in bold. For olfactory function, p-values of unadjusted analyses are shown. Scores on all general cognitive and olfactory functions of the healthy control group were significantly different from those of each patient group. Twelve patents in the PCA group (80%) and 9 patients in the tAD group (90%) were taking a cholinesterase inhibitor at the time of testing.

Key: GNT, Graded Naming Test; HC, Healthy control; MMSE, Mini-mental state examination; n, Number; N/A, not applicable; PCA, posterior cortical atrophy; SRMT, Shorter Recognition Memory Test; tAD, typical Alzheimer's disease; VOSP, Visual Object and Space Perception Battery; WASI, Wechsler Abbreviated Scale of Intelligence. *Corrected identification and categorisation scores were transformed from the raw scores to correct for guessing.

Table S2. Edibility classification of individual UPSIT items

No	Target	Responses				Edibility
		1	2	3	4	
1	**Pizza**	Petrol	Pizza	Peanuts	Lilac	E
2	**Bubblegum**	Chutney	Bubblegum	Liniment	Watermelon	E
3	**Menthol**	Tomato	Baby powder	Strawberry	Menthol	I
4	**Cherry**	Whiskey	Honey	Lime	Cherry	E
5	**Motor oil**	Grass	Pizza	Motor oil	Pineapple	I
6	**Mint**	Dog	Mint	Peach	Cola	E
7	**Banana**	Banana	Garlic	Cherry	Motor oil	E
8	**Clove**	Baby powder	Clove	Spaghetti	Banana	E
9	**Leather**	Clove	Lilac	Leather	Apple	I
10	**Coconut**	Dog	Coconut	Cedar	Honey	E
11	**Onion**	Chocolate	Banana	Onion	Peach	E
12	**Grapefruit**	Soap	Grapefruit	Menthol	Nutmeg	E
13	**Baby powder**	Baby powder	Pineapple	Cheddar cheese	Cherry	I
14	**Coffee**	Paint thinner	Cherry	Coconut	Coffee	E
15	**Cinnamon**	Cola	Cinnamon	Pine	Coconut	E
16	**Petrol**	Rose	Lemon	Peach	Petrol	I
17	**Strawberry**	Strawberry	Chutney	Chocolate	Cedar	E
18	**Cedar**	Cedar	Petrol	Lemon	Liquorice	I
19	**Chocolate**	Lemon	Chocolate	Liquorice	Black pepper	E
20	**Apple**	Menthol	Gingerbread	Apple	Cheddar cheese	E
21	**Lilac**	Lilac	Spaghetti	Coconut	Whiskey	I
22	**Turpentine**	Turpentine	Soap	Dog	Spaghetti	I
23	**Peach**	Chocolate	Peach	Leather	Pizza	E
24	**Liquorice**	Liquorice	Watermelon	Banana	Smoke	E
25	**Chutney**	Pineapple	Chutney	Liquorice	Rose	E
26	**Pineapple**	Smoke	Whiskey	Pineapple	Onion	E
27	**Lime**	Musk	Garlic	Turpentine	Lime	E
28	**Orange**	Cheddar cheese	Orange	Bubblegum	Turpentine	E
29	**Rubber tyre**	Lime	Rubber tyre	Nutmeg	Leather	I
30	**Watermelon**	Spaghetti	Menthol	Orange	Watermelon	E
31	**Paint thinner**	Watermelon	Peanuts	Rose	Paint thinner	I
32	**Grass**	Mint	Gingerbread	Grass	Strawberry	I
33	**Smoke**	Chutney	Grass	Smoke	Peach	I
34	**Pine**	Pineapple	Smoke	Peanuts	Orange	I
35	**Raspberry**	Pizza	Turpentine	Clove	Raspberry	E
36	**Lemon**	Motor oil	Nutmeg	Rose	Lemon	E
37	**Soap**	Soap	Black pepper	Baby powder	Peanuts	I
38	**Natural gas**	Orange	Musk	Cola	Natural gas	I
39	**Rose**	Lime	Rose	Mint	Bubblegum	I
40	**Peanuts**	Peanuts	Lemon	Apple	Liquorice	E

Key: E, Edible; I, Inedible; No, Number

Table S3. Summary of anatomical regions associated with odour identification performance in the combined patient cohort and in the PCA subgroup

Anatomical region	Cluster size (voxels)	Peak MNI coordinates (mm)			T score
		x	y	z	
Combined patient group					
Right parahippocampal gyrus	44	21	-22	-21	5.17*
Right entorhinal cortex	129	22	8	-24	4.71*
Right temporo-parieto-occipital junction	707	58	-52	6	5.56
Right posterior cingulate cortex	156	4	-57	7	5.40
Right posterior inferior temporal gyrus	224	56	-58	-20	4.48
Right premotor cortex	41	51	3	39	4.48
Right hippocampus	71	15	-9	-17	4.30
Right posterior superior temporal sulcus	154	68	-25	-9	4.20
Left hippocampus	55	-32	-9	-20	4.18
PCA subgroup					
Right premotor cortex	499	39	27	45	9.78
Left premotor cortex	54	-9	23	63	7.70
Left planum temporale	112	-44	-28	4	5.66
Right temporo-parieto-occipital junction	76	60	-45	9	5.66
Right hippocampus	92	15	-6	-27	5.24

Data have been thresholded at $p<0.001$ uncorrected for multiple voxel-wise tests over the whole brain volume and clusters larger than 40 voxels are reported. *p value<0.05 after family-wise error (FWE) correction for small volumes of interest.
Key: mm, millimetres; MNI, Montreal Neurological Institute; PCA, posterior cortical atrophy