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Flavour identification in frontotemporal lobar degeneration

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ABSTRACT

Background Deficits of flavour processing may be clinically important in frontotemporal lobar degeneration (FTLD).

Objective To examine flavour processing in FTLD.

Methods We studied flavour identification prospectively in 25 patients with FTLD (12 with behavioural variant frontotemporal dementia (bvFTD), eight with semantic variant primary progressive aphasia (svPPA), five with non-fluent variant primary progressive aphasia (nfvPPA)) and 17 healthy control subjects, using a new test based on cross-modal matching of flavours to words and pictures. All subjects completed a general neuropsychological assessment, and odour identification was also assessed using a modified University of Pennsylvania Smell Identification Test. Brain MRI volumes from the patient cohort were analysed using voxel-based morphometry to identify regional grey matter associations of flavour identification.

Results Relative to the healthy control group, the bvFTD and svPPA subgroups showed significant ($p < 0.05$) deficits of flavour identification and all three FTLD subgroups showed deficits of odour identification. Flavour identification performance did not differ significantly between the FTLD syndromic subgroups. Flavour identification performance in the combined FTLD cohort was significantly ($p < 0.05$ after multiple comparisons correction) associated with grey matter volume in the left entorhinal cortex, hippocampus, parahippocampal gyrus and temporal pole.

Conclusions Certain FTLD syndromes are associated with impaired flavour identification and this is underpinned by grey matter atrophy in an anteromedial temporal lobe network. These findings may have implications for our understanding of abnormal eating behaviour in these diseases.

INTRODUCTION

The brain mechanisms that process flavours are of considerable clinical and neurobiological interest, but remain poorly understood. Flavour processing entails a hierarchy of cognitive operations that integrate gustatory, olfactory and other sensory inputs for mnemonic, semantic and affective analysis.^{1–6} Impairments of flavour processing and particularly flavour agnosia have been associated with focal anterior temporal lobe damage and, in the neurodegenerative disease spectrum, with frontotemporal lobar degeneration (FTLD), especially the syndrome of semantic dementia or semantic variant primary progressive aphasia (svPPA).^{7–12} Limited available data indicate that patients with FTLD retain the ability to encode flavours

perceptually,^{11–13} suggesting that deficits of flavour processing in this group may be primarily semantic or associative in nature. Abnormal eating behaviours are a cardinal feature of behavioural variant frontotemporal dementia (bvFTD)^{13–19}: such abnormalities could be at least partly underpinned by deficits of flavour processing, and have been linked to cortical atrophy in a distributed network including the orbitofrontal cortex (OFC), anterior insula and striatum.^{13–19} Overlapping grey matter correlates have been identified for odour identification performance in neurodegenerative diseases,^{20–22} and these correlates align with the distributed frontotemporal-subcortical network implicated in flavour processing in functional imaging studies of the healthy brain.^{2–6} Previous group analyses of patients with FTLD have examined processing of elementary taste qualities and recognition of the multimodal stimuli embodied in natural foods.¹³ However, the neuropsychology and neuroanatomy of flavour processing have not been systematically assessed in FTLD.

Here we assessed flavour identification and its brain basis prospectively in a cohort of patients diagnosed with each of the major clinical syndromes of FTLD: bvFTD, svPPA and non-fluent variant primary progressive aphasia (nfvPPA). Flavour identification was assessed using a new battery, in relation to odour identification and general neuropsychological functions. The structural neuroanatomical associations of flavour and odour identification were assessed using voxel-based morphometry. On clinical and neuroanatomical grounds,^{1–19} we hypothesised that deficits of flavour identification would be exhibited by each of the syndromic subgroups of FTLD. Based on prior anatomical data,^{1–8} we further hypothesised that these deficits are linked to grey matter loss involving higher-order gustatory and olfactory association cortices and areas engaged in multimodal semantic processing in the anterior temporal lobes and inferior frontal lobes.

