Biological bases of eating behavior disturbance in frontotemporal dementia

Running title: Eating and FTD brain networks

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Abstract word count: 349

Word count: 3029

References: 49

Figures: 2

Tables: 3

Supplementary files: 1

Date of revision; November 2015

Key words: Frontotemporal dementia, eating, metabolism, reward, sucrose, behavior

Abstract

Importance: Abnormal eating behaviors are common in frontotemporal dementia (FTD), yet their exact prevalence, severity and underlying biology are not understood.

Objective: Using ecologically valid methods derived from obesity research, we aimed to define the severity of abnormal eating behavior and sucrose preference and their neural correlates in behavioral variant FTD (bvFTD) and semantic dementia (SD).

Design, setting and Participants: Forty nine dementia patients **(**bvFTD n=19;SD n=15;Alzheimer's disease patients(AD) n=15) were recruited and eating behavior compared to 25 healthy controls.

Main outcomes and measures: Patients participated in an ad-libitum breakfast test meal, where total caloric intake and food preferences were measured. Sucrose preference was tested by measuring liking ratings of 3 desserts of varying sucrose content. Voxel-based morphometry analysis of whole-brain 3-T high-resolution MRI brain scans was used to determine the grey matter density changes across groups and their relations to eating behaviors.

Results: At an ad-libitum test meal, all bvFTD patients had increased total caloric intake (mean=1344 calories) compared to AD (710 calories), SD (573 calories) and control groups (mean=603 calories)(p<0.001). On the experiment involving tasting of desserts of varying sugar content both bvFTD and SD patients exhibited a strong sucrose preference compared to the other groups. Increased caloric intake correlated with atrophy in discrete neural networks that differed between bvFTD and SD, but included the cingulate cortices, thalami, and cerebellum in bvFTD, with the addition of the orbito-frontal cortices and nucleus accumbens in SD. A distributed network of neural correlates was associated with sucrose preference in FTD.

Conclusions and relevance: Marked hyperphagia is restricted to bvFTD, present in all patients with this diagnosis, and support its diagnostic value. Differing neural networks control eating behavior in bvFTD and SD, and are likely responsible for the differences seen, with a similar network controlling sucrose preference. These networks share structures controlling cognitive-reward, autonomic, neuroendocrine and visual modulation of eating behavior. Delineating the neural networks involved in mediating these changes in eating behavior may enable treatment of these features in patients with complex medical needs, and aid in our understanding of structures controlling eating behavior in both FTD and normal individuals.

Introduction

Marked changes in eating behavior are one of the criteria for the diagnosis of behavioral-variant frontotemporal dementia (bvFTD)[1]. Eating behavior changes are also increasingly recognized in semantic dementia (SD), with rigidity (eating same foods repeatedly) and changes in food preference reported.[2,3]

Yet despite their central role in the diagnosis of bvFTD, eating changes have been measured relying mostly on caregiver questionnaires.[2-6] This approach is unlikely to provide a complete account of the extent and severity of changes due to subjective interpretation of a patient's behavior and a tendency for patients to hide these behaviors.

Neuroimaging studies have suggested that overeating in bvFTD is associated with atrophy in the right ventral, insula, striatum and orbitofrontal cortices.[7] Retrospective data analyses have related eating behavior to changes in the right ventral putamen and pallidum, key regions in reward-seeking circuits of the brain.[6] Caregivers of FTD patients often report sweet food seeking behaviors, a behavior that has been associated with grey matter loss involving bilateral orbitofrontal cortices and the right anterior insula.[5]

Ecologically valid assessments are crucial in understanding the characteristics of eating behaviors in these debilitating disorders. Research in obesity has used 'real meals' to examine eating behavior and changes in food preferences, including sucrose preference.[8-10] The present study aimed to: (i) quantify eating behavior in both bvFTD and SD patients using ecologically valid methods, notably an ad-libitum breakfast and sucrose preference approach, and (ii) identify the neural correlates of these eating behaviors using voxel-based morphometry analyses of high-resolution structural brain MRI.

Methods and materials

Patients

Forty-nine dementia patients (19 bvFTD, 15 SD, 15 AD) were recruited at Neuroscience Research Australia. All patients met current clinical diagnostic criteria for probable bvFTD, SD or AD.[11-14] Disease severity was established using the Frontal Rating Scale (FRS).[15] In addition, 25 healthy controls were recruited from a panel of healthy study volunteers in Sydney (19 individuals) and Cambridge, UK (6 individuals). Healthy controls scored above 88/100 on the Addenbrooke's Cognitive Examination-Revised.[16] The patient and control groups were matched specifically for age, sex and BMI to remove their potential effects on eating behavior. In addition to the ad-libitum test meal (see procedure below), changes in eating behavior were measured using caregiver-based questionnaires: the Appetite and Eating Habits Questionnaire (APEHQ)[2,3] and the Cambridge Behavioral Inventory (CBI).[17] Height and weight were measured (shoes removed) and body mass index (BMI) derived (unit: (kg)/(meter)^2).

Study 1: Ad-libitum test meal

Participants presented following a 10-hour fast. The night prior, they were supplied with a meal representing 35% of their calculated predicted total daily intake. Following taking of a fasting blood sample, participants were offered an ad-libitum breakfast meal buffet style and left alone for 30 minutes to eat their breakfast. This buffet comprised a selection of foods including cereals, bread, sweet and savory foods (Total=5424 calories). After completion, each item was weighed to calculate the total

amount consumed in calories and total macronutrients (% fat, protein, carbohydrate and sugar) consumed.

Study 2: Sucrose preference

Following 4 hours of fasting, patients participated in a dessert tasting. Three options of Eton Mess dessert varying in sugar content were offered (A: 26%, B: 39%, C: 60%). Participants were given 10g tasting pots of the each dessert and asked to rank on a visual analogue scale from 0 to 10 how much they liked each dessert and how sweet it was. They were then left in the room with 1 large bowl of each dessert for 15 minutes and asked to consume the dessert until they were comfortably full. The total amount of each dessert consumed in grams was documented.

Imaging analyses

Brain MRI acquisition and analyses

All participants underwent whole-brain 3-T high resolution T1 imaging on the day of the eating experiments. MRI data were analysed with FSL-VBM, a voxel-based morphometry analysis [18] using the FSL-VBM toolbox from the FMRIB software package (http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html)[19] (see references [20,21] for full details of the methods). A voxel-wise general linear model was employed to investigate grey matter intensity differences through permutation-based non-parametric testing[22] with 5000 permutations per contrast. Differences in cortical grey matter intensities between patients (bvFTD, SD, AD) and control subjects were assessed using *t*-tests. Clusters were extracted using the threshold free cluster enhancement method and corrected for Family Wise Error at $p < .05$.

Next, correlations between total caloric intake and regions of grey matter atrophy were investigated in each FTD patient group separately (i.e., SD; bvFTD, given the

differences in behavior). For sucrose preference ratings, the bvFTD and SD groups were combined, due to similar behavior, to examine correlations with liking ratings for the most sweet dessert (60% sucrose) and regions of grey matter intensity. For additional statistical power, a covariate only statistical model with a [-1] t-contrast was used, providing an index of association between decreasing grey matter volume and increased intake/sucrose preference ratings. Age was included as a nuisance variable in the covariate analyses. An unbiased whole-brain approach was used across all atrophy and covariate VBM analyses. Anatomical locations of significant results were overlaid on the MNI standard brain, with coordinates of maximum change provided in MNI stereotaxic space. For all covariate analyses, clusters were extracted using a voxelwise approach and corrected for False Discovery Rate at $p < .05$. Anatomical labels were determined with reference to the Harvard-Oxford probabilistic cortical atlas.

Standard approvals, and consents

This study was approved by the South Eastern Sydney Area Health District and the University of New South Wales human ethics committees. Written informed consent was obtained.

Statistical analyses

Data were analyzed using IBM SPSS statistics (version 21.0). Kolmogorov-Smirnov tests were run to determine suitability of variables for parametric analyses. Analyses of variance (ANOVA), followed by Tukey post hoc tests, were used to determine group differences for the demographic/clinical (age, ACE-R, disease duration, educational background), and eating (APEHQ, total CBI, CBI eating, BMI), ($p \leq 0.05$

regarded as significant) variables. Because of non-normal distribution, group differences in total caloric intake, nutrient intake, and sweet likeness and perceived sweetness scores on the dessert experiment and cognitive measures of executive function and disinhibition were analyzed using non-parametric Kruskal-Wallis tests followed by post hoc Mann Whitney *U* tests corrected for multiple comparisons ($p \leq 0.01$ regarded as significant). Relationships between total intake on the breakfast test meal, BMI and dessert sweet preference with eating behavior surveys, cognitive scores, and disease severity were further explored using Spearman Rank correlations corrected for multiple comparisons ($p \leq 0.01$ regarded as significant).

Results

Demographic variables did not differ across groups (Table 1) (all p values>0.182). Group differences were observed on measures of cognition (ACE-R) and measures of executive function and disinhibition and disease severity (Table 1). The bvFTD group was more functionally impaired relative to the AD (FRS; $p = 0.009$) and SD groups ($p < 0.001$). The bvFTD group showed more severe eating disturbance based on caregiver surveys (all p values<0.005). Groups were matched for BMI (Table 1).

Study 1: Breakfast ad-libitum test meal

Group differences were present for total caloric intake as measured by the ad-libitum test meal ($H(3) = 40.5$, $p<0$ .001) (Figure 1A and Table 2). Notably, total caloric intake in the bvFTD group showed no overlap with the AD and control groups. No group differences were present for macronutrient intake (Table 2) (all p values>0.245), apart from total protein intake, ($H(3) = 18.6$, $p<0.001$) with the

control group consuming a higher percentage protein intake compared to the bvFTD group (U = 61, $p<0.001$).