METHODS

Subjects

Twenty-five consecutive patients (18 male, 20 right-handed, mean (standard deviation) age 65.2 (7.3) years) fulfilling consensus criteria for a diagnosis of FTLD²³ were recruited from the tertiary Specialist Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery (demographic and clinical data for all subjects are summarised in table 1). The patient cohort comprised each of the three canonical FTLD syndromic

Table 1 Summary of subject characteristics and behavioural data

	bvFTD n=12	svPPA n=8	nvPPA n=5	Controls n=17
Demographic data				
Gender M : F	12 : 0	5 : 3	1 : 4	8 : 9
Handedness R : L	8 : 4	7 : 1	5 : 0	15 : 2
Age	66.1 (7.6)	66.1 (6.9)	62.7 (8.2)	66.2 (8.1)
General cognitive functions				
MMSE (/30)	23.5 (6.0)*	22.8 (5.6)*	19.2 (10.8)	29.9 (0.3)
NART (/50)	26.5 (16.1)*	18.7 (11.9)*	17.0 (15.3)*	42.7
RMT				
Words (/50)	32.1 (11.5)*†	32.6 (7.3)*†	42.5 (4.8)	48.2 (2.3)
Faces (/50)	32.4 (5.7)*	31.1 (8.3)*	33.3 (7.1)	42.4 (4.3)
Digit span				
Forward (/12)	7.4 (2.6)	7.1 (2.9)	4.8 (2.2)	9.0 (1.7)
Reverse (/12)	5.2 (2.8)	6.0 (2.9)	3.5 (3.0)	6.6 (1.7)
BPVS (/150)	119.5 (42.3)*, **	68.1 (54.6)*	117.2 (50.8)	148.4 (1.1)
GNT (/30)	9.1 (6.7)*, **	1.1 (2.8)*	9.2 (12.2)*	25.9 (3.1)
Arithmetic (/24)	13.3 (7.3)†	10.8 (9.9)	3.0 (0.0)*	14.6 (4.6)
VOSP object decision (/20)	15.7 (3.1)*	14.3 (4.3)*	15.6 (3.2)	19.4 (0.7)
WASI				
Vocabulary (/80)	41.5 (22.6)*	21.8 (20.8)*	19.4 (19.1)*	70.5 (4.3)
Block design (/71)	19.6 (15.1)*	31.6 (17.9)	23.6 (20.2)	46.2 (11.2)
Similarities (/48)	19.6 (14.0)*	10.3 (11.9)*	12.4 (15.9)*	39.1 (5.1)
Matrices (/32)	13.0 (8.3)*	18.8 (8.4)	15.8 (11.2)	24.7 (2.8)
Stroop ink colour naming (s)	72.2 (19.1)*	111.8 (44.6)*	124.0 (48.5)*	57.3 (9.6)
Stroop word naming (s)	25.9 (10.8)	34.9 (11.7)*	58.4 (28.2)*	20.4 (3.2)
Experimental assessments				
Flavour identification (/20)	12.3 (4.0)*	9.4 (2.9)*	15.0 (3.2)	18.1 (1.3)
Flavour categorisation (/20)‡	17.0 (2.4)*	16.4 (1.7)*	18.8 (0.8)*	19.7 (0.6)
UPSIT (/40)	16.6 (8.4)*	17.5 (6.6)*	26.2 (6.0)*	34.7 (3.0)
Abnormal eating behaviour (n)§	6	5	2	N/A
Flavour symptoms (n)	1	1	0	N/A
Odour symptoms (n)	4	0	0	N/A

Mean (standard deviation) values are shown.

*Significantly worse than controls ($p < 0.05$); **significantly different from svPPA ($p < 0.05$); †significantly different from nvPPA ($p < 0.05$); ‡see text for details.

§Most patients with abnormal eating behaviour exhibited hyperphagia and pathological sweet tooth; one patient with bvFTD exhibited a preference for eating unusual items.

BPVS, British Picture Vocabulary Scale (McCarthy and Warrington, 1992); bvFTD, behavioural variant frontotemporal dementia; GNT, Graded Naming Test (Warrington, 1997); MMSE, Mini-Mental State Examination score (Folstein *et al.*, 1975); NART, National Adult Reading Test (Nelson, 1982); nvPPA, non-fluent variant primary progressive aphasia; RMT, Recognition Memory Tests (Warrington, 1984); svPPA, semantic variant primary progressive aphasia; Stroop, Delis-Kaplan Executive Function System Stroop test (Delis *et al.*, 2001); UPSIT, University of Pennsylvania Smell Identification Test (British version); VOSP, Visual Object and Space Perception Battery (Warrington and James, 1991); WASI, Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

subtypes: 12 patients had bvFTD, characterised by profound personality and behavioural change with frontal and temporal lobe atrophy on brain magnetic resonance imaging (MRI)¹⁴; eight patients had svPPA, characterised by breakdown of verbal and non-verbal knowledge systems with asymmetric, predominantly left-sided temporal lobe atrophy on MRI; and five patients had nvPPA, based on the presence of speech apraxia and/or agrammatism and relatively intact single-word comprehension, with asymmetric predominantly left-sided perisylvian atrophy on MRI.²⁴ All patients included in this series had typical clinical and MRI profiles of bvFTD, svPPA or nvPPA, as previously described and would have fulfilled recent revised consensus criteria for probable bvFTD or PPA.^{14, 24}