Study 2: Sucrose preference dessert experiment

Five SD patients refused to partake in the experiment, stating they did not like the dessert. The mean liking ratings for each of the desserts (A: 26% sucrose, B: 39% sucrose, C: 60% sucrose) and the perceived sweetness of each dessert are reflected in Figure 1B. No group differences were observed for the perceived sweetness of each dessert: all groups ranked A as the least sweet, B as middle sweetness and C as most sweet. (A: $H(3)= 5.3$ $p = 0.150$; B: $H(3) = 4.2$ $p = 0.243$; C: $H(3) = 1.8$ $p = 0.615$). In contrast, group differences emerged regarding the liking rating of each dessert: a group effect was present for the least sweet dessert (A) ($H(3) = 16.7$ $p=0.001$) with the bvFTD group liking this dessert less than the AD (U= 38.5 $p=0.002$), SD (U= 37.0 $p=0.010$) and control (U= 67.5 $p<0.001$) groups. No group differences were evident on liking of the middle sweetness dessert (B) ($H(3) = 3.1$ $p = 0.377$). For the most sweet dessert (C), a group effect was again observed ($H(3) = 34.7$, $p<0.001$), with the bvFTD group liking it more than the AD (U= 11.0, $p <0.001$) and control (U = 27.0, $p < 0.001$) groups. The liking rating of dessert C did not differ between bvFTD and SD. The SD group liked dessert C more than the AD (U= 11.0 $p =0.001$) and control (U= 18.0 $p<0.001$) groups.

Total intake (Table 2) of each dessert significantly varied across groups (A: $H(3) = 21.7$, $p< 0.001$); B: $H(3) = 28.4$ $p < 0.001$; C: $H(3) = 30.1$ $p<0.001$), with the bvFTD group consuming more of each dessert than the other groups (all p values<0.005).

Correlations between eating behavior and clinical/functional measures

Combining all patient groups, total caloric intake on the ad-libitum breakfast test meal was associated with total scores on caregiver ratings of eating changes on the APEHQ (r_s = .496, p<0.001), CBI Eating (r_s = .502, p< 0.001), overall ratings of behavioral changes (CBI total: r_s = .598, p < 0.001) and level of functional impairment (FRS: r_s = -.599, p< 0.001). BMI also correlated with CBI eating (r_s = 0.336, p = 0.005), CBI total (r_s = 0.316, p=0.009), and FRS scores (r_s = -.363, p= 0.012). BMI did not correlate with total caloric intake on the breakfast test meal (r_s =.148, p=0.268). Liking of the least sweet dessert (i.e., Dessert A) was negatively correlated with total APEHQ score (r_s =-.540, p < .001), and total calories consumed during the breakfast study (r_s = -.414, p=.001). In other words, a lower preference for the least sweet dessert correlated with higher abnormal eating behavior. Increased liking of the most sweet dessert (i.e., Dessert C) correlated with total CBI eating (r_s = .594, p< 0.001), CBI total (r_s = .642, p < .001), FRS (r_s = -.464, p= .003), and total calories consumed for the breakfast study (r_s =.539, p < 0.001). No correlations were present between total caloric intake and measures of executive function and disinhibition.

Voxel-based morphometry analyses

In the bvFTD group, high caloric intake on the breakfast study correlated with decrease in grey matter density in the cingulate cortices, inferior temporal structures extending posteriorly, the thalami, right hippocampus, and right cerebellum, occipital cortex and lingual gyrus (Figure 2A, Table 3). Similar regions were associated with caloric intake in the SD group, generally more so in the left than the right hemisphere, with the addition of the bilateral orbitofrontal cortices, and nucleus accumbens (Figure 2B, Table 3).

Combining the bvFTD and SD groups revealed that preference for the most sweet dessert (60% sucrose) was associated with frontal, right insula-striatal reward structures and nucleus accumbens. occipital, and cerebellum grey matter intensity decrease (Figure 2C, Table 3).

Discussion

This study applied novel, ecologically-valid, methods to quantify food intake and sucrose preference in bvFTD and SD which share clinical and pathological features. This innovative approach uncovered an abnormally elevated total caloric intake and hyperphagia exclusively in bvFTD patients, supporting its diagnostic value for this disease, with no overlap in total intake between the bvFTD group and AD and control groups. Its specificity further underlines it as a useful marker to differentiate bvFTD from other dementia syndromes. The SD group overall did not exhibit increased total caloric intake, although a number of the SD patients were rigid in their choices. These findings confirm that the rigidity of SD patients influences their food preferences and eating behavior.[3,23]

On testing of sucrose preference, both bvFTD and SD patients showed a strong liking for the most sweet dessert compared to the AD and control groups, with the bvFTD group also showing a decreased liking for the least sweet dessert. These findings support the strong sweet preference reported in bvFTD[4,5], but also demonstrates that this preference extends to SD. Despite these preferences, the groups did not differ with regards to the *perceived* sweetness of the desserts, indicating that increased sweet preference in FTD is not simply the result of an inability to perceive sweetness[5], but rather likely involves changes in preference for sucrose as a nutrient.

Turning to the neural correlates, previous studies based on caregiver surveys have suggested that eating changes in bvFTD are associated with atrophy in predominantly right-sided anterior and subcortical structures,[5,7] attributable to dysregulation of reward pathways.[6] Our findings uncovered complex mechanisms underlying changes in eating behavior in FTD suggesting changes in distributed functional neural networks[24] involving reward, visual, autonomic and neuroendocrine processes, with subtle differences between bvFTD and SD (Figure 2).

Increased caloric intake in bvFTD on the breakfast test meal correlated with atrophy of bilateral anterior and posterior cingulate gyri, the thalamus, bilateral lateral occipital cortex, lingual gyri and the right cerebellum. Unlike previous studies[5,7,24], we did not find involvement of the orbitofrontal cortex in bvFTD, suggesting that eating behavior in this group is not simply related to a failure of inhibitory control.[25-27]. This position is further supported by an absence of relation between total caloric intake and measures of disinhibition on cognitive testing. Instead, we found involvement of the anterior cingulate gyrus, which participates in decision making, response selection,[28] anticipation of reward, task reinforcement,[26,29] and in controlling visceromotor, endocrine and skeletomotor outputs,[30] potentially via integration of cognitive with autonomic information.[31] In healthy individuals, activity of the cingulate cortex has been associated with increased body mass index suggesting a role for this structure in regulating eating.[32] These cognitive aspects likely interact with reward processes via connections between the cingulate cortex and thalamic nuclei,[30,33] which are implicated in the integration of taste via connections with the gustatory cortex in the insula[34], and reward, acting as a relay center between the basal ganglia and frontal structures.[35]

In addition, the thalamus is connected with the hypothalamus[36] which plays a key role in appetite and satiety control via a system of neuroendocrine peptides. Hypothalamic atrophy has been demonstrated in vivo and pathologically in bvFTD[37] and elevated levels of agouti-related peptide (AgRP), a key hypothalamic peptide that encourages hyperphagic behavior, have been found in bvFTD, suggesting that hypothalamic changes may modulate the control of eating behavior in bvFTD through interactions with cortical structures.[38] In the current study, we also found a significant association between cerebellar integrity and total caloric intake in bvFTD. In healthy individuals, the cerebellum is involved in feeding via autonomic and visceral control[39],[38], and the cerebellum has been found to be involved in bvFTD.[40] Finally contribution of visual information to eating behavior in bvFTD, potentially via feedback into reward pathways is likely, as total caloric intake was associated with volume loss in the lateral occipital and lingual cortices, suggesting a visual association role, which has been shown in other diagnoses with abnormal eating behavior such as Prader-Willi syndrome.[41]

Importantly, different mechanisms underlying eating changes in SD were uncovered. In this group, the brain regions that correlated with total caloric intake differed to those in bvFTD, notably with the involvement of the bilateral orbitofrontal cortices, left hippocampus, left thalamus, left amygdala, left insula, bilateral nucleus accumbens, right temporal fusiform cortex, right temporal occipital fusiform cortex, right parahippocampal gyrus, bilateral lingual gyri, and right cerebellum. Many of these structures are core to the semantic deficits seen in SD[42,43] suggesting a contribution of semantic networks to eating control, possibly secondary to the loss of knowledge concerning foods. Indeed, complex interactions appear to come into play, with the left thalamus and nucleus accumbens implying involvement of reward

processing and taste, the insular cortex the gustatory cortex[34], and the amygdala that of emotional and learning responses to food. Given the lack of association of total intake with the orbitofrontal cortices in bvFTD, it seems plausible that this association in SD reflects evaluative choice and decision-making in keeping with their mental rigidity.

The neural correlates of sucrose preference in bvFTD and SD revealed a brain network different to that involved in overall food intake. Increased liking of the most sweet dessert (60% sucrose) correlated with volume loss in bilateral orbitofrontal cortices and predominantly right-sided insula-striatal structures including the nucleus accumbens, amygdala extending into the temporal occipital cortex, lingual gyrus, and cerebellum. Functional imaging studies of sucrose preference in healthy subjects have implicated a network involving the transmission of sensory information from tongue taste receptors via cranial nerves to the nucleus tractus solitarus and to the thalamic ventro-posterior medial nucleus and then to the primary gustatory cortex involving the frontal operculum and anterior insula.[44] Animal models have also suggested connections between the hypothalamus and reward areas.[45] The network found in bvFTD and SD for sucrose preference hence parallels that known to be implicated in sucrose preference in healthy individuals.

Given the marked increase in food intake in the bvFTD group, one would expect their body mass index to be abnormal. Interestingly, BMI did not correlate with total intake on the breakfast test meal, strongly suggesting that other variables influence BMI, including increased energy expenditure which may be related to involvement of the anterior cingulate and insula, both of which modulate the autonomic nervous

system.[46] Increased energy expenditure ("hypermetabolism") is a well-documented phenomenon in amyotrophic lateral sclerosis[47], which has a strong clinical and pathological overlap with FTD.[48] Future research is required as to whether this phenomenon also exists in bvFTD. Future work should also explore the contribution of impaired semantic knowledge to the eating behavioral changes seen in SD.

Strong sucrose preference is a marker of FTD syndromes, whilst hyperphagia is present in all bvFTD patients, SD is characterised by rigid eating behavior, with dissociated neural networks responsible for these changes. An understanding of the networks controlling this eating behavior offers opportunities for targeted treatments that can modify eating behavior, metabolic abnormalities and disease progression[49], and provides insights into structures controlling eating behavior in normal individuals.

Acknowledgements

We wish to acknowledge the assistance of Ms Heidi Cartwright for assistance with figures.