All patients had an assessment of general neuropsychological functions (see table 1), which supported the clinical syndromic classification. Seventeen healthy control subjects with no history of neurological or psychiatric illness nor history of significant head injury, and matched with the patient group for age and educational background, were also

assessed. Groups varied by gender composition, male subjects being relatively over-represented in the patient cohort overall and in the bvFTD subgroup, in particular (table 1); gender was therefore incorporated as a covariate of no interest in analyses. The presence of any significant performance differences on the neuropsychological assessments between the patient subgroups and controls was examined using standard *t* tests.

Before recruitment, questionnaire data were gathered for all subjects to screen for any prior history of chronic olfactory or gustatory dysfunction (no patients were excluded from the study on this basis). In addition, patients' caregivers completed the Cambridge Behavioural Inventory²⁵ to provide a rating of the presence and severity of any abnormal eating behaviours exhibited by the patient. We also recorded any symptoms of altered flavour or olfactory processing previously reported by the patient or inferred by their caregiver since the onset of the illness (flavours or odours more or less intense, more or less pleasant, or otherwise altered in quality).

Informed consent to participate in the study was obtained for all subjects and the study was approved by the local institutional research ethics committee in accordance with Declaration of Helsinki guidelines.

Experimental assessment of flavour and odour identification

Identification of flavours was assessed using a new battery. Flavour stimuli were commercially available jelly bean candies (JellyBelly). Jelly beans have been used previously to assess flavour processing in patients with FTLT and other dementias in individual case studies,^{11 12} and offer the advantages of wide sampling from the flavour 'space' with relatively uniform stimulus quantity and presentation and minimal extraneous cues to flavour identity. Twenty flavours, highly familiar and identifiable by healthy older British residents (as previously determined using these stimuli¹¹), were presented sequentially. In each trial, three word–picture combinations representing the target flavour, a semantically related foil item and a semantically more distant foil item (eg, target, orange; related foil, lemon; distant foil, popcorn) were shown on a computer monitor and also read aloud to the subject (all flavours and foils are listed in supplementary Table S1 online). The flavour battery was constructed such that target flavours were either fruits or non-fruit items with equal probability; on each trial, the semantically related foil was derived from the same broad food category as the target flavour (ie, 'fruit' or 'non-fruit') and the semantically distant foil was derived from the other category. The task in each trial was to select the word–picture combination matching the target flavour in a three-alternative, forced-choice procedure. Presentation of word–picture combinations was designed to reduce dependency on verbal labelling, as this is likely to be disproportionately impaired in patients with svPPA.

Flavours were presented in randomised order. Jelly beans were placed in the subject's hand out of vision by the examiner, and the subject was instructed to lift them directly to the mouth, to minimise any use of colour cues. Each flavour was administered only once and no feedback about performance was given during the test. Subjects were instructed to rinse their mouth between flavour trials. Visual word–picture trials were presented and subject responses were collected for offline analysis on a notebook computer running Matlab7.0 (<http://www.mathworks.com>).

To provide an index of odour identification performance for comparison with flavour identification, all subjects completed the British version of the University of Pennsylvania Smell Identification Test (UPSIT). This is a widely validated 40-item, four-alternative, forced-choice odour to word matching procedure.²⁶ For this study, the standard UPSIT procedure was modified as previously described,^{10 11} such that word–picture combinations corresponding to the target and each of the three foil items were presented on each trial. As in the flavour identification test, this modified procedure was designed to reduce dependency on a single response modality.

Behavioural data were analysed under Stata using an analysis of variance linear regression model. The model incorporated scores on the flavour and odour identification tests and group membership (bvFTD, svPPA, nfvPPA, healthy control), together with measures of general executive performance (the Stroop ink colour naming score, a measure of interference task response inhibition) and verbal semantic knowledge (British Picture Vocabulary Scale score), subject age and gender as covariates of no interest which might have influenced performance on the experimental tests. For each subject, error trials on the

flavour identification task were classified according to whether these selected the semantically related foil or the semantically more distant foil, and a 'flavour categorisation' score ((number of trials correct+number of semantically related errors)/total number of trials) was derived. Correlations between flavour and odour identification scores were examined in both the patient and control groups. Correlations between flavour and odour identification scores and the presence/severity of abnormal eating behaviours (as indexed using the Cambridge Behavioural Inventory) were also assessed.