Funding: This work was supported by funding to Forefront, a collaborative research group dedicated to the study of frontotemporal dementia and motor neurone disease, from the National Health and Medical Research Council of Australia (NHMRC) program grant (#1037746 to MK and JH) and the Australian Research Council Centre of Excellence in Cognition and its Disorders Memory Node (#CE110001021 to OP and JH) and other grants/sources (NHMRC project grant #1003139). We are grateful to the research participants involved with the ForeFront research studies. RA is a Royal Australasian College of Physicians PhD scholar and MND Australia PhD scholar. MI is an ARC Discovery Early Career Researcher Award Fellow

(#DE130100463). OP is an NHMRC Career Development Research Fellow (#1022684). ISF is supported by the Wellcome Trust, Medical Research Council, European Research Council, NIHR Cambridge Biomedical Research Centre and The Bernard Wolfe Endowment. No funding source had a role in the writing of the manuscript. No funding source had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication

Author disclosures: The authors declare no competing financial interests

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547

548 **Figure Legends**

549 **Figure 1A: Box plot showing total caloric intake for breakfast Ad-libitum test**

550 **meal**

551 Ends of box represent first and third quartiles. Line in box represents median value.

552 Whiskers represent minimum and maximum values. * Mean intake in bvFTD group >

553 all other groups ($p < 0.001$). SD patients exhibited rigid eating behavior often refusing

554 to eat the food on offer (patient who scored 0 intake), or only eating small amounts.

555

556 **Figure 1B Liking and Perceived sweetness of 3 desserts**

557 ii) Patients mean Liking scores for each dessert A (26% sucrose) B (39% sucrose) and

558 C (60% sucrose). ii) Patients mean perceived sweetness scores for each dessert A

559 (26% sucrose) B (39% sucrose) and C (60% sucrose) * bvFTD < all other groups ($p <$

560 0.01), ** BvFTD and SD > all other groups ($p < 0.001$).

561

562

563 **Figure 2: Voxel based morphometry analyses for total intake and sucrose**

564 **preference and visual representation of proposed networks controlling total**

565 **intake and sucrose preference in FTD.**

566 Voxel-based morphometry analyses showing brain regions in which grey matter

567 intensity correlates significantly with total caloric intake in (A) bvFTD (MNI

568 coordinates: x = 18, y = 40,): higher total caloric intake on the breakfast study

569 correlated with grey matter intensity decrease in a number of brain regions likely

570 involving a network connecting the anterior cingulate, which connects to the

571 thalamus, which is involved in taste via connections to the insula and reward via

connections to the basal ganglia. The thalamus also likely connects to the hypothalamus, with neuroendocrine modulation of reward and the lingual gyrus and visual cortex, for visual input to reward processing. The cerebellum also likely modulates eating behavior through autonomic input and cerebellar hypothalamic connections (B) In SD (MNI coordinates: x = 18, y = 40) the orbitofrontal cortex is likely involved in decision making regarding preferences which may explain rigidity of eating behavior in this group. This then aligns with a similar network in bvFTD involving reward and taste (left thalamus, insula, amygdala, bilateral nucleus accumbens). Additional contributions of lingual gyrus and cerebellar inputs are likely in SD eating behavior. (C) Displays significant associations between sucrose preference (liking of most sweet dessert 60% sucrose) in bvFTD and SD patients combined (MNI coordinates: x = 20, y = -8,). The network for sucrose involves the orbitofrontal cortex connecting right insula-striatal reward structures and nucleus accumbens. Again the cerebellum and lingual gyrus are involved in this network. Coloured voxels show regions that were significant in the covariate analyses with $p <$ 0.05 corrected for False Discovery Rate. Clusters are overlaid on the Montreal Neurological Institute Standard brain. Age is included as a covariate in the analyses.

590 **Table 1: Demographic and clinical characteristics of patient groups and healthy controls**

	bvFTD	SD	AD	Controls	F value	Post hoc test
Sex (F:M)	9:10	5:10	6:9	12:13	NS^{+}	N/A
Age (yrs)	62 ± 8.3	64 ± 7.0	66 ± 8.4	66 ± 7.7	1.1	N/A
Disease duration (yrs)	5.5 ± 4.1	5.6 ± 2.3	5.8 ± 4.7	N/A	.01	N/A
ACE-R Total (100)	71 ± 17.4	59 ± 18.8	68 ± 18.4	96 ± 2.7	*** 24.5	Controls > Patient groups
Education (yrs)	11.9 ± 2.9	13.3 ± 3.1	11.9± 3.7	13.8± 2.7	NS^{+}	N/A
FRS (mild/mod/severe)	0/2/17	1/10/4	4/6/5	NA	**17.7^$^{+}$	bvFTD < AD; bvFTD < SD
Hayling	2.6 ± 2.4	4.7 ± 2.5	3.8 ± 2.0	6.0	**11.2$^{\#}$	bvFTD < controls, AD <controls
Trails B-A (seconds)	90.6	91.6	109.1	43.0	**15.1$^{\#}$	bvFTD> controls; AD > controls
APEHQ Total	77± 44	33 ± 39	19 ± 18	NA	*** 10.6	bvFTD > AD; bvFTD > SD
CBI Total (% corrected)	44 ± 13	28 ± 17	27 ± 14	NA	*** 28.8	bvFTD > AD, SD
CBI eating Total (% corrected)	52 ± 27	21 ± 24	15 ± 24	NA	***17.3	bvFTD > AD, SD
BMI	29.5 ± 6.6	26.1 ± 6.1	25.5 ± 5.8	27.9 ± 5.6	1.5	N/A

591 , ** $p < .01$, *** $p < .001$, NS = not significant, N/A= not applicable; $^{+}$ Chi-square test. # Non- parametric analyses H value, ^ The FRS
592 provides logit scores ranging from 4.12 (very mild) to < -4.99 (very severe). Data presented as mean ± standard deviation
593

594 **Table 2: Total intake and percentage macronutrient intake on the ad-libitum breakfast test meal and total intake of each dessert in**

595 **patient groups and controls**

	bvFTD	SD	AD	Controls	H value	Post hoc test
Total intake (calories)	1344 ± 418	573 ± 325	710 ± 201	603 ± 193	***40.5	bvFTD > controls, AD, SD
(range min-max)	(909- 2360)	(0- 1227)	(274- 987)	(251-857)		
% Fat intake	26 ± 6	24 ± 18	20 ± 5	25 ± 13	4.0	N/A
% Protein intake	9 ± 2	11 ± 5	11 ± 4	15 ± 7	***18.6	controls > bvFTD
% Carbohydrate	44 ± 6	37 ± 17	46 ± 5	42 ± 10	4.2	N/A
% Sugar intake	24 ± 5	21 ± 10	27 ± 10	21 ± 10	3.1	N/A
			Dessert sucrose preference- Total intake			
Dessert A (g)	25± 42	2 ± 3	6 ± 22	4 ± 17	***21.7	bvFTD > controls, AD, SD
Dessert B (g)	36 ± 44	2 ± 4	0	1 ± 3	***28.4	bvFTD > controls, AD, SD

Dessert C (g)	98 ± 113	1 ± 2	5 ± 17	1 ± 2	***30.1	bvFTD > controls, AD, SD

Data presented as mean ± standard deviation; *** p <.001

Table 3

Voxel-based morphometry results showing regions of significant grey matter intensity decrease that covary with Total Calories consumed in bvFTD and SD patient groups separately and that covary with Sweet Preference ratings (for most sweet dessert C) in both the bvFTD and SD patient groups combined.

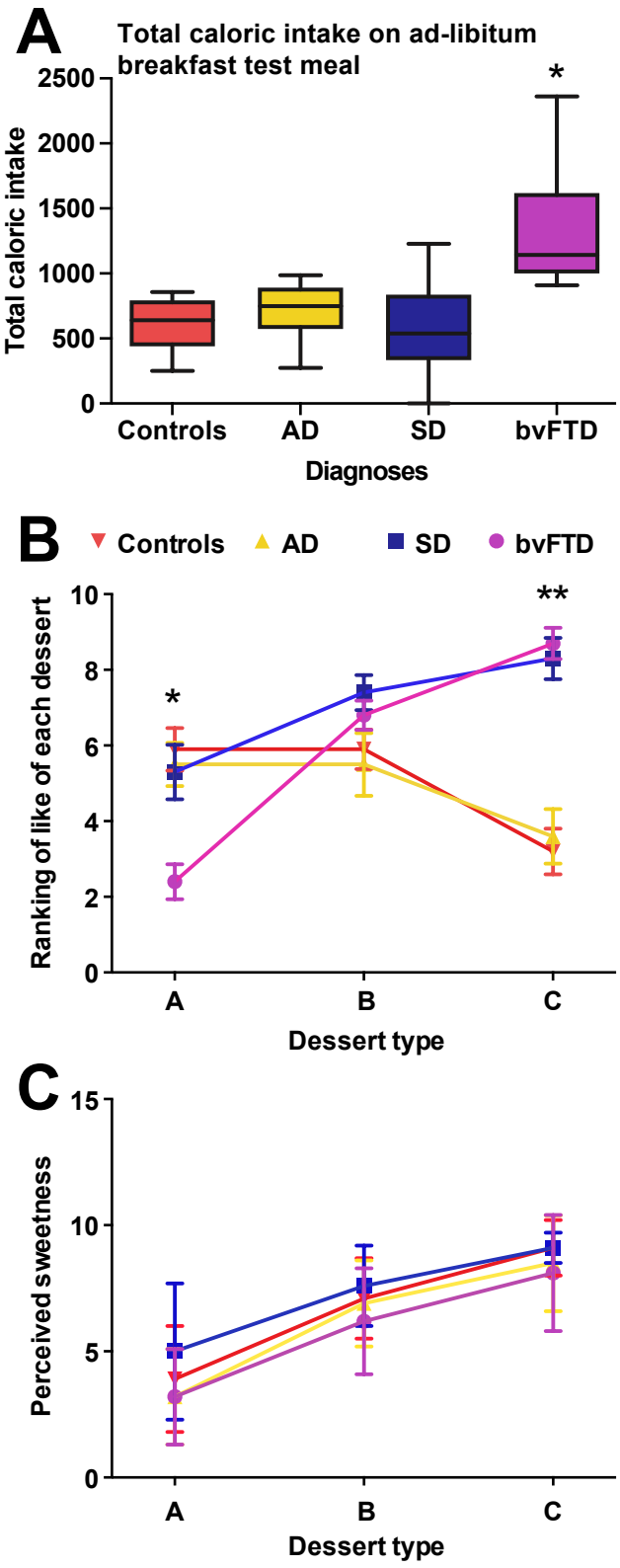
				MNI coordinates		
	Regions	**Side**	**Number of voxels**	**x**	**y**	**z**
Regions that covary with Total Calories consumed in bvFTD and SD patient groups.						
bvFTD	Right lingual gyrus, right precuneus cortex, right posterior cingulate cortex, extending into right parahippocampal gyrus (posterior), right hippocampus (posterior), right thalamus, right temporal occipital fusiform cortex, right occipital fusiform gyrus, left lingual gyrus	B	1532	14	-52	2
	Lateral occipital cortex, extending into inferior temporal gyrus, middle temporal gyrus, temporal occipital fusiform cortex, occipital fusiform gyrus	L	1140	-50	-78	12
	Left thalamus, extending into left anterior cingulate gyrus, right thalamus	B	614	-12	-36	10
	Cerebellum	R	420	18	-44	-58
	Left subcallosal cortex, extending into bilateral anterior cingulate gyrus	B	131	-4	22	2