Brain image acquisition and analysis

Brain MR images were acquired for all patients on a Siemens Trio TIM 3T scanner (Siemens Medical Systems). T₁-weighted volumetric magnetic resonance images were acquired using a three-dimensional magnetisation prepared rapid gradient echo (MP-RAGE) sequence producing 208 contiguous 1.1 mm thick sagittal slices with 28 cm field of view and a 256×256 acquisition matrix, giving approximately isotropic 1.1 mm cubic voxels.

Brain images for the patient cohort were analysed using voxel-based morphometry under MATLAB 7.0 and SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/>) following previously described procedures.^{27–29} Native space study images were affine-registered using the standard SPM2 T1 template, and initial grey matter segmentation was performed. Normalisation parameters were estimated for warping these grey matter segments onto the SPM2 grey matter template in Montreal Neurological Institute (MNI) stereotactic space, and these normalisation parameters were then used to warp the original native space images. Segmentation of the normalised images into grey matter was then performed and these segmentations modulated with the volume changes from the normalisation step. Each grey matter segment had non-brain tissue removed according to a brain mask derived from the corresponding original image using semi-automated segmentation software.³⁰ The images were then smoothed with an 8 mm isotropic Gaussian kernel.

Linear regression was used to examine voxel-wise associations between regional grey matter volume and performance on flavour and odour identification tasks, modelling voxel intensity as a function of identification score and incorporating as covariates of no interest age, total intracranial volume (calculated using a previously described procedure³¹) and Stroop ink colour naming score (as an index of general executive capacity and disease severity). A separate model incorporating additional covariates of FTLT subgroup membership (bvFTD, svPPA or nfvPPA) was also analysed in order to assess neuroanatomical associations of flavour identification performance after taking clinical syndrome into account. In addition, grey matter associations of flavour and odour identification were assessed in a separate analysis restricted to the bvFTD subgroup (the largest syndromic subgroup here). After model estimation an explicit mask was applied using a masking strategy that excluded any voxels for which >30% of images had intensity value <0.05 (ie, consensus 70%, threshold 0.05). This was motivated by previous evidence that SPM2 default threshold masking may exclude the most severely affected regions from statistical analysis in subjects with marked focal atrophy.²⁹

Statistical parametric maps were assessed both at a voxel-wise significance threshold $p<0.001$ uncorrected over the whole brain volume and at a threshold $p<0.05$ after false discovery rate (FDR) correction for multiple voxel-wise comparisons,³² over the whole brain volume and within the anatomical small volumes of interest specified by our prior anatomical hypotheses. These anatomical small volumes were derived by

manual tracing from the template brain image using MRICro (<http://www.mccauslandcenter.sc.edu/micro/index.html>) and comprised bilateral OFC (including the orbital surface of both frontal lobes and the lateral orbital gyri below the inferior frontal sulcus bilaterally), right and left insula cortex and right and left temporal lobes anterior to Heschl's gyrus.

RESULTS

Behavioural data

Behavioural data for patients and control subjects are summarised in table 1 and figure 1. Abnormal eating behaviours (predominantly, hyperphagia and pathological sweet tooth) were exhibited by 50% of patients with bvFTD, 63% with svPPA and 40% with nfvPPA. Olfactory symptoms were reported for 33% of patients with bvFTD but not for patients in the other syndromic subgroups, while 8% of patients with bvFTD and 13% with svPPA but no patients with nfvPPA exhibited symptoms of altered flavour processing. Alterations of both eating behaviour and chemosensory function were reported for 12% of the patient cohort overall.