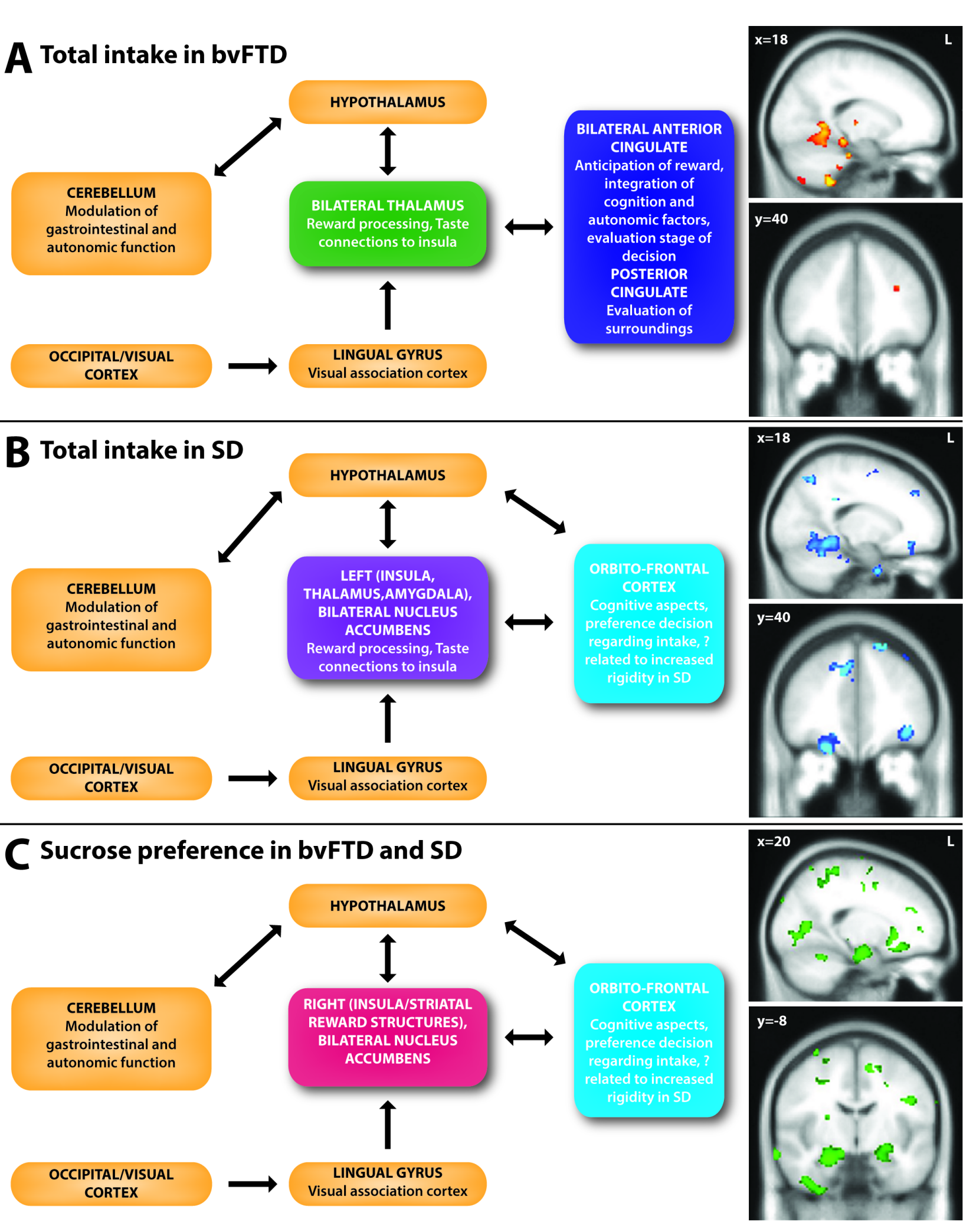
	Parahippocampal gyrus (posterior)	R	129	10	-30	-12
SD	Temporal occipital fusiform cortex, extending into lingual gyrus, cerebellum, parahippocampal gyrus (posterior), temporal fusiform cortex	R	1932	28	-48	-16
	Left parahippocampal gyrus (anterior), extending into left amygdala, left hippocampus, bilateral accumbens, right temporal fusiform cortex, right parahippocampal gyrus (anterior)	B	727	2	2	-28
	Parahippocampal gyrus (posterior), extending into hippocampus, and lingual gyrus	L	413	-10	-38	-10
	Precentral gyrus, inferior frontal gyrus, extending into frontal operculum cortex, temporal pole	R	289	60	10	2
	Frontal pole, orbital frontal cortex, extending into insular cortex, frontal operculum cortex	L	281	-36	40	-10
	Middle frontal gyrus, extending into inferior frontal gyrus	L	170	-38	10	42
	Paracingulate gyrus, extending into superior frontal gyrus, frontal pole	R	166	12	38	34
	Frontal pole, extending into orbital frontal cortex	R	164	24	40	-22
	Lateral occipital cortex, precuneus cortex	R	129	14	-66	50
	Middle frontal gyrus, extending into superior frontal gyrus	L	100	-26	2	46
	Regions that that covary with Sweet Preference ratings (for most sweet dessert C) in both the bvFTD and SD patient groups.					
BvFTD and SD	Bilateral temporal pole, extending into bilateral orbital frontal cortex, bilateral frontal pole, right frontal operculum cortex, right insular cortex, bilateral subcallosal cortex, bilateral putamen, bilateral caudate, bilateral accumbens.	B	3201	44	20	-22
	Cerebellum, extending into temporal occipital fusiform cortex, temporal fusiform cortex, inferior temporal gyrus, middle temporal gyrus	R	1124	24	-50	-26
	Angular gyrus, extending into supramarginal gyrus, lateral occipital cortex, supracalcarine cortex, intracalcarine cortex, precuneus cortex, lingual gyrus, superior parietal lobule, occipital fusiform cortex	R	1096	36	-58	22