On the flavour identification task, the bvFTD subgroup and the svPPA subgroup performed significantly worse ($p<0.05$) than the healthy control group; there was no significant performance difference ($p=0.46$) between the nfvPPA subgroup and healthy controls (perhaps reflecting wide individual performance variation within the nfvPPA group) nor between the three FTLD subgroups. On the odour identification task, each of the three FTLD subgroups performed significantly worse than the healthy control group. However there were no significant performance differences between the FTLD subgroups. Eight patients in the bvFTD group, four in the svPPA group and one in the nfvPPA group scored less than the 5th centile based on published normative data for the UPSIT.²⁶ Examining

the types of errors made on the flavour identification task, patients and healthy control subjects were more likely to select semantically related than semantically unrelated foils, both for fruit and for non-fruit items: for each group, identification within general flavour categories (ie, 'fruit–non-fruit' flavour categorisation, or superordinate flavour knowledge) was better preserved than identification of particular flavours (see table 1). Across the patient cohort, semantically related errors (total of 131 errors) were more frequent than semantically more distant errors (total of 71 errors); and in all but two cases (both with bvFTD), individual subjects made more frequent errors on semantically related than semantically more distant foil items. All three patient groups showed a deficit of flavour categorisation relative to the healthy control group. However, the syndromic subgroups did not differ in their ability to categorise the target flavour.

Flavour and odour identification scores were significantly correlated in the patient group (Spearman's ρ 0.32, $p<0.05$). There was no significant correlation between flavour and odour identification scores in the control population; however, this may reflect controls' near-ceiling performance on the flavour task. There was no evidence of correlation between flavour or odour identification performance and the presence or severity of abnormal eating behaviours (see table 1).

Neuroanatomical data

Performance on the flavour identification task across the FTLD cohort was positively associated with grey matter volume in a network of areas in the left anterior temporal lobe, including entorhinal cortex, hippocampus and parahippocampal gyrus (peak MNI coordinates=−29, −18, −29; z-score=3.77) and temporal pole (peak MNI coordinates=−35, 11, −33; z-score=3.43) ($p<0.05$ after FDR correction for multiple voxel-wise comparisons within the anatomical small volume of interest). Statistical parametric maps of grey matter regions associated with flavour identification performance are shown in figure 2. These same regions remained associated with flavour identification performance after incorporation of covariates of FTLD subgroup membership and in the additional subgroup analysis restricted to the bvFTD subgroup (each assessed at a relaxed threshold $p<0.01$ uncorrected, owing to the reduced degrees of freedom for detection of genuine effects).

No significant grey matter associations were identified for flavour or odour identification performance at threshold $p<0.05$ after correction across the whole brain volume, nor for odour identification at $p<0.05$ after FDR correction for multiple voxel-wise comparisons within the anatomical small volumes of interest.

DISCUSSION

Here we have demonstrated deficits of flavour identification in two major clinical syndromes of FTLD, bvFTD and svPPA, relative to healthy control subjects. The profile of odour identification performance essentially paralleled flavour identification across subgroups, and there was a significant correlation between flavour and odour identification scores in the patient population. Chemosensory identification deficits here were not simply attributable to general executive or semantic impairment, since the deficits were demonstrated after adjusting for these other potentially relevant cognitive variables. An error analysis showed that identification of general flavour categories was better preserved overall than identification of particular flavours. This pattern would be difficult to explain were impaired flavour identification simply the result of impaired cross-modal

Figure 1 Raw scores for flavour identification of individual subjects by subgroup. bvFTD, behavioural variant frontotemporal dementia; nfvPPA, non-fluent variant primary progressive aphasia; svPPA, semantic variant primary progressive aphasia.

Figure 2 Grey matter associations of flavour identification in patients with frontotemporal lobar degeneration. Statistical parametric maps (SPMs) show areas in which grey matter volume was associated with behavioural performance in a voxel-based morphometric analysis. SPMs are displayed on coronal (left) and axial (right) sections of the template MR brain image in Montreal Neurological Institute (MNI) standard stereotactic space, at threshold $p < 0.001$ uncorrected; the grey matter associations shown were significant ($p < 0.05$) after correction for multiple comparisons within the prespecified anatomical small volume (see text). The plane of each section is shown (MNI coordinates in mm); for all sections, the left hemisphere is displayed on the left. This figure is only reproduced in colour in the online version.

labelling. Taken together, the behavioural data suggest that FTLTD is often accompanied by a semantic deficit of flavour processing. Relatively greater vulnerability of specific compared with superordinate flavour knowledge would be consistent with the cognitive organisation previously demonstrated for other knowledge modalities in neurodegenerative diseases.³³ The lack of a significant flavour processing deficit for the nvPPA subgroup here may partly reflect the small size of this cohort. However, it is also possible that flavour identification is relatively less vulnerable in nvPPA than in bvFTD or svPPA, perhaps reflecting differential involvement of chemosensory association cortices (in particular, brain regions engaged in semantic processing of flavours) in these different subgroups of FTLTD.^{14 24} Related to this, perceptual processing of flavours was not directly assessed in this study. It is likely that perceptual and semantic chemosensory mechanisms interact and may contribute differentially to chemosensory function in different FTLTD syndromes.

Flavour identification deficits here were associated with a profile of regional grey matter atrophy in the left anteromedial temporal lobe, overlapping brain regions previously associated with stimulus identification in other modalities in neurodegenerative disease.^{34 35} It is noteworthy that these neuroanatomical associations were not driven simply by general cognitive decline nor by inclusion of a particular disease group (such as svPPA, itself associated with focal left temporal lobe atrophy). Associations were identified even after taking disease severity and syndromic subgroup into account, suggesting that this anteromedial temporal lobe network indexes flavour knowledge across the FTLTD syndromic spectrum.

Grey matter correlates of flavour identification included entorhinal cortex, hippocampus, parahippocampal gyrus and temporal pole. In line with our prior anatomical hypotheses, this neuroanatomical profile comprises brain substrates in the anteromedial temporal lobe previously implicated in the associative processing of chemosensory stimuli.^{1–12} The precise role of each of these structures in flavour analysis remains unclear. However, the hippocampus and parahippocampal region link incoming sensory stimuli with behavioural context,^{36–38} while the temporal pole integrates semantic processing in different sensory modalities,³⁹ functions that are likely to be integral to flavour processing.

These data in this neurodegenerative disease cohort amplify previous work in patients with dementia,^{9–12} and with focal

brain damage^{7 8}: the evidence collectively suggests that the anteromedial temporal lobe is critical for the semantic analysis of flavours. We do not wish to overemphasise the laterality of the present effects: previous evidence suggests that both the right and the left temporal lobes are involved in flavour processing,^{5 7 8} and it is likely that both anterior temporal lobes cooperate in a bihemispheric semantic processing network.⁴⁰ However, the left-sided correlate detected here is consistent with a requirement for verbal semantic labelling of flavour stimuli in the experimental task.

We did not identify a correlate of flavour identification performance in the OFC in the present FTLTD cohort: this is perhaps somewhat surprising in light of previous evidence implicating OFC in processes relevant to flavour identification.^{2 3} We speculate that this may reflect the essentially ‘cognitive’ (ie, semantic) nature of our task here, with minimal requirement for subjects to process the flavour stimuli for behavioural value or reward potential (flavour dimensions which might be particularly likely to engage the OFC²).

From a clinical perspective, our findings have implications for our understanding of abnormal eating behaviour in dementia syndromes. It is plausible a priori that altered flavour processing might contribute to altered eating behaviour; in particular, loss of understanding of food items might lead to unusual or inappropriate food preferences or faddism. Abnormal eating behaviours are, however, complex and probably multifactorial: in addition to semantic gustatory and olfactory impairments, perceptual alterations and more generic behavioural derangements such as disinhibition and impulsivity may also contribute.¹⁹ Standard behavioural rating scales are not equipped to characterise such altered eating behaviours in detail. Although we did not find evidence of a simple correlation between eating behaviour and flavour identification here, this may reflect both the relatively small numbers of patients studied and the relatively crude metrics used to assess eating behaviour (table 1).

This study has several limitations and suggests directions for future work. Our findings are based on data from a relatively small cohort of patients representing a particular disease cluster (FTLD), at a single time point, using a single measure of flavour processing with standard behavioural indices and a single neuroimaging technique. There was a relative gender imbalance in our patient groups: gender is an important factor in chemosensory function and in the small cohort here might still have influenced performance profiles even after statistical

adjustment. The deficits of flavour processing and neuroanatomical associations identified here suggest that impaired flavour processing is an important feature in this degenerative disease population with predictable anatomical substrates and the potential for clinical consequences. This work should motivate further studies in a range of neurodegenerative diseases with larger patient cohorts. These studies should assess different levels of flavour processing (perceptual and semantic) and the longitudinal evolution of flavour deficits in relation to other cognitive and behavioural features, using customised behavioural batteries. The close linkage between flavour processing, food ingestion and emotional value could constitute an informative model system for assessing disease-related changes in complex behaviour, using multimodal structural and functional imaging approaches.

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Contributors RO 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. CJM was involved in study design, acquisition of behavioural and neuroimaging data and drafting and critically revising the paper. AHB was involved in study design, acquisition of general neuropsychological data and in drafting 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.

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Competing interests None.

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