	Middle frontal gyrus, extending into precentral gyrus, inferior frontal gyrus	R	1043	28	12	28
	Angular gyrus, extending into supramarginal gyrus, lateral occipital cortex, precuneus cortex, parietal operculum cortex, supracalcarine cortex, intracalcarine cortex	L	960	-36	-56	20
	Postcentral gyrus, superior parietal lobule, extending into precentral gyrus, lateral occipital cortex	R	798	32	-36	66
	Central opercular cortex, extending into insular cortex, frontal operculum cortex, inferior frontal gyrus, precentral gyrus, planum polare, temporal pole	R	717	44	6	4
	Supplementary motor cortex, extending into precentral gyrus, superior frontal gyrus, middle frontal gyrus	L	618	-14	-8	54
	Central opercular cortex, precentral gyrus, inferior frontal gyrus, extending into postcentral gyrus, planum polare, superior temporal gyrus, temporal pole	L	565	-48	6	8
	Precentral gyrus, extending into precuneus cortex, posterior cingulate gyrus	B	517	10	-24	54
	Hippocampus, extending into parahippocampal gyrus (anterior), amygdala	R	447	24	-12	-22
	Amygdala, extending into hippocampus, parahippocampal gyrus (anterior), pallidum, putamen	L	361	-24	-2	-12
	Cerebellum	L	337	-38	-54	-62
	Frontal pole, extending into middle frontal gyrus, paracingulate gyrus, anterior cingulate gyrus	R	313	30	36	20

All clusters reported using voxel-wise contrasts and corrected for False Discovery Rate (FDR) at $p < .05$. All clusters reported at $t > 1.79$ with a cluster threshold of 100 contiguous voxels. BvFTD = behavioural-variant frontotemporal dementia; SD = semantic dementia; L = Left; R = Right; B=Bilateral; MNI = Montreal Neurological Institute. Age is included as a nuisance variable in the analyses..

612


A
Total caloric intake on ad-libitum breakfast test meal
Total caloric intake
2500
2000
1500
1000
500
0
*
Controls
AD
SD
bvFTD
Diagnoses
B
Controls
AD
SD
bvFTD
Ranking of like of each dessert
10
8
6
4
2
0
*
**
A
B
C
Dessert type
C
Perceived sweetness
15
10
5
0
A
B
C
Dessert type


A Total intake in bvFTD
HYPOTHALAMUS
CEREBELLUM
Modulation of gastrointestinal and autonomic function
BILATERAL THALAMUS
Reward processing, Taste connections to insula
BILATERAL ANTERIOR CINGULATE
Anticipation of reward, integration of cognition and autonomic factors, evaluation stage of decision
POSTERIOR CINGULATE
Evaluation of surroundings
OCCIPITAL/VISUAL CORTEX
LINGUAL GYRUS
Visual association cortex
x=18
L
y=40
B Total intake in SD
HYPOTHALAMUS
CEREBELLUM
Modulation of gastrointestinal and autonomic function
LEFT (INSULA, THALAMUS,AMYGDALA), BILATERAL NUCLEUS ACCUMBENS
Reward processing, Taste connections to insula
ORBITO-FRONTAL CORTEX
Cognitive aspects, preference decision regarding intake, ? related to increased rigidity in SD
OCCIPITAL/VISUAL CORTEX
LINGUAL GYRUS
Visual association cortex
x=18
L
y=40
C Sucrose preference in bvFTD and SD
HYPOTHALAMUS
CEREBELLUM
Modulation of gastrointestinal and autonomic function
RIGHT (INSULA/STRIATAL REWARD STRUCTURES), BILATERAL NUCLEUS ACCUMBENS
ORBITO-FRONTAL CORTEX
Cognitive aspects, preference decision regarding intake, ? related to increased rigidity in SD
OCCIPITAL/VISUAL CORTEX
LINGUAL GYRUS
Visual association cortex
x=20
L
y=-8